CURRICULUM VITÆ, ATTIVITA' ASSISTENZIALE, SCIENTIFICA, DIDATTICA ED ELENCO DELLE PUBBLICAZIONI DEL

Prof. Camillo PORTA

29 Maggio 2023

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Curriculum Vitæ del Prof. Camillo Porta

Informazioni personali

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Nazionalità		Italiana

Data e luogo di nascita		8 Maggio 1965, Pavia

Indirizzo lavorativo		Università degli Studi di Bari "Aldo Moro", Dipartimento Interdisciplinare di Medicina & U.O.C.U. di Oncologia Medica, A.O.U. Consorziale Policlinico di Bari
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Istruzione e formazione: curriculum formativo pre-Laurea

Date (da – a)		**1979 → 1983**
Nome e tipo di istituto di istruzione o formazione		Liceo Classico/Ginnasio 'Ugo Foscolo' di Pavia
Principali materie oggetto dello studio		Materie umanistiche
Qualifica conseguita		Diploma di Maturità Classica
Anno		1983

Date (da – a)		**Anno Accademico 1983/1984 → 1988/1989**

Nome e tipo di istituto di istruzione o formazione		Università degli Studi di Pavia
Facoltà		Medicina e Chirurgia
Corso di Laurea		Medicina e Chirurgia

Date (da – a)		**Anno Accademico 1984/1985 → 1985/1986**
Nome e tipo di istituto di istruzione o formazione		Università degli Studi di Pavia, Facoltà di Medicina e Chirurgia
Internato pre-laurea c/o		Istituto di Anatomia Umana Normale (Direttore: Prof. Luigi Cattaneo)
Competenze acquisite		Metodiche di indagine citologiche, istologiche ed ultrastrutturali

Date (da – a)		**Anno Accademico 1986/1987 → 1988/1989**
Nome e tipo di istituto di istruzione o formazione		Università degli Studi di Pavia, Facoltà di Medicina e Chirurgia
Internato pre-laurea c/o		Istituto di Patologia Medica I/Terapia Medica (Direttori: Prof. Salvatore Carlo Rizzo, Prof. Pietro Fratino, Prof.a Antonia Notario, Prof. Lucio De Caro)
Competenze acquisite		Metodologia clinica in Medicina Interna, Ematologia ed Oncologia; metodologia di ricerca, clinica e sperimentale, in Ematologia ed Oncologia

Istruzione e formazione:
Laurea e curriculum formativo post-Laurea

Data		**20 Ottobre 1989**
Nome e tipo di istituto di istruzione o formazione		Università degli Studi di Pavia
Facoltà		Medicina e Chirurgia
Qualifica conseguita		Laurea in Medicina e Chirurgia
Votazione conseguita		110/110 *cum laude*
Tesi		'Porpora Trombotica Trombocitopenica (PTT): studio retrospettivo su 82 casi e prospettive terapeutiche'

Data		**1989**
Nome e tipo di istituto di istruzione o formazione		Università degli Studi di Pavia
Facoltà		Medicina e Chirurgia
Qualifica conseguita		Abilitazione alla professione di Medico-Chirurgo

Data		**20 Febbraio 1990**
		Iscrizione all'Albo Professionale dei Medici Chirurghi e degli Odontoiatri della Provincia di Pavia
Numero di iscrizione all'Albo		5904

Date (da – a)		**Anno Accademico 1989/1990 → 1992/1993**
Nome e tipo di istituto di istruzione o formazione		Università degli Studi di Pavia
Facoltà		Medicina e Chirurgia
Scuola di Specializzazione		Oncologia (Direttore: Prof. Leonida Santamaria)

Date (da – a)		**Novembre 1989 → Aprile 1997**
Nome e tipo di istituto di istruzione o formazione		Fondazione IRCCS Policlinico San Matteo di Pavia
Internato post-laurea c/o		Istituto di Terapia Medica/Dipartimento di Medicina Interna e Nefrologia (Direttori: Prof.a Antonia Notario, Prof. Antonio Dal Canton)
Attività svolte		Attività clinica di supporto ai Medici Strutturati; attività di ricerca, clinica e di laboratorio

Date (da – a)		**Luglio 1997 → Marzo 1998**
Nome e tipo di istituto di istruzione o formazione		Fondazione IRCCS Policlinico San Matteo di Pavia
Internato post-laurea c/o		Istituto di Medicina Interna ed Oncologia Medica (Direttore: Prof. Edoardo Ascari)
Attività svolte		Attività clinica ed ambulatoriale di supporto ai Medici Strutturati; attività di ricerca, clinica e di laboratorio

Servizio Militare

Date (da – a)		**3 Maggio 1991 → 2 Agosto 1992**
Corso		107° Corso Allievi Ufficiali di Complemento (Scuola di Sanità Militare di Firenze)
Grado		Sottotenente Medico di Complemento
Mansioni/Ruolo		Dirigente del Servizio Sanitario presso il 33° Battaglione Logistico di Manovra 'Ambrosiano' di Milano; Ufficiale Medico di Guardia presso il Policlinico Militare 'L. Annibaldi' di Baggio, in Milano

Istruzione e formazione:
Specializzazione

Data		**14 Giugno 1993**
Nome e tipo di istituto di istruzione o formazione		Università degli Studi di Pavia
Facoltà		Medicina e Chirurgia, Scuola di Specializzazione in Oncologia
Qualifica conseguita		Specializzazione in Oncologia Medica

Votazione conseguita		50/50 *cum laude*
Tesi		'Terapia loco-regionale degli epatocarcinomi inoperabili: alcoolizzazione e chemioembolizzazione'

Istruzione e formazione: altri titoli di studio e certificazioni

Data		**Febbraio-Dicembre 2008**
Nome e tipo di istituto di istruzione o formazione		Istituto Regionale Lombardo di Formazione per l'Amministrazione Pubblica (I.Re.F.) e Consorzio Pavese per gli Studi Post-Universitari
Corso		Corso per Dirigenti di Struttura Complessa – Area Ospedaliera
Tesi		'Identificazione e correzione di criticità nella gestione delle riunioni: applicazione di un questionario valutativo specifico'

Data		**Marzo-Maggio 2016**
Nome e tipo di istituto di istruzione o formazione		Centro di Ricerca Interdipartimentale "Organizzazione e Governance della Pubblica Amministrazione" dell'Università degli Studi di Pavia, accreditato da Eupolis Lombardia – Scuola di Direzione in Sanità
Corso		"Management e Leadership in Sanità" – corso di rivalidazione del certificato manageriale

Istruzione e formazione: *stages* di aggiornamento

Data		**Dicembre 1993**
Sede		Memorial Sloan Kettering Cancer Center, New York, NY (USA)
Corso residenziale		*Current Concepts in Medical Oncology* '93 (Direttore: Prof. Howard J. Scher) – corso a numero chiuso di partecipanti
Oggetto del corso		Presentazione e discussione critica, assieme ai Docenti (provenienti dal MSKCC così come da altre Istituzioni statunitensi), delle più innovative modalità di trattamento per le principali neoplasie solide ed ematologiche; valutazione delle potenziali ripercussioni cliniche delle più recenti scoperte di biologia delle neoplasie

Data		**Giugno 1995**
Sede		Istituto di Ematologia 'L. & A. Seragnoli', Policlinico Sant'Orsola-Malpighi, Università degli Studi di Bologna
Corso residenziale		*Le infezioni in Ematologia* (Direttore: Prof. Sante Tura) – corso a numero chiuso di partecipanti
Oggetto del corso		Acquisizione di una approfondita conoscenza del delicato problema delle infezioni nei pazienti emato-oncologici sottoposti a trattamenti chemioterapici tradizionali, a trapianto di cellule staminali da sangue periferico, o a trapianto di midollo (autologo

		o allogenico). Presentazione e valutazione critica dei protocolli di trattamento anti-infettivi e dei concetti di bio-protezione nelle Unità di Trapianto di Midollo Osseo

Data		**Luglio 1995**
Sede		Unità di Trapianto di Midollo 'Cristina Gandini' dell'Istituto Nazionale Tumori di Milano (Direttore: Prof. Alessandro Massimo Gianni)
Attività svolte		Esperienza pratica con le metodiche di trapianto di cellule staminali mobilizzate da sangue periferico nell'ambito di programmi di chemioterapia sequenziale ad alte dosi per il trattamento dei carcinomi della mammella ad alto rischio di recidiva e per i linfomi non-Hodgkin refrattari

Data		**Settembre 1998**
Sede		Baylor College of Medicine and MD Anderson Cancer Center, Houston, Tx, USA (Direttore dello *stage*: Prof. Philip Dacso) – corso a numero chiuso di partecipanti
Attività svolte		Accurata messa a punto del trattamento multidisciplinare del carcinoma della mammella. Particolare attenzione, oltre al trattamento medico (chemioterapico ed ormonale) era rivolta alle integrazioni con chirurgia e radioterapia, nonchè alle terapie di supporto (riabilitativa, psicologica, ormonale di rimpiazzo, ecc …). Il ruolo della predisposizione genetica allo sviluppo del carcinoma della mammella, unitamente alle più sofisticate tecniche diagnostiche a nostra disposizione, sono stati ulteriori argomenti trattati nel corso dello *stage*

Data		**Febbraio 2014**
Sede		SDA Bocconi, *School of Management*, Milano – corso a numero chiuso di partecipanti
Attività svolte		Corso di formazione economico-manageriale per Oncologie Italiane di eccellenza. Corso incentrato su due grossi argomenti economico-manageriali: 1) sistemi di programmazione e controllo, analisi dei costi ed indicatori di *performance*; 2) sistemi e strumenti di gestione del personale nelle aziende sanitarie

Esperienza lavorativa Ospedaliera

Date (da – a)		**21 Aprile → 28 Giugno 1997**
Ospedale		Casa di Cura (convenzionata con il Sistema Sanitario Nazionale) 'Beato Matteo' di Vigevano
Divisione		Medicina e Oncologia (Primario: Dr. Pietro Gallotti)
Tipo di impiego		Dirigente Medico (contratto libero-professionale)
Principali mansioni e responsabilità		Attività assistenziale presso il reparto di degenza, il Day-Hospital e l'Ambulatorio di Oncologia Medica

Date (da – a)		**1 Aprile 1998 → 22 Marzo 2001**
Ospedale		Fondazione IRCCS Policlinico San Matteo di Pavia
Servizio		Pronto Soccorso ed Accettazione (Primario: Dr.ssa Maria Antonietta Bressan)
Tipo di impiego		Dirigente Medico I livello (Medicina d'Urgenza)

Principali mansioni e responsabilità		Attività di Medicina d'urgenza presso il Pronto Soccorso Medico; consensualmente, attività ambulatoriale di Oncologia Medica (fuori dall'orario di servizio in Pronto Soccorso) presso l'Istituto di Medicina Interna ed Oncologia Medica del medesimo Policlinico

Date (da – a)		**23 Marzo 2001 → 31 Dicembre 2008**
Ospedale		Fondazione IRCCS Policlinico San Matteo di Pavia
Istituto		Medicina Interna ed Oncologia Medica (Direttori: Prof. Edoardo Ascari, Dr. Alberto Vailati – F.F., Prof. Gino Roberto Corazza)
Tipo di impiego		Dirigente Medico I livello (Oncologia Medica)
Principali mansioni e responsabilità		Attività assistenziale presso il reparto di degenza (28 posti letto + 2 stanze sterili per attività di autotrapianto di cellule staminali periferiche – accreditate GITMO ed EBMT – queste ultime attive fino al 2007), con diretta responsabilità su 7 posti letto, e coordinamento dell'attività di 3-5 Medici Specializzandi (in Oncologia Medica e/o Medicina Interna), a seconda degli anni; attività ambulatoriale presso l'Ambulatorio di Oncologia Medica

Date (da – a)		**1 Gennaio 2009 → 16 Ottobre 2014**
Ospedale		Fondazione IRCCS Policlinico San Matteo di Pavia
Istituto		S.C. Ospedaliera di Oncologia Medica (Primari: Dr. Marco Danova – F.F., Dr. Paolo Pedrazzoli)
Tipo di impiego		Dirigente Medico I livello
Principali mansioni e responsabilità		Attività assistenziale presso il reparto di degenza (28 posti letto), con diretta responsabilità su 14 posti letto, e coordinamento dell'attività di 3-5 Medici Specializzandi in Oncologia Medica, a seconda degli anni (fino al 2011); attività ambulatoriale presso l'Ambulatorio di Oncologia Medica

Date (da – a)		**17 Ottobre 2014 → 31 Luglio 2018**
Ospedale		Fondazione IRCCS Policlinico San Matteo di Pavia
Istituto		S.C. Ospedaliera di Oncologia Medica (Primario: Dr. Paolo Pedrazzoli)
Tipo di impiego		Dirigente Medico di Alta Specializzazione
Principali mansioni e responsabilità		Organizzazione dell'attività ambulatoriale della struttura complessa; responsabilità dell'Ambulatorio di Oncologia Medica e Studi Clinici, coordinamento dell'attività dell'Oncology Clinical Trials Center (OCTO) ed attività assistenziale limitata alle guardie presso il reparto di degenza (28 posti letto).

Date (da – a)		**1 Agosto 2018 → 15 Marzo 2020**
Ospedale		IRCCS Istituti Clinici Scientifici Maugeri di Pavia
Reparto		Divisione di Oncologia Traslazionale
Tipo di impiego		Primario
Principali mansioni e responsabilità		Direzione della Divisione (degenza ordinaria, degenza Day-Hospital/Macroattività Ambulatoriale Complessa, Ambulatori), con forte connotazione verso la ricerca

		clinica e traslazionale, integrata con Laboratori di Ricerca ed una Biobanca accreditata AIFA.

Date (da – a)		**17 Aprile 2019 → 15 Marzo 2020**
Ospedale		IRCCS Istituti Clinici Scientifici Maugeri di Pavia
Tipo di impiego		Responsabile Clinical Trial Center
Principali mansioni e responsabilità		Coordinamento e responsabilità amministrativa/scientifica; ccordinamento dell'attività di 1 Study Coordinator, 4 Data Manager, 1 Infermiera di Ricerca, 1 Biologo Laureato.

Date (da – a)		**8 Luglio 2020 → 11 Novembre 2020**
Ospedale		Azienda Ospedaliero-Universitaria Policlinico Consorziale di Bari
Reparto		Unità Operativa Complessa Universitaria di Oncologia Medica
Tipo di impiego		Direttore facente funzioni
Principali mansioni e responsabilità		Direzione dell'Unità (degenza ordinaria – attualmente sospesa causa emergenza COVID, Day-Hospital/Day Service, Ambulatori), coordinamento dell'attività di 7 Strutturati (tra Universitari ed Ospedalieri) e 25 Specializzandi. Coordinamento attività di ricerca presso laboratorio di Oncogenomica afferente alla Struttura di Oncologia.

Date (da – a)		**12 Novembre 2020 → oggi**
Ospedale		Azienda Ospedaliero-Universitaria Policlinico Consorziale di Bari
Reparto		Unità Operativa Complessa Universitaria di Oncologia Medica
Tipo di impiego		Direttore
Principali mansioni e responsabilità		• Direzione dell'U.O.C. (degenza ordinaria – attualmente sospesa, dapprima causa emergenza COVID, ora per ristrutturazione, Day-Hospital/Day Service, Ambulatori); • coordinamento dell'attività di 8 Strutturati (tra Universitari ed Ospedalieri), una contrattista, e 25-30 Specializzandi (a seconda degli annni); • coordinamento attività di ricerca presso Laboratorio di Oncogenomica, afferente alla U.O.C. di Oncologia; • organizzazione dei seguenti Team Multidisciplinari (MDT): Uro-Oncologia, Ginecologia Oncologica, Neuro-Oncologia, Onconefrologia, Epatocarcinoma, Neoplasie dell'Apparato Gastro-Intesinale, Neoplasie del Distretto Cervico-Cefalico; • stesura dei seguenti Percorsi Diagnostico-Terapeutici Assistenziali (PDTA): Neoplasie della Prostata, Neoplasie del Distretto Cervico-Cefalico, Neoplasie della Vescica (in corso di preparazione), Neoplasie del Rene (in corso di preparazione),

Altri tipi di responsabilità lavorativa

Date (da – a)		**Luglio 1991 → Luglio 1992**
Istituzione		Ministero della Difesa

Tipo di impiego		Dirigente del Servizio Sanitario (nel corso del Servizio di Leva, svolto in qualità di Ufficiale Medico di Complemento)
Principali mansioni e responsabilità		Responsabilità sanitaria sul personale del 33° Battaglione Logistico di Manovra 'Ambrosiano' di Milano e della della 3° Officina Riparazioni dell'Esercito di Milano

Date (da – a)		**Febbraio 1994 → Febbraio 1996**
Ospedale		Fondazione IRCCS Policlinico San Matteo di Pavia
Tipo di impiego		Vincitore, attraverso concorso pubblico per titoli ed esami, di Borsa di Studio annuale, rinnovata per un secondo anno, intitolata: 'Monitoraggio di farmaci antineoplastici in relazione all'attività terapeutica'
Principali mansioni e responsabilità		Attività di ricerca in campo Oncologico

Date (da – a)		**Aprile 1996 → Marzo 1997**
Ospedale		Fondazione IRCCS Policlinico San Matteo di Pavia
Tipo di impiego		Vincitore, attraverso concorso pubblico per titoli ed esami, di Borsa di Studio annuale intitolata: 'Ruolo dei flussi di Ca^{++} nella biologia cellulare. Studio in linee cellulari umane'
Principali mansioni e responsabilità		Attività di ricerca in campo Oncologico ed Onco-Ematologico

Date (da – a)		**1993 → 1996**
Ospedale		Fondazione IRCCS Policlinico San Matteo di Pavia
Istituto		Patologia Medica I, poi Terapia Medica (Direttore: Prof.a Antonia Notario)
Tipo di impiego		Co-responsabile (con il Dr. Mauro Moroni) del Laboratorio di Colture Cellulari, sotto la diretta supervisione dell'allora Direttore dell'Istituto, Prof.a Antonia Notario
Principali mansioni e responsabilità		Attività di ricerca in campo Oncologico ed Onco-Ematologico

Date (da – a)		**Marzo 2003 → Dicembre 2009**
Ospedale		Fondazione IRCCS Policlinico San Matteo di Pavia
Istituto		Medicina Interna ed Oncologia Medica (Direttore: Prof. Gino Roberto Corazza), quindi S.C. di Oncologia Medica (Primario F.F.: Dr. Marco Danova)
Tipo di impiego		Responsabile del Laboratorio di Oncologia Pre-Clinica e Terapie Sperimentali
Principali mansioni e responsabilità		Attività di ricerca in campo Oncologico e coordinamento dell'attività di una Biologa Laureata

Date (da – a)		**Maggio 2008 → 2013**
Ospedale		Fondazione IRCCS Istituto Neurologico 'Casimiro Mondino' di Pavia
Tipo di impiego		Consulente Oncologo esterno

Attività Didattica a contratto

Date (da – a)		**Anno Accademico 1998/1999 → 2008/2009**
Sede		Università degli Studi di Pavia, Facoltà di Medicina e Chirurgia, Cattedra di Oncologia Medica (Direttore: Prof. Alberto Riccardi)
Posizione		Cultore della Materia di Oncologia Medica
Principali mansioni e responsabilità		Attività didattica nel Corso di Laurea, attività di Tutorato per gli studenti, partecipazione alle Commissioni d'esame di tale insegnamento

Date (da – a)		**Anno Accademico 2000/2001 → 2013/2014**
Sede		Università degli Studi di Pavia, Facoltà di Medicina e Chirurgia, Scuola di Specializzazione in Oncologia Medica (Direttore: Prof. Edoardo Ascari, quindi Prof. Alberto Riccardi)
Posizione		Professore a Contratto
Principali mansioni e responsabilità		Attività didattica nel Corso di Specializzazione, attività di Tutorato per l'attività clinica e di ricerca degli specializzandi, partecipazione alle Commissioni d'esame di tale insegnamento

Date (da – a)		**Anno Accademico 2002/2003**
Sede		Università degli Studi di Pavia, Dipartimento di Genetica e Microbiologia "A. Buzzati Traverso", Scuola di Specializzazione in Genetica Applicata (Direttore: Prof.a Nadia Ranzani)
Posizione		Lettore
Principali mansioni e responsabilità		Attività didattica nel Corso di Specializzazione

Date (da – a)		**Anno Accademico 2002/2003 → 2003-2004**
Sede		Università degli Studi di Pavia, Facoltà di Medicina e Chirurgia, Scuola di Specializzazione in Medicina Interna (Direttore: Prof. Roberto Fogari)
Posizione		Professore a contratto
Principali mansioni e responsabilità		Attività didattica nel Corso di Specializzazione, attività di Tutorato per l'attività clinica degli specializzandi

Date (da – a)		**Anno Accademico 2002/2003 → 2006/2007**
Sede		Università degli Studi di Pavia, Facoltà di Medicina e Chirurgia, Scuole di Specializzazione in Chirurgia Generale II e Chirurgia Generale III, indirizzo in Chirurgia d'Urgenza (Direttori: Prof. Aris Zonta, quindi Prof. Paolo Dionigi)
Posizione		Lettore
Principali mansioni e responsabilità		Attività didattica nel Corso di Specializzazione

Date (da – a)		**Anno Accademico 2007/2008 → 2009/2010**
Sede		Università degli Studi di Pavia, Facoltà di Medicina e Chirurgia, Scuole di Specializzazione in Chirurgia Generale II e Chirurgia Generale III, indirizzo in Chirurgia d'Urgenza (Direttore: Prof. Paolo Dionigi)
Posizione		Professore a contratto

Principali mansioni e responsabilità		Attività didattica nel Corso di Specializzazione

Date (da – a)		**Anno Accademico 2003/2004 → 2004/2005**
Sede		Università degli Studi di Pavia, Corso di Laurea Specialistica in Biotecnologie Mediche e Farmaceutiche, indirizzo in Biotecnologie Mediche e Ricerca Biomedica (Direttore: Prof. Gianpaolo Merlini)
Posizione		Lettore
Principali mansioni e responsabilità		Attività didattica

Date (da – a)		**Anno Accademico 2004/2005 → 2009/2010**
Sede		Università degli Studi di Pavia, Corso di Laurea Specialistica in Biotecnologie Mediche e Farmaceutiche, indirizzo in Biotecnologie Mediche e Ricerca Biomedica (Direttore: Prof. Cesare Balduini)
Posizione		Titolare del Corso Opzionale di 'Terapie a Bersaglio Molecolare in Oncologia'
Principali mansioni e responsabilità		Attività didattica ed attività di Tutorato per l'attività di laboratorio degli studenti

Date (da – a)		**Anno Accademico 2008/2009 → Anno Accademico 2017/2018**
Sede		Università degli Studi di Pavia, Facoltà di Medicina e Chirurgia, Corso di Laurea "Golgi", corso di Semeiotica Medica (Titolare: Prof.a Eugenia Marchesi)
Posizione		Tutor
Principali mansioni e responsabilità		Attività didattica (40 ore annuali) per attività teorico-pratica di Semeiotica Medica

Date (da – a)		**Anno Accademico 2002/2003**
Sede		Università degli Studi di Milano, Scuola di Specializzazione in Nefrologia (Direttore: Prof. Piergiorgio Messa)
Posizione		Lettore
Principali mansioni e responsabilità		Attività didattica nel Corso di Specializzazione

Abilitazione Scientifica Nazionale (ASN)

Data		**Aprile 2017**
Settore Concorsuale		06/D3 – Malattie del sangue, Oncologia e Reumatologia – II fascia
SSD		MED06
Validità		dal 06 Aprile 2017 al 06 Aprile 2023

Data		**Settembre 2017**
Settore Concorsuale		06/D3 – Malattie del Sangue, Oncologia e Reumatologia – I fascia
SSD		MED06

Validità		dal 05 Dicembre 2017 al 05 Dicembre 2023

Attività Didattica ufficiale

Date (da – a)		**1 Agosto 2019 → 15 Marzo 2020**
Sede		Università degli Studi di Pavia, Dipartimento di Medicina Interna e Terapia Medica
Posizione		Professore Associato di Oncologia Medica (SSD: MED/06)
Principali mansioni e responsabilità		Attività didattica presso i seguenti corsi di Laurea: • General Surgery II [506555] – corso di Studi in Medicina e Chirurgia in lingua Inglese; • Scienze Mediche [503579] – corso di Studi in Fisioterapia; • Diagnostic Imaging and Radiotherapy [501883] – corso di Studi in Medicina e Chirurgia in lingua Inglese Attività didattica presso le seguenti Scuole di Specializzazione: • Oncologia Medica; • Medicina Interna

Date (da – a)		**10 Ottobre 2018 → 15 Marzo 2020**
Sede		Università degli Studi di Pavia, Scuola di Specializzazione in Oncologia Medica
Posizione		Direttore della Scuola di Specializzazione
Principali mansioni e responsabilità		Organizzazione e coordinamento dell'attività didattica della Scuola di Specializzazione

Data		**16 Marzo 2020 → oggi**
Sede		Università degli Studi di Bari "Aldo Moro", Dipartimento di Scienze Biomediche ed Oncologia Umana, quindi Dipartimento Interdisciplinare di Medicina
Posizione		Professore Ordinario di Oncologia Medica (SSD: MED/06)
Principali mansioni e responsabilità		Attività didattica presso i seguenti Corsi di Laurea: • Specialità Medico-Chirurgiche 3, canale A-K – Unità Didattica: Oncologia Medica; • Specialità Medico-Chirurgiche 3, canale L-Z – Unità Didattica: Oncologia Medica; • Medical-Surgical Specialties 3 (in lingua Inglese) – Unità Didattica: Medical Oncology; • Specialità Mediche (Fisioterapia, sede di Bari) – Unità Didattica: Oncologia Medica; • Specialità Mediche (Fisioterapia, sede jonica di Taranto) – Unità Didattica: Oncologia Medica; • Scienze Mediche I (Odontoiatria e Protesi Dentarie) – Unità Didattica: Oncologia Medica • Tecniche della Prevenzione nell'ambiente e nei luoghi di lavoro – Unità Didattica: Oncologia Medica Attività didattica presso le seguenti Scuole di Specializzazione: • Oncologia Medica;

		• Urologia; • Cardiologia

Date (da – a)		**8 Febbraio 2021 → oggi**
Sede		Università degli Studi di Bari 'A. Moro', Scuola di Specializzazione in Oncologia Medica
Posizione		Direttore della Scuola di Specializzazione
Principali mansioni e responsabilità		Organizzazione e coordinamento dell'attività didattica della Scuola di Specializzazione

Formale attribuzione di incarichi di insegnamento o di ricerca (*fellowship*) presso qualificati Atenei e istituti di ricerca esteri o sovranazionali

Date (da – a)		**Marzo 2004**
Sede		Brown University and Rhode Island Hospital, Department of Medicine, Division of Clinical Pharmacology (Direttore: Prof. Paul Calabresi)
Posizione		*Visiting Professor*
Principali mansioni e responsabilità		Attività di co-cordinamento per un progetto di ricerca sull'attività antitumorale del Bortezomib in un modello sperimentale murino di mesotelioma; svolgimento di un seminario presso la sopracitata struttura

Date (da – a)		**Dicembre 2014**
Sede		Department of Urology, Semmelweis University, Budapest, Ungheria (Direttore: Prof. Péter Nyrády)
Posizione		*Visiting Professor*
Principali mansioni e responsabilità		Attività didattica nell'ambito di un programma supportato dall'Europen School of Oncology (ESO)

Conseguimento di premi e riconoscimenti per l'attività scientifica, inclusa l'affiliazione ad Accademie di riconosciuto prestigio nel settore

Data		**Dicembre 1995**
Ente bandente il premio		Schering-Plough S.p.A.
Titolo della ricerca premiata		Ruolo dei radicali liberi nella tossicità sistemica da farmaci antiblastici in Oncologia: fisiopatologia e prospettive terapeutiche

Data		**Dicembre 1998**
Ente bandente il premio		Università degli Studi di Pavia e Società Medico-Chirurgica Pavese
Premio		'Gaetano Fichera' (premio biennale intitolato alla memoria del primo Direttore dell'Istituto Nazionale Tumori di Milano)

Motivazione		'La produzione scientifica del Dr. Camillo Porta, tutta di argomento strettamente Oncologico, persegue due filoni di rilievo attinenti rispettivamente alla problematica del trattamento dell'epatocarcinoma, e alla definizione del ruolo dell'immunoterapia nei carcinomi renali. I lavori presentati sono la risultanza di protocolli clinici e di ricerche laboratoristiche e pongono in evidenza la grande operosità e la costante attenzione del candidato per I più aggiornati approcci di terapia Oncologica'

Partecipazione a *Boards* di industrie farmaceutiche (in ordine cronologico)

Industrie		1. Angelini Pharma; 2. ArQule Inc.; 3. Astellas; 4. AstraZeneca; 5. Bayer-Schering Pharma; 6. BMS; 7. Boehringer-Ingelheim; 8. Eisai Co.; 9. EUSA Pharma; 10. Exelixis; 11. Eximias Pharmaceutical Company; 12. General Electrics; 13. Glaxo Smith Kline; 14. Hoffman La Roche/Genentech; 15. Ipsen; 16. Janssen Cilag; 17. Merck-Serono; 18. MSD; 19. Novartis Pharma; 20. OSI Pharmaceuticals; 21. Peloton Therapeutics; 22. Pfizer Oncology; 23. Taiho Pharmaceuticals; 24. Wyeth Pharmaceuticals

Responsabilità di studi e ricerche scientifiche affidati da qualificate istituzioni pubbliche o private

Data		**2007**
Mansioni/Ruolo		Membro del *Board* scientifico dell'*Institut de Recherches Internationales Servier (IRIS)* per lo sviluppo clinico e pre-clinico della molecola citotossica S23906

Data		**2008**

Mansioni/Ruolo		Membro del *Data Monitoring Committee* dello studio "*Safety evaluation in an open-label, dose escalation, safety and tolerability trial of the combination of s.c. human IL-21 (rIL-21) and Sunitinib (phase 1), followed by an open-label stratified randomized 2-arm trial of rIL-21 plus Sunitinib alone (phase 2a) in subjects with stage IV renal cell carcinoma*", sponsorizzato dalla Novo Nordisk

Data		**2012→ 2016**
Mansioni/Ruolo		Membro dello *Steering Committee* dello studio ARQ197-A-U303 "*A phase 3 Trial of ARQ197 in Patients with C-Met+ Inoperable Hepatocellular Carcinoma (HCC) Treated with One Prior Systemic Therapy*", sponsorizzato da ArQule e Daiichi Sankyo

Data		**2013 → 2019**
Mansioni/Ruolo		Membro dello *Steering Committee* del protocollo "*InlytA in aDvanced/metastatic renal cell carcinOma – a Non-interventional study of real world treatment outcomes in patients receiving 2nd line Inlyta after 1st line Sutent (ADONIS)*", sponsorizzato da Pfizer Oncology

Data		**2016 → 2021**
Mansioni/Ruolo		Membro dello *Steering Committee* del protocollo "*E7080-G000-307, a multicenter, randomized, open-label, phase 3 trial to Compare the efficacy and safety of Lenvatinib in combination with Everolimus or Pembrolizumab versus Sunitinib alone in first-line treatment of subjects with Advanced Renal cell carcinoma (CLEAR)*", sponsorizzato da Eisai e MSD.

Data		**2017 → 2018**
Mansioni/Ruolo		Membro dello Steering Committee dello studio CPZP034A2411 "*A prospective, observational study to evaluate the real-world effectiveness and safety of the available treatment patterns for patients with advanced/metastatic Renal Cell Carcinoma (mRCC)*", sponsorizzato da Novartis

Data		**2022**
Mansioni/Ruolo		Membro dello Steering Committee dello studio MK-6482-011 "*A study of Belzutifan (MK-6482) in combination with Lenvatinib versus Cabozantinib for the treatment of renal cell carcinoma*", sponsorizzato da MSK

Responsabilità scientifica di/partecipazione a progetti di ricerca internazionali e nazionali, ammessi al finanziamento sulla base di bandi competitivi che prevedano la revisione tra pari

Data inizio/fine		**1 Giugno 2006 → 1 Gennaio 2011**
Tipo di finanziamento		Ricerca Corrente (c/o Fondazione I.R.C.C.S. Policlinico San Matteo di Pavia)
Titolo della ricerca		Studio preclinico e clinico di inibitori tirosinchinasici nelle neoplasie urologiche

Data inizio/fine		**1 Febbraio 2009-31 Gennaio 2012**

Tipo di finanziamento		Bando Cariplo 'Ricerca Medica 2008'
Titolo della ricerca		Regulation of telomere transcription in normal and tumor cells
Ruolo		Principal Investigator
Somma finanziata		€ 48.000

Data inizio/fine		**Gennaio 2011 → Gennaio 2016**
Tipo di finanziamento		Ricerca Corrente (c/o Fondazione I.R.C.C.S. Policlinico San Matteo di Pavia)
Titolo della ricerca		*Kidney Cancer Cachexia Study*: studio multicentrico, longitudinale, internazionale, per valutare la prevalenza ed il valore prognostico della cachessia nei pazienti affetti da carcinoma renale
Ruolo		Principal Investigator
Somma finanziata		€ 25.000

Data inizio/fine		**Luglio 2011 → Luglio 2020**
Tipo di finanziamento		Ricerca Corrente (c/o Fondazione I.R.C.C.S. Policlinico San Matteo di Pavia)
Titolo della ricerca		Studio dei processi di angiogenesi e di metastatizzazione in pazienti affetti da neoplasie solide
Ruolo		Collaboratore
Somma finanziata		€ 138.350

Data inizio/fine		**Gennaio 2013 → Gennaio 2018**
Tipo di finanziamento		Ricerca Corrente (c/o Fondazione I.R.C.C.S. Policlinico San Matteo di Pavia)
Titolo della ricerca		Fattibilità di un programma di terapia cellulare con linfociti citotossici anti-tumorali in pazienti affetti da tumore renale metastatico
Ruolo		Principal Investigator
Somma finanziata		€ 60.000

Data inizio/fine		**Gennaio 2015 → Gennaio 2020**
Tipo di finanziamento		Ricerca Corrente (c/o Fondazione I.R.C.C.S. Policlinico San Matteo di Pavia)
Titolo della ricerca		Farmacocinetica clinica di anticorpi monoclonali utilizzati in ambito oncologico ed onco-ematologico in pazienti adulti e pediatrici
Ruolo		Collaboratore
Somma finanziata		€ 122.111

Data inizio/fine		**Luglio 2015 → Luglio 2019**
Tipo di finanziamento		Ricerca Corrente (c/o Fondazione I.R.C.C.S. Policlinico San Matteo di Pavia)
Titolo della ricerca		Studio dei meccanismi molecolari alla base del processo di tumorigenesi in cellule di tumore primario o metastatico di pazienti affetti da carcinoma colorettale e carcinoma renale
Ruolo		Collaboratore
Somma finanziata		€ 50.916

Data inizio/fine		Progetto approvato per il finanziamento, ma non attivato, per trasferimento del Principal Investigator presso altra struttura Ospedaliera
Tipo di finanziamento		Ricerca Corrente (c/o Fondazione I.R.C.C.S. Policlinico San Matteo di Pavia)
Titolo della ricerca		Evaluation of NK-mediated immunological response in renal cell carcinoma (RCC) patients treated with or without immune checkpoint inhibitors. A longitudinal, prospective, cohort study
Ruolo		Principal Investigator
Somma finanziata		€ 129.000

Data inizio/fine		**1 Gennaio 2020 → oggi**
Tipo di finanziamento		Bando Europeo 'Horizon 2020'
Titolo della ricerca		CAncer PAtients Better Life Experience ('CAPABLE')
Ruolo		Collaboratore (Principal Investigator della parte clinica del progetto)
Somma finanziata		€ 426.000 su un budget complessivo di € 6.000.000

Data inizio/fine		**2021 → 2022**
Tipo di finanziamento		Fondi della Regione Puglia (Riparto definitivo delle risorse del FSR 2020 e delle risorse COVID-19 per l'esercizio 2020 alle Aziende Sanitarie Locali, Aziende Ospedaliero-Universitarie, IRCCS pubblici e GSA) – delibera della Giunta Regionale n.1346 del 4 Agosto 2021
Titolo della ricerca		Il Team Oncogenomico: modello operativo per il miglioramento dell'assistenza sanitaria in Oncologia
Ruolo		Principal Investigator
Somma finanziata		€ 400.000 (€ 200.000 annuali)

Data inizio/fine		**2022**
Tipo di finanziamento		Fondi della Regione Puglia – delibera della Giunta Regionale n.2219 del 29 Dicembre 2021
Titolo della ricerca		Tipizzazione molecolare e medicina per il trattamento personalizzato del carcinoma dell'endometrio
Ruolo		Co-Principal Investigator (con il Prof. E. Cicinelli)
Somma finanziata		€ 120.000

Direzione o partecipazione a Comitati Editoriali di riviste, collane editoriali, enciclopedie, e trattati di riconosciuto prestigio

Date (da – a)		**1993 → 2002**
Mansioni/Ruolo		Membro dell'*Editorial Board* della rivista Acta Gerontologica, successivamente divenuta Acta Gerontologica et Oncologica (*Editor-in-Chief*: E. Bobbio-Pallavicini)

Date (da – a)		**2000 → 2002**

Mansioni/Ruolo		*Executive Editor* della rivista Acta Gerontologica, successivamente divenuta Acta Gerontologica et Oncologica (*Editor-in-Chief*: E. Bobbio-Pallavicini)

Date (da – a)		**2007 → 2008**
Mansioni/Ruolo		Membro dell'*Editorial Advisory Board* della rivista Kidney Cancer Journal International (*Editors*: B. Escudier e T. Eisen)

Date (da – a)		**Novembre 2008 → oggi**
Mansioni/Ruolo		Membro dell'*Editorial Advisory Board* della rivista World Journal of Gastroenterology (*Editor*: Lian-Sheng Ma)

Date (da – a)		**Gennaio 2007 → oggi**
Mansioni/Ruolo		*Editor-in-Chief* della rivista Oncology Reviews, edita dapprima da Springer, quindi da PagePress, ed attualmente dal gruppo Frontiers

Date (da – a)		**Aprile 2008 → 2010**
Mansioni/Ruolo		Membro dell'*Editorial Board* della versione italiana del Journal of Clinical Oncology per la sezione 'Genito-Urinary Cancer'

Date (da – a)		**Aprile 2008 → oggi**
Mansioni/Ruolo		Membro dell'*Editorial Board* della rivista on-line Terapia Evidence-Based, edita da Wolters-Kluwers

Date (da – a)		**Giugno 2009 → oggi**
Mansioni/Ruolo		Membro dell'*Editorial Board* della rivista Advances in Therapy, edita da Springer

Date (da – a)		**Giugno 2009 → 2016**
Mansioni/Ruolo		Membro dell'*Editorial Board* e *Section Editor* della rivista Rare Tumors, edita da PagePress

Date (da – a)		**Gennaio 2009 → oggi**
Mansioni/Ruolo		Co-responsabile (con il Dr. Sergio Bracarda) del Gruppo di Lavoro "Tumori genito-urinari" dell'Accademia Nazionale di Medicina

Date (da – a)		**Gennaio 2011 → Febbraio 2021**
Mansioni/Ruolo		*Editor-in-Chief* della rivista Clinics and Practice, edita da PagePress

Date (da – a)		**Agosto 2013 → oggi**
Mansioni/Ruolo		Membro dell'*Editorial Board* della rivista Kidney Cancer and VHL

Date (da – a)		**Gennaio 2014 → oggi**
Mansioni/Ruolo		Membro dell'*Editorial Board* della rivista Frontiers in Genitourinary Oncology

Date (da – a)		**Agosto 2016 → oggi**
Mansioni/Ruolo		Co-*Editor-in-Chief* (con L. Cosmai, V. Launay-Vacher [poi dimissionario] e M.A. Perazella) della rivista Journal of Onco-Nefrology, edita dapprima da Wichtig, e quindi da SAGE

Date (da – a)		**Maggio 2017 → oggi**
Mansioni/Ruolo		Membro dell'*Editorial Board* della rivista Kidney Cancer

Date (da – a)		**Gennaio 2018 → oggi**
Mansioni/Ruolo		Membro dell'*Editorial Board* della rivista European Urology Oncology

Mansioni/Ruolo		*Referee* ufficiale per le seguenti riviste scientifiche, nazionali ed internazionali: 1. Acta Gerontologia (*Editor-in-Chief*: E. Bobbio-Pallavicini); 2. Acta Oncologica (*Editor-in-Chief*: B. Glimelius); 3. Advances in Therapy (*Associate Editor for Oncology*: C. Twelves); 4. Advances in Urology; 5. African Journal of Biotechnology (*Editor*: N.J. Tonukari); 6. American Journal of Kidney Diseases (*Editor-in-Chief*: A.S. Levey); 7. American Journal of Physiology – Renal Physiology (*Editor-in-Chief*: P. Darwin-Bell); 8. Annals of Oncology (*Editor-in-Chief*: D.J. Kerr); 9. Annals of the New York Academy of Science (*Editor-in-Chief*: D. Braaten); 10. BBA Reviews on Cancer (*Executive Editor*: K. Polyak); 11. Biologics: Targets and Therapies (*Editor-in-Chief*: S. Awasthi); 12. Biomarker Insights (*Editor-in-Chief*: S.F. Kingsmore, quindi K. Pulford); 13. Biomarkers in Medicine (*Editors-in-Chief*: A. Terzic & S.A. Waldman); 14. Biomarker Research (*Editors*: C.T. Hsueh, D. Liu & H. Wang); 15. BioMed Research International; 16. BMC Cancer (*Executive Editor*: C. Chap, quindi Co-Editors: L. Gummlich & N. Stead); 17. BMC Infectious Diseases (*Editors-in-Chief*: A. Gonzalez Lopez); 18. BMJ Open (*Editor-in-Chief*: A. Aldcroft); 19. British Journal of Cancer (*Editor-in-Chief*: A.L. Harris); 20. British Journal of Urology International (*Editor-in-Chief*: J. Fitzpatrick, quindi F. Hamdy); 21. Cancer (*Editor-in-Chief*: R.E. Pollock); 22. Cancers; 23. Cancer Chemotherapy and Pharmacology (Co-*Editors-in-Chief*: H. Newell & E.A. Sausville); 24. Cancer Journal (*Editor-in-Chief*: Prof. J.C. Salomon); 25. Cancer Letters (*Editor-in-Chief*: M. Schwab); 26. Cancer Medicine (*Editor-in-Chief*: Q. Wei); 27. Cancer Science (*Editor-in-Chief*: Y. Nakamura);

		28. Cancer Treatment Reviews (*Editors*: N. Pavlidis & R.A. Stahel, quindi A. Cervantes); 29. Case Reports in Medicine (*Responsible Editor*: T. Vogl); 30. Case Reports in Transplantation; 31. Cellular Physiology and Biochemistry (*Editor-in-Chief*: F. Lang); 32. Clinical Cancer Research (*Editor-in-Chief*: K.C. Anderson, e quindi K.T. Flaherty); 33. Clinical Drug Investigation (*Editor-in-Chief*: J. Singh); 34. Clinical Genitourinary Cancer (*Editor-in-Chief*: N.J. Vogelzang, e quindi O. Sartor); 35. Clinical Immunotherapeutics (*Editor-in-Chief*: A.S. Beedle); 36. Clinical Investigation (*Senior Editor*: E.M. Lewiecki); 37. Clinical Medicine Insights Oncology (*Chair of the Editorial Board*: W. Cho); 38. Critical Reviews in Oncology and Hematology (*Editor-in-Chief*: M.S. Aapro); 39. Cureus (*Editors-in-Chief*: J.R. Adler Jr & A. Muacevic); 40. Current Medical Research & Opinion (*Editor-in-Chief*: D.P. Mikhailidis); 41. Current Medicinal Chemistry (*Editor-in-Chief*: A. ur-Rahman); 42. Disease Markers; 43. Drugs (*Editor-in-Chief*: D.C. Peters); 44. Drugs in R&D (*Editor-in-Chief*: J. Singh); 45. EBio Medicine; 46. ESMO Open (*Editor-in-Chief*: C. Zielinski); 47. European Journal of Cancer (*Editor-in-Chief*: A.M.M. Eggermont); 48. European Respiratory Journal (*Editor-in-Chief*: U. Costabel); 49. European Urology (*Editor-in-Chief*: F. Montorsi, e quindi J. Catto); 50. European Urology Focus (*Editor-in-Chief*: J. Catto); 51. European Urology Oncology (*Editor-in-Chief*: A. Briganti); 52. European Urology Open Science (*Editor-in-Chief*: J. Catto); 53. Evidence-Based Complementary and Alternative Medicine (*Editor-in-Chief*: E.L. Cooper); 54. Expert Opinion on Biological Therapy (*Editor-in-Chief*: M. Morse); 55. Expert Opinion on Drug Metabolism and Toxicology (*Drug Evaluation Editor*: E. Knowles); 56. Expert Opinion on Emerging Drugs; 57. Expert Opinion on Investigational Drugs (*Editor-in-Chief*: D. Mikalidis); 58. Expert Opinion on Orphan Drugs (*Editor-in-Chief*: M.I. Phillips); 59. Expert Opinion on Pharmacotherapy (*Editor-in-Chief*: D. Mikhailidis); 60. Expert Review of Molecular Diagnostics (*Editor-in-Chief*: A.T. Lorincz); 61. Expert Review on Pharmacoeconomics & Outcomes Research (*Senior Editor*: A. Bottomley); 62. Expert Review on Precision Medicine and Drug Development (*Commissioning Editor*: J. Walsh); 63. Expert Review on Anticancer Therapy; 64. Future Oncology;

65. Frontiers Oncology (*Field Chief Editor*: G. Giaccone);
66. Frontiers Pharmacology (*Field Chief Editor*: H. Wulff);
67. Global and Regional Health Technology Assessment (*Editor-in-Chief*: C. Jommi);
68. Haematologica (*Editor-in-Chief*: E. Ascari, e quindi M. Cazzola);
69. Hepatic Oncology (*Editors-in-Chief*: J. Bruix, R.S. Finn & R.T.P. Poon);
70. Immunotherapy (*Senior Editors*: Y. Kawakami, F.M. Marincola & D.C. Wraith);
71. Infectious Agents and Cancer (*Editors-in-Chief*: F.M. Buonaguro & S.M. Mbulaiteye);
72. International Brazialian Journal of Urology (*Editor*: S. Glina);
73. International Immunopharmacology (*Editor-in-Chief*: J.E. Talmadge);
74. International Journal of Molecular Sciences (*Editor-in-Chief*: M.L. Richter);
75. International Journal of Cancer (*Editor-in-Chief*: P. Lichter);
76. International Journal of Urology (*Editor-in-Chief*: Y. Homma, quindi N. Nonomura);
77. International Medical Case Report Journal (*Editor-in-Chief*: R. Prineas);
78. International Journal for Quality in Healthcare (*Editor-in-Chief*: Y.C. Li);
79. International Research Journal of Oncology (*Editor-in-Chief*: G.A. Bounda);
80. JAMA Network Open (*Editor*: F.P. Rivara, *Associate Editor*: D.V.T. Catenacci);
81. Journal of Bone Oncology (*Editors-in-Chief*: R. Coleman, P. Hadji, D. Heymann);
82. Journal of Cancer Metastasis and Treatment (*Editor-in-Chief*: L. Miele);
83. Journal of Cancer Research and Clinical Oncology (*Editor-in-Chief*: K. Höffke);
84. Journal of Clinical Medicine (*Editors-in-Chief*: E. Andrès & M.G. Hennerici);
85. Journal of Clinical Oncology (*Editor-in-Chief*: D.G. Haller);
86. Journal for Immunotherapy of Cancer (*Editor-in-Chief*: P.J. Romero);
87. Journal of Medical Case Reports (*Editor-in-Chief*: M. Kidd);
88. Journal of Nephrology (*Editor-in-Chief*: G. Gambaro);
89. Journal of Oncology (*Editor-in-Chief*: B. Vincenzi);
90. Journal of Pharmacogenomics and Personalized Medicine (*Editor-in-Chief*: M.H. Bluth);
91. Journal of Translational Medicine (*Editor-in-Chief*: F. Marincola);
92. Journal of Urology (*Editor-in-Chief*: M.I. Resnick);
93. Kidney and Blood Pressure Research (*Editor-in-Chief*: V. Tesai);
94. Lung Cancer (*Editor-in-Chief*: R.A. Stahel);
95. Medical Oncology (Co-*Editors-in-Chief*: A. Osterborg & P.H. Wiernik);
96. Mini Reviews in Medical Chemistry (*Co-Editors*: A. ur-Rahman, I. Choudhary & G. Perry);
97. Nature Communications (*Editor-in-Chief*: E. De Ranieri);
98. Nature Reviews Clinical Oncology (*Editor-in-Chief*: L. Hutchinson);

		99. Nature Reviews Nephrology (*Editor-in-Chief*: A. Aguilar); 100. Nature Reviews Urology (*Editor-in-Chief*: A. Fenner); 101. Oncology (*Editor-in-Chief*: D.L. Trump); 102. Oncology and Therapy (*Publishing Editor*: A. Brown); 103. Oncotarget (*Editors*: A.V. Gudkov & M.V. Blagosklonny); 104. Onkologie (*Editors*: H.J. Schmoll & M. Hallek); 105. PLoS One (*Editorial Director*: D. Pattinson); 106. Rare Tumors (*Editor-in-Chief*: R.C. Miller); 107. Rare Cancer and Therapy (*Editor-in-Chief*: J. Capdevila); 108. Recent Patents on Biomarkers (*Executive Editor*: K. Zaman); 109. Regulatory Toxicology and Pharmacology (*Editor-in-Chief*: G.B. Gori); 110. Science Progress (*Editors*: E. Ellerton & J. Baldwin); 111. Scientific Reports (*Editor-in-Chief*: R. White); 112. SN Comprehensive Clinical Medicine (*Editors-in-Chief*: M. Mahmoudi & P. Martelletti); 113. Société Internationale d'Urologie Journal (*Editor-in-Chief*: P.C. Black); 114. Sultan Qaboos University Medical Journal (*Editor-in-Chief*: L. Al-Lamki); 115. Targeted Oncology (*Editor-in-Chief*: J.F. Morére, e quindi M. Chopra); 116. The Oncologist (*Editor-in-Chief*: B.A. Chabner); 117. Therapeutic Advances in Urology (*Editor-in-Chief*: A. Atala); 118. Therapeutic Advances in Medical Oncology (*Managing Editor*: G. Mallarkey, e quindi G. Patey); 119. Translational Oncology (*Editor-in-Chief*: T.S. Lawrence); 120. Trends in Pharmacological Sciences (*Editor-in-Chief*: J. Madukwe); 121. Tumori (*Editor-in-Chief*: F. Zunino, e quindi U. Pastorino); 122. World Journal of Surgical Oncology (*Editor-in-Chief*: M. Pandey); 123. World Journal of Urology (*Editors-in-Chief*: M. Burchardt & A. de la Taille); 124. Journal of Onco Pathology (*Editors*: S. Peters & J. Teruya-Feldstein).

Direzione o partecipazione alle attività di Gruppi di Ricerca caratterizzati da collaborazioni a livello nazionale ed internazionale

Data		**2006**
Mansioni/Ruolo		*Referee* per il *Medical Research Council* (MRC) britannico, in particolare per un progetto di ricerca sul mesotelioma pleurico)

Data		**2011, 2014 e 2018**
Mansioni/Ruolo		*Referee* per il *Narodowe Centrum Nauki* (NCN – Centro nazionale per le Scienze) polacco

Data		**2011→ 2020**

Mansioni/Ruolo		*Referee* degli abstracts sottomessi all'annuale Congresso Nazionale dell'Associazione Italiana di Oncologia Medica (AIOM) – sessione: apparato Genito-Urinario

Data		**2012 → 2015**
Mansioni/Ruolo		Membro del *Board* Scientifico del progetto DATECAN (*Définition, évaluation et Analyse des criTères de survie dans les Essais randomisés en CANcérologie*) per il carcinoma renale.

Data		**2013 → 2015**
Mansioni/Ruolo		Membro del *Board* Scientifico della Scuola di Uro-Oncologia, organizzata congiuntamente dalla Società Italiana di Urologia (SIU) e dall'Associazione Italiana di Oncologia Medica (AIOM).

Data		**2013 → oggi**
Mansioni/Ruolo		Membro del *Working Group* congiunto tra Società Italiana di Nefrologia (SIN) ed Associazione Italiana di Oncologia Medica (AIOM) sull'Onco-Nefrologia

Data		**2014 → 2018**
Mansioni/Ruolo		Membro del *Board* Scientifico delegato ad organizzare il programma scientifico del congresso annuale EIKCS (European International Kidney Cancer Symposium)

Data		**2014 → 2017**
Mansioni/Ruolo		*Referee* degli abstracts sottomessi all'annuale Congresso Nazionale della Società Italiana di Urologia Oncologica (SIUrO)

Data		**2014**
Mansioni/Ruolo		*Referee* per l'Israel Science Foudation (ISF), in particolare per un progetto di ricerca sull'epatocarcinoma

Data		**2014**
Mansioni/Ruolo		*Referee* per la Kidney Research UK, in particolare per un progetto di ricerca sul carcinoma renale

Data		**2014 → 2017**
Mansioni/Ruolo		*Referee* degli abstracts di pertinenza Oncologica sottomessi all'annuale Congresso Nazionale della Società Italiana di Medicina Interna (SIMI)

Data		**Agosto 2014 → oggi**
Mansioni/Ruolo		Membro dell'Italian PRO-CTCAE Study Group, finalizzato a validare i PRO-CTCAE in Italia, in collaborazione con la Federazione delle Associazioni di Volontariato in Oncololgia (FAVO), l'Associazione Italiana di Oncologia Medica (AIOM), la Fondazione Smith-Kline, ed il National Cancer Institute statunitense (NCI)

Data		**2014**
Mansioni/Ruolo		*Referee* per l'Istituto Tumori Toscano (ITT)

Data		**2015**
Mansioni/Ruolo		*Referee* per il *Marsden Fund (Te Putea Rangahau a Marsden)* e la *Royal Society of New Zealand (Te Aparangi)*, in particolare per un progetto di ricerca sui meccanisi di attivazione del *pathway* oncogenico di PI3Kα

Data		**2015**
Mansioni/Ruolo		*Referee* per il *Research Foundation – Flanders (Fonds Wetenschappelijk Onderzoek – Vlaanderen, FWO)* olandese

Data		**2015**
Mansioni/Ruolo		*Referee* per l'*Institut National du Cancer (INCa)* francese, in particolare per un progetto di ricerca sul ruolo delle citochine ELR+CXCL nel carcinoma renale metastatico

Data		**2016 e 2017**
Mansioni/Ruolo		*Referee* per lo *Swiss National Science Foundation (FNSNF)* svizzero

Data		**Maggio-Dicembre 2016**
Mansioni/Ruolo		Membro del del Comitato di Valutazione dei progetti di ricerca sottomessi all' *Institut National du Cancer* (INCa) francese per essere finanziati nell'ambito del "*Programme de Recherche Translationelle en Cancérologie* PRT-K16".

Data		**2016 → oggi**
Mansioni/Ruolo		Membro del Comitato Scientifico – *track* Neoplasie genito-urinarie, non prostata – dell'European Society of Medical Oncology (ESMO)

Data		**2017 → oggi**
Mansioni/Ruolo		*Referee* degli abstracts sottomessi al Congresso annual dell'European Society of Medical Oncology (ESMO) – track: neoplasie genito-urinarie, non prostata

Data		**2017**
Mansioni/Ruolo		*Referee* per il *Genesis Oncology Trust* neozelandese per un progetto di ricerca sul ruolo delle mutazioni di SWI/SNF, e sul controllo cooperativo di IL-6 da parte di p63, nella regolazione, da parte di mTOR, di un programma di trascrizione genica via C/EBPβ, esitante in un potenziamente della capacità di metastatizzazione tumorale

Data		**2019**
Mansioni/Ruolo		*Referee* per l'Università 'La Sapienza' di Roma per un progetto di ricerca sul ruolo immunomodulante dei TKIs nei pazienti affetti da carcinoma renale

Data		**2020 → oggi**
Mansioni/Ruolo		Membro (rappresentante dell'European Society of Medical Oncology – ESMO) presso il Comitato Scientifico dell'European Multidisciplinary congress on Urological Cancers (EMUC), organizzato congiuntamente da ESMO, European Society for Radiology & Oncology (ESTRO) ed European Association of Urology (EAU)

Data		**2022**
Mansioni/Ruolo		*Referee* per il Ministero della Salute per un progetto (Joint Translational Call 2021) relativo alla call ERA-NET TRANSCAN-3, finanziata dalla Commissione Europea, avente come oggetto "*Next generation cancer immunotherapy: targeting the tumor microenvironment*"

Data		**2022**
Mansioni/Ruolo		Revisore esterno per la stesura delle "*International Guideline for anticancer drug dosing in kidney dysfunction (ADDIKD)*" Australiane

Data		**2022 → oggi**
Mansioni/Ruolo		Esperto invitato a valutare il progetto "*ESMO Lines of Therapy*" dell'European Society of Medical Oncology (ESMO) per il sottogruppo sulle neoplasie urologiche

Partecipazione a stesura di Linee Guida nazionali ed internazionali

Data		**2008**
Mansioni/Ruolo		Revisore esterno per la stesura delle linee guida dell*'European Organization for Research and Treatment of Cancer* (EORTC) per la gestione dei pazienti affetti da carcinoma renale

Data		**2008**
Mansioni/Ruolo		Membro del *Board* responsabile della stesura delle linee guida italiane (CNR/Alleanza contro il cancro) per la gestione dei pazienti affetti da carcinoma renale

Data		**2010-2011**
Mansioni/Ruolo		Membro del *Board* responsabile della stesura delle linee guida AURO (Associazione Urologi Ospedalieri) per il trattamento dei pazienti affetti da carcinoma renale

Data		**2015**
Mansioni/Ruolo		Revisore esterno per la stesura delle linee guida dell*'European Society of Medical Oncology* (ESMO) per la gestione dei pazienti affetti da carcinoma prostatico

Data		**2014 e 2019**

Mansioni/Ruolo		Revisore esterno per la stesura delle linee guida dell'*European Association of Urology* (EAU) per la gestione dei pazienti affetti da carcinoma renale

Data		**2017**
Mansioni/Ruolo		Revisore esterno per la stersura delle linee guida 2016 dell'*Italian Prostate Biopsies Group*, patrocinate dalla Società Italiana di Urologia Oncologica (SIUrO) e dalla Società Italiana di Diagnostica Integrata in Urologia, Andrologia e Nefrologia (SIEUN)

Data		**2011 → oggi**
Mansioni/Ruolo		Membro del *Board* responsabile della stesura delle linee guida AIOM (Associazione Italiana Oncologia Medica) per il trattamento dei pazienti affetti da carcinoma renale

Data		**2012 → oggi**
Mansioni/Ruolo		Membro del *Board* responsabile della stesura delle linee guida ESMO (European Society of Medical Oncology) per il trattamento dei pazienti affetti da carcinoma renale

Data		**2020**
Mansioni/Ruolo		Membro del *Board* responsabile della stesura delle Raccomandazioni intersocietarie (Società Italiana di Radiologia Medica – SIRM, Società Italiana di Nefrologia – SIN ed Associazione Italiana di Oncologia Medica – AIOM per la "Valutazione e prevenzione del danno renale nel paziente da sottoporre a esami con mezzo di contrasto"

Data		**2021**
Mansioni/Ruolo		Membro (rappresentante dell'European Society of Medical Oncology – ESMO) del Comitato Scientifico deputato ad adattare le linee guida ESMO per il carcinoma renale alla realtà dei paesi Asiatici (*Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with renal cell carcinoma*)

Data		**2022**
Mansioni/Ruolo		Membro (per il sottogruppo tumore-specifico: "Urologic cancer") del gruppo di esperti dell'European Society of Medical Oncology (ESMO) chiamata a definire in maniera univoca il concetto di "linee di terapia Oncologica" (ESMO Lines of Therapy Project)

Appartenenza a Società Scientifiche

Precedenti affiliazioni		1. Gruppo Cooperativo Italiano per lo studio ed il trattamento della Porpora Trombotica Trombocitopenica (PTT); 2. Società Medico-Chirurgica Pavese; 3. Meta-Analysis Group in Cancer;

		4. International Society for Cytokines and Interferons Research (ISICR); 5. Gruppo Italiano Mesoteliomi (GIMe) – Membro del Consiglio Direttivo e Tesoriere; 6. International Mesothelioma Interest Group (IMIG); 7. Mediterranean Multidisciplinary Oncology Forum (MMOF); 8. Renal Cell Carcinoma Group (RCCG); 9. Società Italiana di Medicina Interna (SIMI).
Affiliazioni attuali		1. New York Academy of Sciences (NYAS); 2. European Society of Medical Oncology (ESMO); 3. American Society of Clinical Oncology (ASCO); 4. Associazione Italiana di Oncologia Medica (AIOM); 5. Gruppo Italiano di Oncologia Nefrologica (GION) – Presidente e Socio Fondatore; 6. Gruppo di lavoro congiunto AIOM/SIN sull'Onco-Nefrologia; 7. International Metastatic RCC Database Consortium (IMDC); 8. Società Italiana di Nefrologia (SIN); 9. Innovators in Genito-Urinary Oncology (iGO).

Ulteriori attività divulgative

In qualità di esperto di carcinoma renale, il Dr. Porta è stato più volte intervistato da testate giornalistiche nazionali (TG1 mattina, Giornale Radio 1, TG Medicina 33 – due apparizioni televisive, Sky News 24, Corriere della Sera, Il Giorno, Libero, Tele Lombardia, Leggo, Gazzetta del Mezzogiorno, Tele Norba, Repubblica – edizione di Bari), ed internazionali (in Corea, Cina, Grecia, Svizzera ed a Cipro); gli sono stati inoltre specificatamente dedicati due articoli sui supplementi de Il Giornale, Sanissimi (nel Settembre 2009), e Dossier Lombardia (Aprile 2010)

Capacità e competenze personali

Acquisite nel corso della vita e della carriera ma non necessariamente riconosciute da certificati e diplomi ufficiali.

Prima lingua		Italiano

Altre lingue		Inglese

Capacità di lettura		eccellente
Capacità di scrittura		eccellente
Capacità di espressione orale		buona

Capacità e competenze tecniche		Corrente utilizzo di *personal computer* e dei sistemi operativi per Macintosh (preferenzialmente) e Windows, nonchè di svariati *software*, generici (MS Word, MS Excel, MS Powerpoint, ecc …) e più specifici (Acrobat, QuarkXPress, Photoshop, ecc …)

Il sottoscritto dichiara che i dati sopra esposti sono esatti e corrispondenti al vero e autorizza chi interessato al trattamento di tali dati nel rispetto della Legge 675/96 sulla 'Tutela delle persone e di altri soggetti rispetto al trattamento di dati personali'.

Bari, 29 Maggio 2023

ATTIVITA' SCIENTIFICA del Prof. Camillo PORTA

Porpora Trombotica Trombocitopenica (PTT) 1987-1996

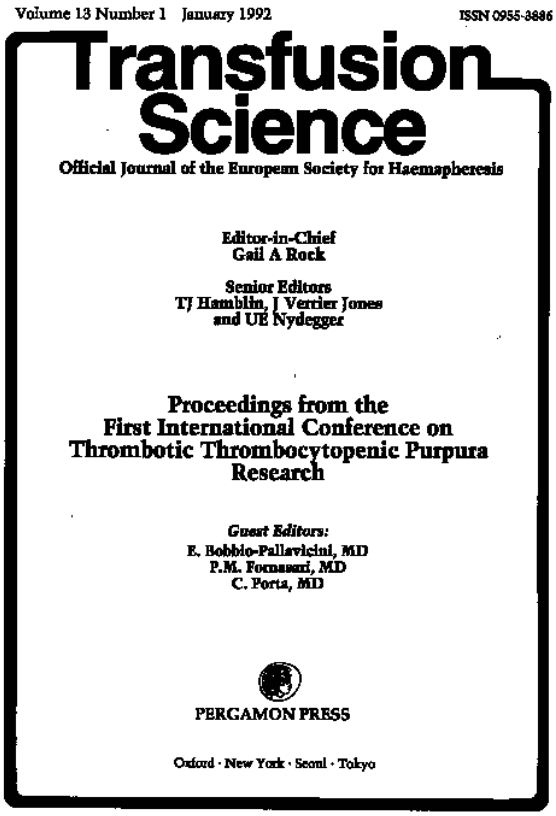
La Porpora Trombotica Trombocitopenica (PTT) è una rara sindrome ematologica che colpisce tipicamente giovani donne, caratterizzata clinicamente da anemia emolitica microangiopatica e schistocitica, grave trombocitopenia determinante una severa diatesi emorragica, manifestazioni neurologiche, febbre e talora alterazioni della funzionalità renale; per quanto la patogenesi della PTT sia nota oramai da diversi anni, solo recentemente i suoi più fini meccanismi eziologici sono stati, almeno in parte, chiariti.
Solo da pochi decenni, inoltre, la PTT non rappresenta più uno sconfortante problema terapeutico; grazie alle tecniche di manipolazione plasmatica (*plasma-infusion* e, soprattutto, *plasma-exchange*), infatti, questa rara malattia è oramai guaribile in oltre il 75-80% dei casi; rimane tuttavia una quota non sottovalutabile, data anche la giovane età di insorgenza della PTT, di pazienti che si dimostrano refrattari ad ogni trattamento e che conseguentemente muoiono, a dispetto di ogni sforzo intrapreso.

Ricerca clinica - Fin da studente, il Prof. Porta si è occupato della raccolta e dell'elaborazione dei dati relativi ai pazienti affetti da PTT reclutati su tutto il territorio nazionale dai centri appartenenti al *Gruppo Cooperativo Italiano per lo studio ed il trattamento della PTT* (Coordinatore: Prof. Edoardo Ascari, Responsabile Nazionale: Prof. Enrico Bobbio-Pallavicini), gruppo del quale è stato attivo collaboratore fin dal 1987.
La casistica raccolta retrospettivamente dal Gruppo Cooperativo Italiano rappresenta una delle più imponenti casistiche mondiali ed i dati da essa estrapolati sono stati oggetto di numerose ed autorevoli pubblicazioni.
In particolare, oltre alla descrizione della casistica clinica raccolta nel corso degli anni, è stato affrontato il problema del trattamento di quelle rare, ma pur sempre presenti, forme di PTT refrattarie al trattamento plasmaferetico tradizionale; l'utilizzo di presidi 'di salvataggio' quali la vincristina (VCR), le immunoglobuline ad alte dosi (HDIgG) e la prostaciclina (PGI_2) sono stati analizzati criticamente, basandosi sui dati retrospettivamente raccolti dal *Gruppo Cooperativo Italiano*; tali dati sembrerebbero supportare in particolare l'utilizzo della VCR, mentre minori certezze continuano a sussistere per le altre modalità terapeutiche esaminate.
Particolare attenzione è stata anche rivolta al *pattern* di recidiva evidenziabile nel nostro paese, che appare ben distinto da quanto osservato in altri paesi, quali Stati Uniti ed Israele.
Successivamente, il Prof. Porta è stato responsabile della raccolta dei dati relativi ad uno studio clinico randomizzato, condotto dal *Gruppo Cooperativo Italiano* su tutto il territorio nazionale e sponsorizzato dalla *European Society for Apheresis - Section IV* e dalla *Società Italiana di Emaferesi*, finalizzato a valutare: a) il ruolo terapeutico svolto dagli antiaggreganti piastrinici (aspirina e dipiridamolo), in associazione alla *plasma-exchange* ed ai corticosteroidi, nella fase acuta della PTT, e b) il ruolo della ticlopidina come terapia preventiva nei confronti delle possibili, e non certo rare, recidive della malattia, in quei pazienti che abbiano ottenuto una remissione completa dalla fase acuta.
I risultati di questo importante studio hanno dimostrato come gli antiaggreganti piastrinici siano in grado di ridurre la mortalità nei primi 15 giorni di trattamento (2.8% nei pazienti trattati con antiaggreganti vs. 13.5% nei pazienti che non li hanno ricevuti); inoltre, per la prima volta, è stata dimostrata la possibilità di prevenire le recidive tardive della malattia, ricorrendo ad un trattamento di mantenimento annuale con Ticlopidina; in effetti, solo il 6.25% dei pazienti trattati con Ticlopidina è recidivato a distanza dall'episodio acuto, di contro al 21.4% dei pazienti non sottoposti a terapia di mantenimento.

Ricerca di base - Pazienti affetti da Lupus Eritematoso Sistemico (LES) o da altre malattie autoimmuni, possono sviluppare disturbi della coagulazione caratterizzati dall'associazione di piastrinopenia e di fenomeni trombotici, proprio così come comunemente osservabile in corso di PTT; in questi casi, tali anomalie sono generalmente associate con la presenza di anticorpi anti-fosfolipidi. LES, PTT e sindrome da anticorpi anti-fosfolipidi primitiva (o sindrome di Hughes) possono inoltre condividere una rilevante quantità di sintomi e segni, tanto da causare spesso importanti problemi di diagnosi differenziale (e quindi, anche di trattamento); tale confusione può essere poi aggravata dalla possibile, anche se rara, insorgenza di una PTT in corso di LES.
I rapporti tra PTT ed autoimmunità in generale, spesso nebulosi e solo recentemente tornati prepotentemente alla ribalta, sono stati oggetto di due *reviews* scritte dal Dr. Porta in collaborazione con i Reumatologi del Policlinico San Matteo di Pavia.
Il Prof. Porta, proprio in collaborazione con i Reumatologi del Policlinico San Matteo, si è infatti occupato per diverso tempo dei complessi rapporti esistenti tra PTT, LES ed anticorpi anti-fosfolipidi, e tra PTT ed altri autoanticorpi. In particolare, sulla base degli studi condotti, si è arrivati ad escludere un ruolo, sia degli anticorpi anti-fosfolipidi. che degli anticorpi diretti contro il citoplasma dei neutrofili (ANCA), nell'eziopatogenesi della PTT.
Particolare attenzione è stata poi dedicata al probabile ruolo svolto dal danno endoteliale nella genesi delle manifestazio-

ni cliniche caratteristiche della PTT. E' infatti postulabile che come *primum movens* della malattia possa intervenire proprio una disfunzione endoteliale, così come suggerito da numerosi ed autorevoli Autori. Dal momento che l'ossido nitrico (NO), uno dei principali prodotti biologici di quel vero e proprio organo endocrino che è l'endotelio vascolare, gioca un ruolo essenziale nella regolazione non solo del tono vascolare basale (in senso vasodilatatorio), ma anche della funzionalità e dell'aggregazione piastrinica, la produzione di tale labile molecola è stata studiata nei pazienti affetti da PTT attraverso il dosaggio (mediante una sensibile metodica HPLC) dei prodotti terminali del suo metabolismo, nitriti e nitrati. Dai risultati emersi da tale studio (valori nei pazienti affetti da PTT sovrapponibili a quelli osservabili in controlli sani), appare altamente improbabile che il NO possa avere un qualche ruolo nell'eziopatogenesi della PTT.
In un secondo studio, i dosaggi di NO non hanno permesso di differenziare tra loro pazienti affetti da PTT, LES (con o senza la concomitante presenza di anticorpi anti-cardiolipina) o da sindrome di Hughes.

Altre attività - Il Prof. Porta ha fatto parte del Comitato Scientifico che ha organizzato, in data 15 e 16 Giugno 1990, il primo Congresso Internazionale sulla PTT, svoltosi presso l'Almo Collegio Borromeo di Pavia, al quale hanno partecipato i più noti esperti mondiali di questa malattia (J.L. Moake, L.A. Gutterman, A. Eldor, G. Remuzzi, ecc...). In quell'occasione, un particolare riconoscimento è giunto dall'*Editor-in-Chief* della rivista Transfusion Science, la Prof.ssa Gail Rock, la quale ha voluto offrire un'intero numero per la pubblicazione degli atti del Congresso, concedendo il prestigioso ruolo di *Guest-Editors* al Prof. Bobbio-Pallavicini, al Dr. Fornasari ed al Prof. Porta.
Il Prof. Porta ha quindi cooperato, alla realizzazione di un *registry* internazionale per questa rara malattia, in collaborazione con ricercatori statunitensi (*TTP Medical Research Group*, Coordinatore: Dr. Lorence A. Gutterman) e canadesi (*Canadian Apheresis Group*, Coordinatrice: Prof.a Gail Rock).



Oncologia clinica
1989-oggi

Oltre a dedicare gran parte della propria attività clinica al trattamento dei pazienti affetti da neoplasie solide, il Prof. Porta ha partecipato in prima persona all'elaborazione ed all'attuazione di numerosi protocolli di trattamento per tali pazienti.

Carcinomi del colon-retto - I gruppi dei quali il Prof. Porta ha fatto parte hanno condotto, nel corso degli anni, numerosi studi clinici incentrati sul trattamento di queste comuni neoplasie, in un periodo storico antecedente lo sviluppo dei farmaci a bersaglio molecolare. Trattasi, in tutti i casi, di studi spontanei.
In un primo studio di fase III, randomizzato e multicentrico, sono stati messi a confronto due diversi trattamenti: 5-FU in monochemioterapia vs. 5-FU modulato dall'acido folinico racemico (*d,l*-AF) secondo la *schedula* classica originariamente proposta da David Machover. Tale studio ha evidenziato una superiorità dell'associazione 5-FU/*d,l*-AF sul solo 5-FU, sia in termini di attività antitumorale (cioè di risposte obiettive), che di sopravvivenza.
I dati relativi a ciascun paziente arruolato in questo studio, sono stati utilizzati per una meta-analisi internazionale (effettuata sotto l'egida del *Meta-Analysis Group in Cancer,* coordinato dal Prof. Pascal Piedbois), i cui risultati sono stati successivamente pubblicati sul *Journal of Clinical Oncology*. Tale sforzo internazionale ha definitivamente dimostrato la superiorità della modulazione sulla monochemioterapia con

5-FU, indipendentemente dai parametri di efficacia considerati.
In un successivo studio di fase II, è stata valutata l'efficacia anti-tumorale e la tossicità dell'associazione tra 5-FU ed acido folinico levogiro puro (*l*-AF), partendo dall'osservazione che l'isomero levogiro è l'unico ad essere biologicamente attivo, mentre la controparte destrogira potrebbe inficiarne l'azione. La percentuale di risposte obiettive ottenute, così come il profilo tossicologico, sono risultati sostanzialmente sovrapponibili a quanto osservabile utilizzando la forma racemica.
Un altro studio di fase II è stato incentrato sul trattamento combinato loco-regionale e sistemico delle metastasi epatiche da carcinoma del colon; pazienti presentanti lesioni secondarie epatiche come unica sede di malattia, sono stati infatti trattati con una combinazione di chemioterapia sistemica (5-FU e *d,l*-AF) e chemioembolizzaione dell'arteria epatica. Purtroppo, di contro ad un'attività terapeutica sovrapponibile a quella ottenibile con la sola chemioterapia sistemica, si sono anche osservati significativi effetti collaterali, condizionanti una conseguente bassissima *compliance* da parte dei pazienti.
Un successivo studio di fase II ha valutato l'attività di una combinazione di 5-FU, *l*-AF, cisplatino e mitomicina-C come trattamento di seconda linea in pazienti refrattari all'associazione 5-FU e *d,l*-AF. Non essendosi evidenziate risposte obiettive nei primi 14 pazienti trattati, lo studio è stato interpretato come negativo e conseguentemente sospeso, in accordo con gli usuali criteri di conduzione degli studi clinici.
All'interno di un ulteriore studio di fase II, si è voluta poi testare l'ipotesi che il 5-metiltetraidrofolato (MeTHF), una fonte di folati ridotti alternativa all'AF, potesse efficacemente modulare l'attività citotossica del 5-FU. Tale combinazione è risultata scarsamente efficace, ancorchè ben tollerata, e pertanto il suo utilizzo, in sostituzione della classica associazione 5-FU/AF (sia esso racemico che levogiro puro), è stato sconsigliato.
Infine, è stato condotto uno studio (di fase II) di chemioterapia sequenziale, sistemica ed intra-epatica, in pazienti con metastasi epatiche come unica sede di malattia. Di 32 pazienti valutabili, 17 (53.1%) hanno presentato una risposta obiettiva, mentre 8 (25%) hanno avuto una stabilizzazione di malattia come miglior risposta al trattamento. Il tempo alla progressione mediano è risultato pari a 32 settimane (range: 8-104), mentre la sopravvivenza mediana è stata di sole 39 settimane (range: 9-109). Un'incompleta perfusione del fegato è stata poi l'unica variabile che correlava con una scadente sopravvivenza (p = 0.046). In conclusione, i risultati dello studio, in accordo con quanto riportato da altri Autori, suggeriscono un'efficacia tutto sommato modesta per un simile approccio sequenziale.
Successivamente, il Prof. Porta ha lasciato l'attività di ricerca clinica in questo settore ad altri Colleghi, concentrandosi su altre neoplasie.

Epatocarcinomi - Particolare attenzione, sia da un punto di vista terapeutico che clinico-biologico, è stata prestata agli epatocarcinomi (HCC), neoplasie un tempo considerate esclusiva dei paesi dell'estremo oriente e sub-Sahariani, ed oggi in drammatico incremento anche in Occidente, come conseguenza dell'elevata incidenza di infezioni croniche da virus epatitici di tipo B e C.
Da un punto di vista clinico, sono stati valutati diversi approcci terapeutici per i pazienti che non possono ricorrere alla chirurgia, a causa dell'estensione della malattia e/o della concomitante presenza di una cirrosi epatica condizionante una scadente funzionalità epatica residua.
La chemioembolizzazione arteriosa (TACE) è stata una prima metodica valutata in collaborazione con i Radiologi dell'Istituto di Radiologia e Terapia Fisica dell'Università di Pavia; tale metodica, come ora ben noto, è in grado di indurre, sia una significativa citoriduzione, sia un impatto sulla sopravvivenza di questi pazienti, ma rimane una metodica di trattamento con precisi limiti e precise indicazioni.
Un successivo studio condotto utilizzando, come metodica di trattamento loco-regionale, l'alcoolizzazione percutanea ecoguidata (PEI) è stato condotto in cooperazione con altri Centri, ed ha permesso di confermare l'estrema efficacia e l'ottima tollerabilità di tale metodica di trattamento, limitata però ai noduli neoplastici di dimensioni più piccole.
Per quanto, fino ad oggi, la chemioterapia sistemica solo occasionalmente abbia dato luogo a risultati positivi nel trattamento dei pazienti affetti da epatocarcinomi, risultati interessanti, in termini di attività antitumorale, sono stati osservati all'interno di due studi di fase II che hanno testato l'associazione 5-FU/*d,l*-AF, ovvero una combinazione di Epirubicina ed Etoposide (VP-16). In particolare, quest'ultima combinazione ha consentito di ottenere un eccellente tasso di risposte obiettive, pari al 38.8% (95% CI: 22.5-55%).
Al contrario, nonostante un solido razionale a sostegno dell'infusione continua loco-regionale della Fluoro-deossiuridina (FUdR), la somministrazione per via inta-epatica di questa fluoropirimidina ha determinato dei risultati globalmente insoddisfacenti.
Il Prof. Porta ha anche partecipato ad uno studio multicentrico internazionale registrativo di fase III, finalizzato a comparare l'impatto sulla sopravvivenza di un nuovo chemioterapico, il Nolatrexed (un inibitore superselettivo della Timidilato Sintetasi), allorchè confrontato ad una chemioterapia di riferimento (Doxorubicina). Alla luce dell'elevato arruolamento nello studio (primo tra tutti i Centri partecipanti allo studio), il Prof. Porta è stato scelto per presentare oralmente i dati definitivi dello studio all'*ASCO Annual Gastro-Intestinal Meeting*, svoltosi ad Orlando nel Gennaio 2006. I risultati dello studio,

che purtroppo hanno sorprendentemente evidenziato una superiorità del braccio di controllo sul braccio sperimentale, sono stati successivamente accettati per una pubblicazione *in extenso* sul *Journal of Clinical Oncology*.
Il Prof. Porta ha quindi partecipato ad uno studio registrativo internazionale di fase III, randomizzato contro plecebo, finalizzato a valutare l'efficacia del Sorafenib (BAY 43-9006), un inibitore sia dell'angiogenesi, che del *pathway* proliferativo di MAP-chinasi, in pazienti affetti da epatocarcinoma che avessero ancora una funzionalità epatica residua adeguata (stadio A di Child-Pugh). Tale studio, i cui risultati definitivi sono stati preannunciati in una conferenza stampa effettuata in data 12 Febbraio 2007, è risultato il primo studio nella storia del trattamento dell'epatocarcinoma ad aver dimostrato un beneficio in termini di sopravvivenza per un determinato farmaco. Il Prof. Porta è stato quindi invitato a far parte dello *Steering Committee* che ha elaborato l'articolo riportante i risultati completi e definitivi dello studio in oggetto, articolo che è stato successivamente pubblicato sulle pagine del prestigioso *New England Journal of Medicine* e che, a tutt'oggi, risulta uno degli articoli più citati degli ultimi dieci anni nel campo delle Scienze Bio-Mediche.
Dopo aver partecipato ad uno studio di fase III con l'inibitore di mTOR Everolimus, studio anch'esso risultato negativo, più recentemente, il Prof. Porta ha attivamente partecipato allo sviluppo di un inibitore di C-Met, il Tivantinib (o ARQ 197), per il trattamento dell'epatocarcinoma. Un primo studio di fase II, randomizzato contro placebo, è stato condotto in pazienti refrattari al Sorafenib. Questo studio, non solo ha dimostrato come il Tivantinib possa rappresentare un'opzione di seconda linea attiva in pazienti affetti da HCC (e cirrosi epatica ben compensata), ma ha soprattutto dimostrato come l'espressione immunoistochimica di Met rappresenti un fattore prognostico in questi pazienti e permetta di selezionare un sottogruppo di pazienti particolarmente responsivi a questo nuovo farmaco a bersaglio molecolare.
Purtroppo, molto recentemente, il conseguente studio di fase III finalizzato (auspicabilmente) alla registrazione del Tivantinib come trattamento di seconda linea in pazienti affetti da HCC iperesprimenti Met, è fallito mettendo in discussione l'effettiva attività del Tivantinib, il suo meccanismi d'azione, ma anche il ruolo predittivo/prognostico dell'espressione di Met nell'epatocarcinoma.

Dal punto di vista delle correlazioni clinico-biologiche ed epidemiologiche, in collaborazione con ricercatori di altri Centri, sono stati inizialmente studiati i rapporti esistenti tra infezione da virus epatitico di tipo C ed incidenza dell'epatocarcinoma in una importante popolazione del nord Italia.
E' stata inoltre studiata la frequenza dell'espressione degli antigeni HLA di classe I e II in una popolazione di 205 pazienti affetti da epatocarcinoma; il confronto con una popolazione di controllo composta da 749 soggetti sani, ha evidenziato una significativa prevalenza degli antigeni Cw7, B8 e DR3 tra i pazienti affetti da epatocarcinoma. Dal momento che è ben noto come gli aplotipi antigenici HLA A1, Cw7, B8 e DR3 siano associati con un rapido declino dei linfociti $CD4^+$, e come i soggetti HLA A1, Cw7, B8 e DR3-positivi tendano a presentare un quadro immunologico alterato, è stato possibile ipotizzare che l'epatocarcinoma possa essere il risultato di una anormale risposta del sistema immunitario, geneticamente predeterminata, agli stimoli mitogenici rappresentati dai virus epatitici B e/o C.
In un successivo studio caso-controllo, è stato dimostrato il ruolo dell'Interleuchina-6 (IL-6) come *marker* dell'epatocarcinoma; i risultati di questo studio sono stati pubblicati *in extenso* su *Annals of Oncology*.

Carcinoma renale - Il carcinoma renale rappresenta, da sempre, il principale interesse clinico-scientifico del Prof. Porta.
Pur non essendo una delle neoplasie maligne epidemiologicamente più rilevanti (è solo la settima neoplasia al mondo per incidenza), il carcinoma renale rappresenta indubbiamente un modello particolarmente affascinante a causa di caratteristiche biologiche peculiari, quali la chemioresistenza, l'immunogenicità, ed il ruolo giocato dall'angiogenesi nella sua patogenesi.
Inizialemente, il Prof. Porta si è attivamente occupato di sviluppare protocolli di trattamento chemio-immunoterapico ed immunoterapico per pazienti affetti da carcinoma renale, abbinando a tali studi clinici studi biologici finalizzati, tra l'altro, ad evidenziare fattori prognostici della risposta o meno al trattamento immunoterapico con IL-2 per via sottocutanea ed IFN-α.
In questo senso vanno ricordati gli studi condotti in collaborazione con il Prof. Carlo Buzio della *Cattedra di Nefrologia dell'Università di Parma*, e la partecipazione a due protocolli nazionali di immunoterapia adiuvante e di fase avanzata nell'ambito del *Gruppo Oncologico Italiano di Ricerca Clinica* (G.O.I.R.C.).
In particolare, lo studio di terapia adiuvante - ancorchè purtroppo negativo - è stato presentato in sessione plenaria al Congresso Nazionale dell'*American Society of Clinical Oncology* (ASCO) e successivamente pubblicato *in extenso* sul *Journal of Immunotherapy*.
La qualità delle ricerche condotte su questo argomento è attestata anche dall'attribuzione, nel Dicembre 1998, del *Premio 'Gaetano Fichera'* per la produzione scientifica in campo oncologico; nella motivazione ufficiale del premio sono state infatti evidenziate le ricerche condotte dal Prof. Porta sull'immunoterapia del carcinoma renale (oltre che quelle sul trattamento degli epatocarcinomi inoperabili).
In anni più recenti, il Prof. Porta ha poi partecipato a svariati

protocolli internazionali che hanno dimostrato l'attività di tutta una serie di nuovi farmaci a bersaglio molecolare in questa neoplasia, fino a pochi anni orsono sostanzialmente orfana di trattamenti attivi. Nel corso degli anni, il Prof. Porta ha infatti partecipato allo sviluppo clinico praticamente di tutti i farmaci attualmente registrati o in corso di registrazione per il trattamento del carcinoma renale: gli inibitori multichinasi Sorafenib, Sunitinib, Pazopanib, Axitinib, Tivozanib e Dovitinib, e gli inibitori di mTOR Everolimus e Temsirolimus. Praticamente per tutti gli studi di questi farmaci, il Prof. Porta è risultato il maggior reclutatore in Italia ed uno dei principali reclutatori a livello globale.
Attualmente, il Prof. Porta è *Principal Investigator*, locale o nazionale, di oltre 10 studi. di fase I, II o III, incentrati sul trattamento del carcinoma renale, in diverse linee e setting terapeutici, incluso quello dei carcinomi renali non a cellule chiare.
La riconosciuta competenza nel campo della terapia del carcinoma renale lo ha reso un *Opinion Leader* a livello internazionale, come dimostrato dalla partecipazione agli *Advisory Board* della principali aziende impegnate nello sviluppo di nuovi farmaci per queste neoplasie; tale partecipazione, che comporta anche una costante e fattiva collaborazione scientifica, è condivisa con personalità del calibro di Bernard Escudier, Ron Bukowski, Robert Figlin, Tim Eisen, Brian Rini, Martin Gore, Joaquim Bellmunt, Manuela Scmidinger, il compianto Peter DeMulder, ed altri.
Per tale motivo, negli ultimi anni, il Prof. Porta ha partecipato alla stesura delle linee guida per il carcinoma renale di svariate organizzazioni: l'*European Society of Medical Oncology* (ESMO), l'Associazione Italiana di Oncologia Medica (AIOM), l'Associazione Urologi Italiani (AURO) ed il Consiglio Nazionale delle Ricerche (CNR). Quando non coinvolto direttamente nella stesura delle linee guida, è stato coinvolto come revisore esterno indipendente, come nel caso dell'*European Organization for Research and Treatment of Cancer* (EORTC), della Società Italiana di Urologia (SIU), o dell'*European Association of Urology* (EAU).

Dal punto di vista della ricerca translazionale, l'attenzione del Prof. Porta, in collaborazione con i ricercatori dell'Istituto di Fisiologia dell'Università di Pavia, si è concentrato sul possibile ruolo dei progenitori endoteliali circolanti come possibile meccanismo di *escape* dall'attività anti-angiogenica ed antiproliferativa degli inibitori di VEGF/VEGFR e di mTOR in pazienti affetti da carcinoma renale, e del relativo ruolo dei flussi di Ca^{++} transmembrana in tali meccanismi di *escape*, flussi che presentano caratteristiche distintive rispetto ad altre neoplasie e che potrebbero rappresentare dei nuovi, promettenti, *target* terapeutici (vedasi più avanti).

Terapia di supporto - Particolare attenzione è stata anche dedicata dal Prof. Porta alla terapia di supporto nei pazienti Oncologici ed al trattamento delle complicanze dei trattamenti chemioterapici.
In un primo studio, randomizzato, condotto in doppio cieco contro placebo, è stata dimostrata l'attività dell'Allopurinolo, uno *scavenger* di radicali liberi, nel lenimento delle stomatiti indotte dal 5-FU. Gli sciacqui del cavo orale con una sospensione di Allopurinolo si sono dimostrati efficaci nel proteggere le mucose del cavo orale anche in pazienti affetti da Artrite Reumatoide trattati con Metotrexate a basso dosaggio. Tale osservazione, presuppone la possibilità di applicare tale facile ed economica procedura, terapeutica (e profilattica), anche in pazienti trattati con chemioterapici diversi dal 5-FU e dal Metotrexate. Lavande con Allopurinolo sembrerebbero infine in grado di lenire anche le vaginiti indotte da trattamenti chemioterapici comprendenti antimetaboliti. Più recentemente, il Prof. Porta è stato ideatore e *Principal Investigator* di uno studio finalizzato a valutare l'efficacia di un colluttorio a base di prodotti naturali (tra i quali il Lapacho), dotati di attività anti-infiammatoria ed antibatterica, nella prevenzione della stomatite da Everolimus. La pubblicazione dei risultati di tale studio sono attesi per i prossimi mesi.
Partendo da dei fondati presupposti fisiopatologici, in un successivo studio randomizzato, anch'esso eseguito in doppio cieco contro placebo, è stata dimostrata l'attività del disodiocromoglicato per via inalatoria nel trattamento della fastidiosa tosse irritativa, così comune nei pazienti affetti da neoplasie polmonari. Tale studio, pubblicato sul *British Journal of Cancer*, è stato selezionato dal Prof. Eli Glatstein, uno degli editori del *Mosby-Year Book of Oncology*, per essere inserito nel volume relativo al 1997 del suddetto *Year Book,* in quanto uno degli studi clinici più importanti dell'anno.

Sviluppo di nuovo farmaci - come già ampiamente accennato, il Prof. Porta si è dedicato allo sviluppo, pre-clinico e clinico, di nuovi farmaci antitumorali, siano essi chemioterapici tradizionali, *target therapies*, o nuove forme di immunoterapia (vaccini ed inibitori dei *checkpoints* immunologici), in particolar modo nel tumore del rene, ma anche in altre patologie quali l'epatocarcinoma, il carcinoma della prostata, il carcinoma della vescica, il mesotelioma, ecc ...).
Tra le molecole sviluppate nel corso degli anni (da sole o in combinazione), vanno ricordate: il WR-2721 (Amifostina), il BBR-3438, il Nolatrexed, la Rampirnasi, il BAY 43-9006 (Sorafenib), l'Imatinib mesilato, il Bortezomib, la Taurolidina, il RPR-109881, il SUO11248 (Sutent), il RAD001 (Everolimus), il TAC-101, l'AV951 (Tivozanib), l'ARQ 197 (Tivantinib), il Dovitinib, l'Ipilimumab, il Nivolumab, il Telaglenastat, il Sapanisertib, il Belzutifan, il MK-1308 (Quavonlimab), ed altri.

Onco-Nefrologia - L'Onco-Nefrologia è nuova una sottospecialità in rapida evoluzione che si concentra sulle complesse relazioni esistenti tra il rene e il cancro. Le aree in cui i Nefrologi e gli Oncologi dovrebbero lavorare a stretto contatto per fornire le migliori cure possibili per i pazienti affetti da cancro e malattie renali sono svariate ed includono: 1) il danno renale acuto e la malattia renale cronica nei pazienti oncologici; 2) gli effetti nefrotossici delle terapie antitumorali, siano essi i chemioterapici tradizionali, gli agenti a bersaglio molecolare, o i nuovi immunoterapici; 3) le sindromi renali paraneoplastiche; 4) la gestione dei pazienti nefrectomizzati per un carcinoma renale; 5) i rapporti tra terapia sostitutiva renale e cure oncologiche attive; 6) il trapianto di rene in pazienti sopravvissuti ad una neoplasia, ed il rischio oncologico nei pazienti con malattia renale terminale, in dialisi, o trapiantati; 7) il ruolo dei trattamenti oncologici nei pazienti sottoposti a trapianto di rene; 8) la gestione del dolore nei pazienti con cancro e malattie renali; 9) lo sviluppo di linee guida integrate per i pazienti affetti da problematiche onco-nefrologiche ed 10) il disegno e la conduzione di studi clinici ideati specificamente per l'Onco-Nefrologia. E' quindi ovvio come un team onco-nefrologico multidisciplinare sia fondamentale per fornire la migliore assistenza possibile, sia nella fase acuta che in quella cronica di malattia, a questi pazienti. Il Prof. Porta è stato identificato dall'Associazione Italiana di Oncologia Medica (AIOM) come referente per i rapporti con la Società Italiana di Nefrologia (SIN) proprio al fine di contribuire allo sviluppo dell'Onco-Nefrologia, anche in collaborazione con l'analogo gruppo di lavoro dell'American Society of Nephrology (ASN).

Oncologia ed onco-ematologia sperimentale
1989-oggi

Il Prof. Porta è stato per anni co-responsabile (con il Dr. Mauro Moroni, sotto la supervisione della Prof.a Antonia Notario) del Laboratorio di Colture Cellulari dell'Istituto di Terapia Medica.
Successivamente, è stato responsabile del Laboratorio di Oncologia Pre-Clinica e Terapie Sperimentali dell'Istituto di Medicina Interna ed Oncologia Medica della Fondazione IRCCS Policlinico San Matteo di Pavia, dove ha condotto numerose ricerche translazionali, coordinando l'attività di una Biologa, finanziata con una borsa IRCCS bandita su progetti di ricerca dei quali è stato direttamente ideatore.

Radicali liberi, tumori ed Amifostina - Sia lo stress ossidativo che le specie reattive dell'ossigeno (o radicali liberi) sono fattori implicati, tanto nella patogenesi di numerose malattie degenerative, così come negli stadi iniziali della carcinogenesi e nel processo di metastatizzazione; oltre a ciò, l'azione di numerosi chemioterapici antitumorali è mediata dalla produzione di radicali liberi, così come modificazioni nella produzione dei e nella sensibilità ai radicali liberi si osservano spesso nei processi di differenziazione cellulare.
In collaborazione con il Dr. Fulvio Marzatico e Coll. del Dipartimento di Scienze Fisiologiche-Farmacologiche Cellulari e Molecolari dell'Università di Pavia, sono stati studiati, *in vitro*, i rapporti esistenti tra proliferazione neoplastica, produzione di radicali liberi ed espressione di meccanismi di difesa contro il danno perossidativo indotto dai radicali liberi stessi.
Successivamente, ottenuta in esclusiva dalla ditta Schering-Plough S.p.A. la possibilità di sperimentare *in vitro* l'Amifostina (WR-2721), un chemioprotettore allora non ancora in commercio nel nostro Paese, ne sono stati studiati l'attività di *scavenger* di radicali liberi e gli effetti sulla proliferazione di popolazioni cellulari sane e neoplastiche in presenza o meno di farmaci citotossici, *in vitro,* e sui midolli di pazienti affetti da Sindromi Mielodisplastiche, *in vivo*.

Ruolo dei flussi di Ca^{++} nella proliferazione cellulare neoplastica e nella fisiopatologia cellulare - Le interazioni tra neoplasie e sistema emostatico hanno suscitato crescente interesse negli ultimi decenni. Dati clinici e sperimentali suggeriscono che questi eventi non solo possano giocare un ruolo rilevante nell'insorgenza della diatesi emorragica e/o trombofilica così comune nei pazienti portatori di neoplasie, ma possono anche influenzare la crescita stessa del tumore ed il processo di metastatizzazione.
A tal proposito, in una serie di iniziali ricerche, condotte in collaborazione con il gruppo del Prof. Guido Grignani, è stato valutato se l'attivazione dell'emostasi possa indurre aumento dei livelli citoplasmatici di Ca^{++} nelle cellule tumorali coltivate *in vitro*, stimolandone in tal modo la proliferazione.
E' stato osservato come l'ADP, che viene liberato dalle piastrine durante l'attivazione, sia stato in grado di indurre flussi transitori di Ca^{++} nelle cellule di diverse linee tumorali *in vitro*, mentre collagene e trombina hanno mostrato un effetto particolarmente eclatante in alcune linee, ma non in altre. Inoltre, il calcio antagonista Verapamil è stato in grado di ridurre i flussi di Ca^{++} indotti dagli agonisti efficaci e, soprattutto, ha dimostrato di poter inibire, almeno *in vitro*, la crescita delle cellule neoplastiche.
Nella fisiopatologia cellulare, il calcio-ione (Ca^{++}) rappresenta un importante 'secondo messaggero', in quanto in grado di trasmettere all'interno della cellula messaggi che arrivano alla membrana plasmatica dall'ambiente esterno.
Il Ca^{++}, per agire come 'secondo messaggero', deve essere in grado di aumentare la sua concentrazione intracellulare; ciò può avvenire o attraverso l'entrata di Ca^{++} nella cellula, o attraverso la mobilizzazione di parte del Ca^{++} intracellulare. L'entrata del Ca^{++} nella cellula avviene attraverso il passaggio per canali specifici: i canali voltaggio-dipendenti ed i

canali la cui apertura è conseguenza del legame tra un agonista ed il suo specifico recettore. I canali voltaggio-dipendenti, a loro volta, sono suddividibili in tre tipi: i canali T (*transient*), i canali L (*long-lasting*) - i più importanti -, e quelli N (*neuronal*), fino ad oggi evidenziati solo a livello delle cellule nervose.
Per quanto riguarda l'interazione recettoriale, una volta che un agonista si lega con il suo recettore, si induce l'idrolisi del fosfatidil-inositolo di membrana, con conseguente formazione di diacil-glicerolo ed apertura della porta del canale, e di inositolo-trifosfato, che consente la liberazione del Ca^{++} dal reticolo sarcoplasmatico. Una volta che i livelli intracellulari del Ca^{++} sono aumentati, alcune proteine solubili citoplasmatiche legano il Ca^{++} e vanno così ad attivare altri enzimi o strutture intracellulari, trasducendo ulteriormente il messaggio.
Più recentemente, come precedentemente accennato e successivamente maggiormente esplicitato, in collaborazione con il gruppo del Dr. Francesco Moccia dell'Istituto di Fisiologia dell'Università di Pavia, il Prof. Porta è tornato ad occuparsi del ruolo dei canali del Ca^{++} come meccanismo pro-angiogenico nei progenitori endoteliali di pazienti affetti da carcinoma renale avanzato.

Biologia molecolare del Mesotelioma pleurico - Il mesotelioma maligno pleurico (MMe) è un tumore aggressivo e altamente invasivo, che colpisce comunemente le cellule mesoteliali di rivestimento della cavità pleurica. La lesione è generalmente limitata al torace, ma nel 25% dei casi si ritrovano metastasi in altri siti
Sono stati individuati molteplici fattori di rischio, tra i quali quello più specifico in assoluto è rappresentato da una precedente esposizione all'asbesto. Una volta raggiunte le vie respiratorie inferiori, le fibre di asbesto esercitano sulle cellule mesoteliali bersaglio sia un danno diretto, conseguente all'interazione con cromosomi o proteine ad essi associate, sia un danno indiretto, attraverso la liberazione di radicali ossidanti e fattori stimolanti la crescita delle stesse cellule maligne.
L'impiego di asbesto nel corso del XX secolo è cresciuto fino agli anni '60-'70, quindi è calato negli ultimi decenni, almeno nel mondo occidentale. La mortalità per MMe, a conferma dell'esistenza di una stretta correlazione con l'esposizione a questo inquinante ambientale, ha avuto un andamento analogo ma a distanza di decenni, a causa del lungo periodo di latenza della patologia.
Si è osservato che l'incidenza è maggiore negli individui nati tra gli anni '40 e '50 di sesso maschile, perché i primi 10-20 anni della loro attività lavorativa hanno coinciso con un picco nell'importazione e nell'impiego di asbesto nell'edilizia e nell'industria in generale. In considerazione del lungo periodo di latenza di questa forma di tumore, è stato stimato che, in mancanza di sensibili miglioramenti nei protocolli diagnostici nell'immediato futuro, la mortalità per MMe sarà ancora in fase di crescita e il picco di incidenza della malattia sarà raggiunto attorno al 2020.
Gli approcci terapeutici convenzionali (asportazione chirurgica, radioterapia, chemioterapia e terapie combinate) non sono stati giudicati applicabili alla maggior parte dei casi di MMe e, quando sono stati impiegati, hanno avuto scarso successo ed hanno portato a benefici estremamente modesti in termini di incrementata aspettativa di vita.
Anche se l'incidenza del MMe continua ad aumentare nel mondo, come conseguenza di una precedente, comune, esposizione all' asbesto, almeno il 20% dei casi di mesotelioma non è associato (almeno apparentemente) a tale esposizione; inoltre, tra coloro che si sono pesantemente esposti, esistono anche casi in cui la neoplasia non si è manifestata. Perciò, altri agenti cancerogeni potrebbero indurre il mesotelioma, o potrebbero rendere particolari soggetti più suscettibili agli effetti cancerogeni dell'asbesto. Tra le ipotesi più accreditate, vi è quella di un sinergismo tra l'esposizione all'asbesto e quella al virus delle scimmie SV40.
Un primo quesito che il gruppo di ricercatori con i quali il Prof. Porta ha collaborato si è posto, è il ruolo di SV40 nella genesi del MMe, dipendentemente o indipendentemente dall'asbesto.
Il MMe è una patologia caratterizzata a livello cellulare da spiccate proprietà di crescita e di migrazione. HGF (*Hepatocyte Growth Factor*), è un fattore pleiotropico solubile il cui recettore è codificato dall'oncogene Met. In seguito al legame con il suo ligando HGF, Met è attivato ed è in grado di innescare la trasduzione del segnale che induce nelle cellule gli effetti biologici di proliferazione e di motilità. E' stato dimostrato in alcuni casi di tumori che Met è costitutivamente attivo perché si instaura un meccanismo autocrino, mediante il quale HGF e Met vengono espressi contemporaneamente nella stessa cellula. I risultati ottenuti hanno rivelato che questo fenomeno di autocrinia, relativamente a Met, è presente in un certo numero di linee cellulari continue, derivate da pazienti di MMe. Queste linee cellulari sono state ottenute dagli essudati pleurici di pazienti di mesotelioma per i quali era stata accertata una precedente esposizione a fibre di asbesto. In queste cellule, mediante analisi di *Western blotting* con anticorpi anti-Met e anti-fosfotirosina, si è dimostrato che Met è espresso e fosforilato in tirosina in assenza di stimolazione con HGF esogeno. Inoltre, nel genoma di queste stesse cellule sono state messe in evidenza sequenze del virus SV40 e, mediante l'uso di anticorpi specifici, è stata evidenziata l'espressione dell'antigene virale Tag di SV40. Invece, nelle cellule di mesotelioma, dove Met è espresso ma non autonomamente fosforilato in tirosina, SV40 e Tag si sono dimostrati assenti. Il sistema di coespressione di Met e Tag è stato poi riprodotto in cellule

mesoteliali normali (HMC), che sono state trasfettate con il cDNA di SV40 e di Tag. In queste condizioni è stato possibile determinare l'instaurarsi del circuito autocrino osservato nelle cellule di MMe. Questi risultati hanno confermato l'esistenza di una correlazione fra espressione della proteina virale Tag e l'induzione dell'espressione di fattori di crescita, in modo dipendente dalla proteina Rb (Retinoblastoma). Inoltre è stato dimostrato che il virus SV40 è trasmissibile in poco tempo da poche cellule mesoteliali infettate ad altre cellule mesoteliali in modo esponenziale, innescando così un processo a catena, che potrebbe concorrere, insieme all'asbesto, all'induzione della tumorigenesi. Infatti, nelle cellule mesoteliali infettate dal virus il ritmo di crescita risulta aumentato rispetto a quello delle cellule normali. Inoltre, queste cellule vanno incontro a cambiamenti morfologici, che fanno loro assumere le caratteristiche tipiche delle cellule tumorali di mesotelioma.

Dal momento che HGF media un effetto protettivo da apoptosi (anti-apoptotico o di *survival*), attraverso l'attivazione del suo recettore Met, che a sua volta innesca la via di trasduzione del segnale mediata dalla Lipide Chinasi Fosfoinositide-3-chinasi (PI3K), che a sua volta attiva la Proteina Serina/Treonina chinasi Akt/PKB, questo *pathway* molecolare è stato oggetto di approfondite ricerche.

L'ipotesi proposta è che la progressiva resistenza all'apoptosi rappresenti parte di un processo multifasico di trasformazione neoplastica delle cellule mesoteliali normali. Inoltre, postuliamo che la presenza di SV40, attraverso l'espressione di HGF, induca l'attivazione di Met e conseguentemente sopravvivenza, mediante le proprie specifiche vie di trasduzione del segnale, in particolare quella di PI3K/Akt. L'effetto di sopravvivenza, mediato da PI3K/Akt, prolungando la vita delle cellule esposte all'asbesto, permettebbe a quest'ultimo di esplicare appieno l'effetto cancerogeno.

Questi meccanismi, basati sulle vie di trasduzione coinvolgenti SV40, HGF/Met e PI3K/Akt nella risposta citotossica delle cellule mesoteliali normali e delle cellule di MMe all'asbesto e altri agenti tossici, suggerisce la possibilità di un ruolo di co-carcinogenesi fra SV40 e asbesto nella genesi del MMe.

La definizione di nuovi *target* molecolari, ha inoltre portato a testare, sia *in vitro* che *in vivo* (nel modello animale) nuove molecole e combinazioni di farmaci (chemioterapici e *smart drugs*) contro il MMe.

La rilevanza delle ricerche condotte in questo campo, oltre ad essere testimoniata dalla numerose, ed autorevoli pubblicazioni, è attestata anche dalla collaborazione in essere con i principali gruppi impegnati, a livello mondiale, nella ricerca sul mesotelioma.

In tal senso, alcuni tra i principali lavori scientifici pubblicati dal Prof. Porta sull'argomento sono stati effettuati in collaborazione con personalità quali il Dr. Nicholas J. Vogelzang, il Dr. Dean Fennell, la Dr.ssa Brooke Mossman, ed altri.

Proprio per la competenza su quest'argomento, il Prof. Porta è stato scelto come revisore indipendente per progetti di ricerca sul mesotelioma da parte del *Medical Research Council* (MRC) britannico.

Studio del ruolo dei progenitori endoteliali circolanti nei meccanismi di angiogenesi tumorale - Negli ultimi anni il Prof. Porta ha condotto e partecipato a studi, a livello di ricerca sperimentale, sul ruolo dell'angiogenesi neoplastica associata (in particolare) al tumore del rene, con particolare riguardo al significato dei progentiori endoteliali circolanti in questa malattia.

In dettaglio, sono stati studiati inizialmente la frequenza, il fenotipo e gli aspetti funzionali di queste cellule *in vitro*. Sono stati condotti quindi studi, in collaborazione coll'IRCCS Istituto Farmacologico Mario Negri di Milano ed il Dipartimento di Biologia e Biotecnologie dell'Universita' di Pavia, volti ad indentificare il profilo di espressione genica di tali progenitori, confrontandolo con quello della loro controparte sana e con quello di progenitori isolati dal sangue periferico di pazienti affetta da carcinoma mammario, arrivamdo all'individuazione di una "*molecular signature*" dei progenitori circolanti neoplastici che ne identifica il profilo e ne indica un possibile ruolo nell'angiogenesi neoplastica. Tale studio è stato recentemente pubblicato sull'*European Journal of Cancer*.

In collaborazione con il Dipartimento di Biologia e Biotecnologie dell'Universita' di Pavia, sono poi stati svolti studi indirizzati alla comprensione dei fini meccanismi regolatori di questi progenitori con particolare interesse all'effetto del VEGF ed al bilancio del Ca^{++} intracellulare.

Per quanto riguarda quest'ultimo aspetto, le ricerche svolte hanno permesso di individuare come l'ingresso di Ca^{++} operato dai depositi dello stesso (cosiddetto SOCE) sia rimodellato nei progenitori endoteliali di pazienti con carcinoma renale rispetto a quelli di soggetti sani, e come le proteine associate a questa funzione (per esempio, Orai1 e TRPC1) controllino la proliferazione e la tubologenesi di queste cellule, suggerendo così come tutti questi mediatori possano divenire nuovi possibili *targets* per future terapie mirate.

Piu' recentemente, e' stato dimostrato come SOCE sia invece espresso e funzioni in cellule endoteliali primitive di tumore renale metastatico, ma in questo caso, non controlli la proliferazione di queste cellule.

Attualmente, sono in via di conclusione gli esperimenti volti a chiarire la risposta al VEGF dei progenitori endoteliali circolanti di pazienti affetti da carcinoma renale, esperimenti che preliminarmente indicherebbero come tali cellule, a differenza della loro controparte isolata da soggetti sani, non siano sensibili al VEGF, nonostante la presenza del suo recettore sulla superficie delle cellule, suggerendo un possi-

bile meccanismo di resistenza delle stesse ai farmaci inibitori del VEGF.

Immuno-Oncologia ed immunoterapia 1990-oggi

Fin dalla fine degli anni '90, l'attenzione del Prof. Porta è stata attirata dall'immunologia dei tumori e dall'utilizzo dell'immunoterapia come strategia di trattamento antineoplatico. In quegli anni, l'immunoterapia era rappresentata da citochine quali l'Interferone e l'Interleuchina-2 (IL-2), una forma "primitiva" di modulazione della risposta immunitaria antitumorale, in grado beneficiare un numero limitato di pazienti, spesso a scapito di importanti tossicità. La limitata efficacia di tali terapie sappiamo ora essere legata all'attivazione di meccanismi di feed-back negativo della risposta immune, quali l'espansione di sottopopolazioni cellulari ad attività soppressoria (linfociti Treg, cellule mielodi soppressorie, ecc ...), la produzione di citochine immunosoppressive e, soprattutto, l'attivazione di checkpoint immunologici inibitori dell'attivazione delle popolazioni effettrici della risposta immune.
Proprio l'identificazione di questi checkpoint, ad attività sia inibitoria, che stimolatoria, ha portato allo sviluppo di anticorpi monoclonali diretti contro due checkpoints inibitori, il CTLA4 ed il complesso PD1-PD-L1.
Così come l'immunoterapia a base di citochine ha avuto come uno dei principali campi di utilizzo il carcinoma renale (oltre al melanoma), i primi inibitori dei sopracitati immune checkpoints sono stati testati, tra le tante patologie, anche nel carcinoma renale, core business dell'attività clinica e di ricerca del Prof. Porta, ampliatasi all'utilizzo dell'immunoterapia anche in altre neoplasie urologiche (soprattutto, i carcinomi uroteliali della vescica e della alte vie escretrici).
Più recentemente, ha iniziato ad occuparsi, in modelli pre-clinici, dello sviluppo di immunoterapie cellulari adottive quali le CAR-T cells, linfociti ingegnerizzati ad esprimere un recettore specifico per un antigene preferenzialmente (o meglio, esclusivamente) espresso sulle cellule tumorali. Una prima esperienza in tal senso, condotta su un modello murino di neoplasie neuroendocrine (NET), è stato recentemente pubblicato sull'autorevole rivista Journal of Immunotherapy of Cancer.
Dal punto di vista della ricerca traslazionale nel campo dell'Immuno-Oncologia, il Prof. Porta si è occupato e si sta occupando della ricerca di potenziali biomarkers di attività dell'immunoterapia, di fattori biologici predittivi di risposta (o non risposta) a questi farmaci, e del possibile ruolo di priming sulla risposta immune da parte di farmaci a bersaglio molecolare, in particolare gli antiangiogenici.
In particolare, l'atenzione della ricerca si sta orientando verso caratteristiche genetico-molecolari (quali: tumor mutational burden, quantità di neo-antigeni, mutazioni tipo in-del, ecc ...), come possibili predittori di efficacia dell'immunoterapia, predittori auspicabilmente da implementare in un prossimol futuro nella pratica clinica Oncologica.
La competenza e la qualità dell'attività di ricerca, clinica e biologica, svolta dal Prof. Porta nel campo dell'Immuno-Oncologia gli è stata riconosciuta dall'invito, da parte della European Society of Medical Oncology (ESMO) a partecipare, in qualità di Tutor, ad una serie di corsi (Preceptorships) dedicati a giovani Oncologi, provenienti soprattutto (ma non esclusivamente) da Paesi meno agiati, dove l'implementazione dell'immunoterapia sta avvenendo più lentamente rispetto ai Paesi più ricchi ed avanzati in campo Sanitario.

Congressi di carattere locale/regionale

1. Incontro: Le leucemie acute. Considerazioni sulle più recenti acquisizioni diagnostiche e terapeutiche, Crema, 14 Marzo 1991
   Relazione: «La clinica nel paziente leucemico»

2. XVIII Riunione di Ematologia ed Oncologia, Pavia, 11-12 Settembre 1997
   Discussione di Casistica Clinica Oncologica: «Porpora Trombotica Trombocitopenica (PTT) in paziente affetta da carcinoma polmonare non a piccole cellule trattata con chemioterapia sistemica non comprendente Mitomicina-C»

3. Workshop e Meeting del Gruppo Cooperativo Italiano per la Porpora Trombotica Trombocitopenica (PTT), Bologna, 18 Giugno 1999
   Relazione: «L'ipotesi autoimmune nella patogenesi della Porpora Trombotica Trombocitopenica»

4. Workshop e Riunione del Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), Parma, 24 Giugno 1999
   Relazione: «Meccanismi di attività e di resistenza al trattamento con interleuchina-2 nel carcinoma renale»

5. Giornata di studio: Il carcinoma del rene, Pavia, 13 Aprile 2000
   Relazione: «Basi biologiche dell'immunoterapia»

6. Giornata di studio: Il mesotelioma, Pavia, 30 Marzo 2001
   Relazione: «Mesotelioma e risposta immune»

7. Convegno: Mesotelioma pleurico: la terapia. Terapie tradizionali e terapie translazionali, Brescia, 16 Ottobre 2001
   Relazione: «Antiangiogenetici»

8. Convegno: Complicanze ematologiche della chemioterapia antitumorale, Crema, 17 Novembre 2001
   Relazione: «Trattamento della piastrinopenia chemioindotta»

9. 1° Sessione di Ricerca e Terapia Translazionale in Oncologia – Primo stage: l'immunoterapia del cancro, Vercelli, 15 Giugno 2002
   Relazione: «Nuove applicazioni dell'immunoterapia del cancro»

10. Giornata Oncologica Lombarda: Il malato Oncologico nella realtà sociale della Lombardia, Milano, 14 Dicembre 2002
    Relazione: «Nuovi farmaci per nuovi bersagli»

11. Convegno: Problemi ematologici cancro-correlati, Monza, 20 Dicembre 2002
    Relazione: «Anemia e piastrinopenia post-trapianto autologo nei tumori solidi»

12. Convegno: Il trattamento medico del dolore oncologico, Pavia, 21 Marzo 2003
    Relazione: «Il punto di vista dell'Oncologo medico»

13. 15° Evento speciale SICO (Società Italiana di Chirurgia Oncologica), Salice Terme, 11-12 Aprile 2003
Relazione: «L'immunoterapia»

14. Convegno: Le mucositi in Oncologia ed Onco-Ematologia, Pavia, 29 Gennaio 2004
Relazione: «Il trattamento delle mucositi da chemioterapia nelle neoplasie solide»

15. Convegno: Metastasi epatiche colo-rettali: attualità diagnostiche e terapeutiche, Pavia, 23 Ottobre 2004
Relazione: «Terapia medica chemioterapica»

16. Convegno: Implicazioni medico-legali in Oncologia Medica, Pavia, 5 Novembre 2004
Relazione: «Criteri standard per l'interpretazione e la valutazione delle ricerche cliniche»

17. Convegno: Aspetti biologici e terapia del carcinoma renale: stato dell'arte e prospettive future, Crema, 17-18 Giugno 2005
Relazione: «Nuovi farmaci»

18. XII Incontro Pavese di Citometria. Terapie oncologiche innovative: il contributo del laboratorio, Pavia, 9 Settembre 2005
Relazione: «Terapie 'bersaglio' nel mesotelioma maligno»

19. Convegno: Terapie orali in Oncologia, Pavia, 7 Ottobre 2005
Relazione: «Temozolomide»

20. 56° Incontro di Aggiornamento Scientifico: Target Therapies in Oncologia, Milano, 27 Ottobre 2006
Relazione: «I nuovi farmaci nel trattamento del carcinoma renale: Sunitinib e Temsirolimus»

21. Corso monografico: Chirurgia d'organo: il fegato. Tecniche alternative alla chirurgia per la terapia dei tumori epatici, Pavia, 27 Novembre 2006
Relazione: «Terapia medica delle metastasi epatiche da carcinoma del colon-retto»

22. Convegno: Fondazione Buzzi Unicem per la ricerca sul Mesotelioma – Un modello di ricerca translazionale grazie all'integrazione pubblico-privato, Casale Monferrato, 8 Giugno 2007
Relazione: «Imatinib e Gemcitabina: i primi risultati clinici»

23. Convegno: Novità nel trattamento delle neoplasie urologiche, Roma, 21 Gennaio 2008
Relazione: «Studi registrativi e in atto»

24. Convegno: Il tumore del rene, Rezzato (BS), 25 Gennaio 2008
Relazione: «Dalle citochine ai nuovi farmaci a bersaglio molecolare»

25. Convegno: Nuovi approcci per la diagnosi ed il trattamento della malattia ossea, Pavia, 16 Maggio 2008
Relazione: «Secondarismi ossei da neoplasie solide»

26. Workshop: Confronti clinici sulle nuove terapie del carcinoma renale, Alba (CN), 7 Luglio 2008
Relazione: «Il trattamento del carcinoma renale: passato, presente e futuro»

27. VIII Convegno della Sezione Regionale Sardegna dell'Associazione Italiana di Oncologia Medica (AIOM), Cagliari, 21-22 Novembre 2008
Relazione: «I tumori del rene: La terapia medica»

28. Convegno: Novità nel trattamento dl carcinoma renale metastatico, Rozzano, 16 Dicembre 2008
Relazione: «I fattori di rischio come indicatori di prognosi»

29. Meet the Professor: carcinoma del rene, Teramo, 13 Maggio 2009
Relazione: «Carcinoma del rene: inquadramento della patologia ed opzioni terapeutiche disponibili»

30. Convegno: 10 risposte a 10 problemi di tutti i giorni, Treviglio, 6 Novembre 2009
Relazione (insieme a G. Cartenì): «Carcinoma del rene: rivoluzione farmacologica»

31. Meeting: Il tumore renale metastatico. Incontro di consenso regionale al trattamento medico, Calatabiano (CT), 28 Maggio 2010
Relazione: «Il contesto clinico: storia ed attualità»

32. Convegno: Il mesotelioma pleurico, Pavia, 1 Ottobre 2010
Relazione: «La terapia medica del mesotelioma: da dove veniamo e dove vogliamo (e dobbiamo) andare»

33. Convegno: La gestione del paziente con carcinoma renale avanzato, Milano, 17 Novembre 2010
Relazione: «Pazopanib nel carcinoma renale avanzato: stato dell'arte e prospettive future»

34. Convegno: Update sul carcinoma renale: nuove evidenze nell'approccio chirurgico ed oncologico, Genova, 1 Dicembre 2010
Relazione: «Esiste un ruolo per le terapie adiuvanti alla chirurgia?»

35. Convegno: Update sul carcinoma renale: nuove evidenze nell'approccio chirurgico ed oncologico, Genova, 1 Dicembre 2010
Relazione: «La terapia della malattia metastatica: la terapia biologica e la strategia sequenziale»

36. 60° Convegno della Società degli Urologi del Nord Italia (SUNI), Bologna, 15-16 Aprile 2011
Tavola rotonda: Facciamo il punto sulla terapia chirurgica delle metastasi da carcinoma renale. Relazione: «La chirurgia e la terapia medica in associazione nel trattamento delle metastasi»

37. Convegno: Carcinoma renale avanzato – l'importanza di una scelta terapeutica appropriata, Modena, 11 Maggio 2011
Relazione: «La tossicità cardiaca associata ai farmaci a bersaglio molecolare»

38. Convegno: attualità e prospettive nella cura del carcinoma renale (POTENT), Genova, 6 Luglio 2011
Discussant del caso clinico presentato dal Dr. Brian Rini

39. Convegno: Aggiornamento su neoplasie della prostata e neoplasie del rene, Piacenza, 7 Luglio 2011
Relazione: «Il trattamento adiuvante e neo-adiuvante del carcinoma renale»

40. Convegno: Aggiornamento su neoplasie della prostata e neoplasie del rene, Piacenza, 7 Luglio 2011
Relazione: «Il trattamento della malattia avanzata: il ruolo dei biomarkers»

41. Expert Meeting ('DOCTEAM'): Dermatologia ed Oncologia – confronto su inibitori delle tirosin chinasi (TKIs) ed eventi avversi: management e prevenzione, Rozzano, 14 Ottobre 2011
Relazione: «Strategia sequenziale nel trattamento del carcinoma renale»

42. Convegno: Il trattamento del carcinoma renale oltre la seconda linea e lo studio 'GOLD', Milano, 24 Ottobre 2011
Relazione: «I meccanismi di resistenza ai farmaci anti-angiogenici FGF-mediati nel carcinoma renale e lo studio GOLD»

43. Convegno: attualità e prospettive nella cura del carcinoma renale (POTENT), Mogliano Veneto, 25 Ottobre 2011
Relazione: «Il carcinoma renale avanzato / metastatico a prognosi buona o intermedia. Quale terapia scegliere?»

44. Convegno: attualità e prospettive nella cura del carcinoma renale (POTENT), Pavia, 31 Ottobre 2011
Relazione: «Il ruolo delle terapie target nel trattamento del carcinoma renale: stato dell'arte»

45. Convegno: attualità e prospettive nella cura del carcinoma renale (POTENT), Roma, 14 Dicembre 2011
Relazione: «Linee guida ed algoritmo terapeutico»

46. Expert Meeting RESET (retrospective analysis of Sorafenib as the first or second target therapy administration in mRCC patients): three years italian experience, Milano, 30 Gennaio 2012
Relazione: «Trattamento sequenziale nel carcinoma renale: l'algoritmo italiano»

47. Convegno: mesotelioma pleurico, Stradella (PV), 31 Marzo 2012
Relazione: «Terapia medica del mesotelioma: risorse correnti e prospettive future»

48. Convegno: l'evoluzione terapeutica in Oncologia Urologica: progressi nel carcinoma del rene e nel carcinoma della prostata, Saronno, 22 Giugno 2012
Relazione: «Nuovi farmaci e prospettive nella terapia del carcinoma renale»

49. Convegno: problemi vecchi e nuovi in Oncologia – nuove molecole antitumorali: caratteristiche biologiche e loro impiego clinico, Pavia, 21 Settembre 2012
Relazione: «Molecole attive e loro sequenziamento nel trattamento del carcinoma renale»

50. Convegno: L'evoluzione della terapia del carcinoma renale, Udine, 10 Dicembre 2012
Relazione: «Algoritmo 2012 del trattamento del carcinoma renale e prospettive future»

51. Convegno: Update sul carcinoma del rene, Macerata, 10 Maggio 2013
Lettura Magistrale: «Algoritmo 2012 del trattamento del carcinoma renale e prospettive future»

52. Convegno: Challenge nel trattamento del mBC HER2+ e del mRCC: la centralità del paziente, Padova, 26-27 Giugno 2013
Relazione: «La preferenza del paziente nel trattamento del mRCC: lo studio PISCES»

53. Convegno: Il razionale dell'inibizione di mTOR nei tumori metastatici, Modena, 24 Ottobre 2013
Relazione: «Inibizione di mTOR nel mRCC: le evidenze scientifiche»

54. Convegno: Guardiamo il paziente con occhi diversi – dalla terapia alla strategia terapeutica, Treviglio, 25 Ottobre 2013
III Sessione: Il rene. Relazione: «Le sequenze terapeutiche: dal nulla al troppo»

55. Convegno: Tumori urogenitali: cosa c'è di nuovo? Busto Arsizio, 26 Ottobre 2013
Relazione: «Carcinoma Renale metastatico»

56. Convegno: Il melanoma metastatico tra efficacia delle terapie e governance, Pavia, 20 Novembre 2013
Relazione: «Efficacia e tossicità delle terapie nel melanoma metastatico»

57. Evento ECM: La pratica clinica nel carcinoma renale avanzato, Milano, 25 Novembre 2013
Coordinamento dell'evento e Relazione: «Il management clinico del paziente con carcinoma del rene avanzato in trattamento: la gestione degli eventi avversi»

58. Convegno congiunto UroLombardia ed Associazione Urologi Lombardi, Milano, 13-14 Dicembre 2013
Relazione: «Tumore del rene: seconda linea di trattamento e successive»

59. Corso: Gestione del paziente Uro-Oncologico – modulo 1: Il paziente con carcinoma renale, Modena, 12 Marzo 2014
Relazione: «Il trattamento di prima linea del carcinoma renale metastatico: quale terapia per quale paziente?»

60. Corso: Focus sul tumore del rene, Su Gologone, Oliena (NU), 21 Giugno 2014
Relazione: «Il trattamento del carcinoma renale metastatico: terapie o strategia terapeutica?»

61. Corso: Gestione del paziente Uro-Oncologico – modulo 2: Il paziente con carcinoma renale, Modena, 28 Gennaio 2015
Relazione: «Il trattamento di prima linea del carcinoma renale»

62. Convegno: Carcinoma renale metastatico: continuità terapeutica e approccio multidisciplinare, Cagliari, 27-28 Marzo 2015
Relazione: «Stato dell'arte e *highlights* congressuali»

63. Convegno: I farmaci a bersaglio molecolare: luci ed ombre, Fano (PU), 17-18 Aprile 2015
Relazione: «Farmaci a bersaglio molecolare nelle neoplasie del rene: farmaci anti-VEGFR»

64. Corso monografico: Stress: dalla fisiopatologia alla clinica, sfatando i miti di una diagnosi 'pigliatutto', Pavia, 25 Maggio 2015
Relazione: «Stress ed Oncologia: dalle basi molecolari al letto del paziente»

65. Convegno: Pratica clinica nel carcinoma renale avanzato, Bologna, 29 Giugno 2015
Relazione: «Update e nuove prospettive terapeutiche nel carcinoma renale avanzato»

66. Convegno: Tumori GU: ricerca e pratica clinica nel 2015 ed oltre, Colombaro di Cortefranca, 5-6 Novembre 2015
Discussant (con G. Pappagallo) della sessione: Tumori del rene

67. Convegno: Appropriatezza ed Etica in Oncologia: curare o prendersi cura? Alzano Lombardo, 27 Novembre 2015
Tavola rotonda (con S. Blotta, G. Procopio, A. Iaculli e A. Ranieri): Tumori del tratto genito-urinario

68. 2° meeting autunnale T.E.R.Rene (Team Emilia Romagna Rene), Castel San Pietro Terme, 23 Settembre 2016
Relazione: «La terapia di prima linea del mRCC: quale futuro per l'immunoterapia?»

69. Convegno: Il tempo dell'immunoterapia nel trattamento dei tumori renali. Stato dell'arte e prospettive future della pratica clinica, Modena, 21 Ottobre 2016
Relazione: «L'immunoterapia nei tumori uro-oncologici: carcinoma renale»

70. Convegno: I tumori GU: ricerca e pratica clinica-organizzativa nel 2016 ed oltre, Colombaro di Cortefranca, 10-11 Novembre 2016
Moderatore (con G. Pappagallo e C. Del Boca) della sessione: Tumori del rene

71. Convegno: Il tempo dell'immunoterapia nel trattamento dei tumori renali. Stato dell'arte e prospettive future della pratica clinica, Pavia, 14 Novembre 2016
Presidenza dell'intero Convegno

72. Convegno: Il tempo dell'immunoterapia nel trattamento dei tumori renali. Stato dell'arte e prospettive future della pratica clinica, Pavia, 14 Novembre 2016
Relazione: «Immunoterapia ed antiangiogenetici nel trattamento del tumore del rene»

73. Convegno: Immunoterapia dei tumori: dalle promesse alle possibilità di cura, Cremona, 16 Maggio 2017
Relazione: «Immunoterapia del carcinoma renale: prospettive per il futuro»

74. Meet the Expert – Immunoterapia nel trattamento del carcinoma polmonare e renale avanzato, Novara, 3 Luglio 2017
Relazione: «Il valore della Overall Survival nell'immunoterapia del RCC»

75. Meet the Expert – Immunoterapia nel trattamento del carcinoma polmonare e renale avanzato, Novara, 3 Luglio 2017
Relazione: «La gestione degli eventi avversi nell'immunoterapia del RCC»

76. Convegno: Immunoterapia dei tumori, Cremona, 22 Maggio 2018
Relazione: «Immunoterapia nei tumori del rene: novità»

77. Convegno: Carcinoma renale avanzato. Nuove strategie terapeutiche, Milano, 26-27 Ottobre 2018
Relazione: «Evoluzione del trattamento di prima linea nel mRCC»

78. 17° Corso Regionale di Formazione in Oncologia del Gruppo Oncologico dell'Italia Meridionale (GOIM), 3° giornata di studio: L'evoluzione delle ricerche nelle neoplasie genito-urinarie, 3 Settembre 2020 (virtual)
Lettura: «Le nuove possibilità terapeutiche nel carcinoma renale»

79. Convegno: Immunoncologia BAT: non solo immunoterapia, 23 Settembre 2020 (virtual)
Relazione: «Il carcinoma renale in stadio IV: quale combinazione e posizione dell'immunoterapia nell'algoritmo di trattamento»

80. Live webinar: La terapia farmacologica del mRCC: hot topics, 12 Ottobre 2020 (virtual)
Moderazione dell'intero webinar (con G. Di Lorenzo)

81. Convegno: Strategie terapeutiche nel carcinoma prostatico, 20 Novembre 2020 (virtual)
Moderazione della Sessione: Indentificazione e gestione del paziente con mCRPC

82. Convegno: Anemia sideropenica e carenza marziale: un approccio multidisciplinare può migliorare la strategia terapeutica, 20 Novembre 2020 (virtual)
Moderazione (con L. Chiovato) della V Sessione

83. 56° Convegno Multidisciplinare di Oncologia e XXXIV Riunione dei Ricercatori del Gruppo Oncologico dell'Italia Meridionale (GOIM): L'Oncologia di precisione: cosa abbiamo imparato, le attese ed il futuro, 26 Febbraio 2021 (virtual)
Moderazione (con N. Borsellino e P. Tagliaferri) della III Sessione: Altri tumori

84. FAD Webinar: Novità nel trattamento del carcinoma renale metastatico, 26 Marzo 2021 (virtual)
Relazione: «Biologia del carcinoma renale: nuove sfide»

Videoconferenza presso il Circolo della Sanità di Bari, 10 Aprile 2021 (virtual)
85. Relazione: «Precision Oncology: come sta cambiando l'Oncologia ed il ruolo dell'Oncologia Medica del Policlinico di Bari»

86. Webinar: Hot topics in mRCC: le opzioni di trattamento in prima linea, 5 Maggio 2021 (virtual)
Moderazione (con G. Cartenì e E. Naglieri) della Sessione: Le opzioni di trattamento in prima linea

87. Webinar: RCC talks live: un possibile trattamento su misura del paziente, 25 Giugno 2021 (virtual)
Moderazione (con E. Naglieri) di tutto il webinar

88. Webinar: L'impatto delle terapie di combinazione nel trattamento del tumore del polmone, del melanoma e del tumore del rene, 6 Luglio 2021 (virtual)
Relazione: «I dati di efficacia relativi alle terapie di combinazione nel trattamento del carcinoma renale»

89. Webinar: Il melanoma cutaneo BRAF mutato: real life e nuove strategie terapeutiche, 21 Settembre 2021 (virtual)
Responsabilità scientifica di tutto il Webinar (con M. Tucci)

90. Webinar: Il melanoma cutaneo BRAF mutato: real life e nuove strategie terapeutiche, 21 Settembre 2021 (virtual)
Moderazione (con G. Palmieri) della I Sessione: Highlights sul trattamento del melanoma

91. Webinar: Tumore del rene e della vescica: la risposta degli esperti, 30 Settembre 2021 (virtual)
Relazione: «Algoritmo terapeutico del carcinoma renale»

92. Webinar: Nuove soluzioni e nuove opportunità nel trattamento del carcinoma renale, 20 Ottobre 2021 (virtual)
Lettura: «Novità nel trattamento del carcinoma renale metastatico»

93. Webinar: Take hand RCC, 8 Novembre 2021 (virtual)
Lezione Magistrale: «Novità nel trattamento del carcinoma renale metastatico»

94. Webinar: Immunoterapia 2021: cosa dobbiamo sapere? 25 Novembre 2021 (virtual)
Lettura magistrale: «Il trattamento del carcinoma renale metastatico»

95. Convegno: Oncologia di precisione: da dove veniamo e dove stiamo andando (tra fughe in avanti e problemi di sostenibilità), Bari, 17-18 Dicembre 2021
Presidenza di tutto il convegno

96. Convegno: Oncologia di precisione: da dove veniamo e dove stiamo andando (tra fughe in avanti e problemi di sostenibilità), Bari, 17-18 Dicembre 2021
Lettura Magistrale: «Trattamento del carcinoma renale: stato dell'arte»

97. Convegno: Oncologia di precisione: da dove veniamo e dove stiamo andando (tra fughe in avanti e problemi di sostenibilità), Bari, 17-18 Dicembre 2021
Moderazione (con L. Vincenti e N. Quaranta) della III Sessione: Neoplasie del Sistema Nervoso Centrale, del distretto cervico-cefalico e NET

98. Convegno: Il carcinoma prostatico: l'alleanza tra Medicina Specialistica e Medicina Generale, Bari, 21 Maggio 2022
Moderazione (con I. Grattagliano, N. Calabrese e I. Martines) della I Sessione: Carcinoma prostatico: dallo screening alle cure simultanee

99. Convegno: Il carcinoma prostatico: l'alleanza tra Medicina Specialistica e Medicina Generale, Bari, 21 Maggio 2022
Moderazione (con I. Grattagliano, N. Calabrese e M. Rizzo) della Tavola Rotonda: Presa in carico multispecialistica

100. Convegno: Top picks in RCC: networking e management del carcinoma renale, Palermo, 9 Giugno 2022
Relazione: «Il trattamento del carcinoma renale metastatico: come scegliere l'approccio terapeutico di prima linea?»

101. Convegno: Nuove soluzioni e nuove opportunità nel trattamento del carcinoma renale. L'esperienza della Puglia, Acquaviva delle Fonti, 30 Giugno 2022
Relazione: «Il trattamento medico del carcinoma renale»

102. Convegno: GEP-NET: attualità e pospettive diagnostico-terapeutiche, Bari, 6 Luglio 2022
Presidenza del Convegno (con S. Leo e I. Lolli)

103. Convegno: GEP-NET: attualità e pospettive diagnostico-terapeutiche, Bari, 6 Luglio 2022
Lettura Magistrale: «Terapia antiangiogenica nel carcinoma renale: cosa può essere traslato alla patologia neuroendocrina?»

104. Congresso: Il carcinoma dell'endometrio – la centralizzazione delle cure nell'era delle tecniche mini-invasive, deep learning, robotica e biologia molecolare, Bari, 24 Settembre 2022
Presidente del Congresso (con E. Cicinelli)

105. Congresso: Il carcinoma dell'endometrio – la centralizzazione delle cure nell'era delle tecniche mini-invasive, deep learning, robotica e biologia molecolare, Bari, 24 Settembre 2022
Moderazione della Sessione: Terapia medica – stato dell'arte e nuove prospettive legate alla valutazione genetica (con M. Marinaccio, E. Naglieri e M. Piombino)

106. Convegno: Nessun dolore, Bari, 2 Dicembre 2022
Presidente del Congresso (con F. Puntillo)

107. Convegno: Nessun dolore, Bari, 2 Dicembre 2022
Relazione: «L'Oncologia oggi: nuove opportunità terapeutiche»

108. Convegno: L'Oncologia Medica oggi: come sta cambiando la gestione del paziente Oncologico tra nuovi farmaci, Medicina di precisione e problemi di sostenibilità), Bari, 27-28 Gennaio 2023
Presidenza di tutto il convegno

109. Convegno: Intelligenza Artificiale in Urologia Oncologica: attualità e prospettive, Rende, 29-30 Marzo 2023
Relazione: «Attualità e work in progress nelle terapie del tumore della prostata: cosa è cambiato e cosa ci aspetta ancora»

Congressi nazionali

110. VI Congresso Nazionale della Società Italiana di Emaferesi (SIdE), Montesilvano Lido (PE), 1-4 Giugno 1993
Relazione: «Terapia di salvataggio nella PTT refrattaria alla Plasma-Exchange: IgG ad alte dosi e Vincristina»

111. Consessus Meeting on Interleukin-2 therapies, Milano, 8 Luglio 1999
Panel discussion

112. 4° Congresso Nazionale del Collegio dei Reumatologi Ospedalieri e 11° Seminario di Aggiornamento in Reumatologia Clinica, Pavia, 14-16 Settembre 2000
Relazione: «TTP e LES»

113. Corso Residenziale dell'Accademia Nazionale di Medicina: Stress ossidativo e cancro: aspetti sperimentali, clinici e nuove prospettive terapeutiche, Cagliari, 25-26 Giugno 2001
Relazione: «Amifostina»

114. Stage in Ematologia: Anemie, neutropenie e piastrinopenie secondarie, Bologna, 21-25 Ottobre 2002
Relazione: «Piastrinopenia e porpora trombotica trombocitopenica»

115. 9th Workshop of the International School of Gerontology and Geriatrics and III Couse of the Italian Society of Geriatric Oncology (SIGERO), Erice, 6-10 Novembre 2002
Relazione: «Prostate cancer»

116. Discutiamone insieme della Società Italiana di Ematologia Sperimentale (SIES): Mobilizzazione di cellule staminali periferiche e attecchimento post-trapianto: aspetti innovativi e problematiche, Firenze, 7 Marzo 2003
Relazione: «Produzione di 8-idrossi-deossiguanosina da progenitori emopoietici circolanti e attecchimento post-trapianto autologo»

117. Convegno Nazionale CNR: Progetti strategici in Oncologia, Rimini, 24-26 Marzo 2003
Relazione del I anno di attività del progetto Strategico SP5: Caratterizzazione biologica e strategie terapeutiche innovative nei tumori solidi

118. VII Congresso Nazionale del Collegio Italiano dei Primari Oncologi Medici Ospedalieri (CIPOMO), Alba, 6-8 Novembre 2003
Relazione: «Trattamento del carcinoma del polmone non microcitoma e ruolo del Docetaxel»

119. Congresso: Nuovi approcci nel trattamento del cancro, Milano, 17-19 Marzo 2004
Relazione: «Oxaliplatino nel trattamento delle neoplasie del distretto cervico-cefalico»

120. XV Congresso Nazionale della Società Italiana di Urologia Oncologica (SIUrO), Giardini Naxos, 3-6 Novembre 2005
Relazione: «Nuovi bersagli per nuove terapie»

121. I Convegno di Aggiornamento CIPOMO (Collegio Italiano dei Primari di Oncologia Medica Ospedalieri) in Oncologia, Roma, 1-2 Febbraio 2007
Relazione: «Le terapie target nel tumore del rene»

122. Convegno: Carcinoma renale metastatico: progressi concreti nella terapia. Meet the Professor Robert Motzer, Milano, Napoli, Roma, 16-18 Maggio 2007
Relazione: «La gestione degli eventi avversi al trattamento con terapie multitarget nel RCC»

123. Congresso: Approcci innovativi al trattamento del carcinoma renale avanzato, Perugia, 15-16 Giugno 2007
Relazione: «Immunoterapia: presente e passato»

124. XI Congresso Nazionale CIPOMO (Collegio Italiano dei Primari di Oncologia Medica Ospedalieri), Siena, 28-30 Giugno 2007
Relazione: «Sorafenib: nuovi dati e linee di sviluppo»

125. Grandangolo 2007: un anno di Oncologia, Genova, 17-18 Dicembre 2007
Relazione: «Rene»

126. Expert Summit 2008: Innovazione in Oncologia, Baveno (VB), 4-6 Aprile 2008
Relazione: «Carcinoma del rene»

127. Corso: Special Ca.Re. (Specialisti in carcinoma renale), edizione 2008, Milano, 22-23 Maggio 2008
Relazione: «Stato dell'arte nel trattamento sistemico del carcinoma renale metastatico»

128. Congresso nazionale del Gruppo Oncologico dell'Italia Meridionale (GOIM) 'L'appropriatezza in Oncologia', Napoli, 22-25 Giugno 2008
IV sessione educazionale: il carcinoma renale. Relazione: «I fattori prognostici nella pratica clinica»

129. Congresso del Centenario della Società Italiana di Urologia (SIU), Roma, 22-28 Settembre 2008
Question Time: La gestione integrata del paziente con carcinoma renale: utopia o realtà.
Relazione: «Dalle citochine alle terapie target»

130. X Congresso Nazionale di Oncologia Medica (AIOM), Verona, 11-14 Ottobre 2008
Relazione: «Sorafenib in patients with advanced renal cell carcinoma (ARCC): results of the European expanded access program (EU-ARCCS)»

131. X Congresso Nazionale di Oncologia Medica (AIOM), Verona, 11-14 Ottobre 2008
Relazione: «Sunitinib in metastatic renal cell carcinoma (mRCC): safety and efficacy data in 458 Italian patients in an expanded-access program (EAP)»

132. X Congresso Nazionale di Oncologia Medica (AIOM), Verona, 11-14 Ottobre 2008

Sessione Educazionale 12: Tossicità emergenti con la targeted therapy.
Relazione: «Altre tossicità da molecole targeted»

133. Corso della Mediterranean School of Oncology: Highlights in the management of kidney cancer, Roma, 7-8 Novembre 2008
Round Table discussion (con G. Cartenì e P. Marchetti): «Activities and toxicities associated with the administration of novel targeted agents in patients with metastatic renal cell carcinoma»

134. XVIII Congresso Nazionale della Società Italiana di Urologia Oncologica (SIUrO), Montesilvano Lido (PE), 26-29 Novembre 2008
Corso: Approcci innovativi al trattamento medico delle neoplasie renali. Relazione: «Il punto sulla terapia: gestione ottimale degli effetti collaterali»

135. Grandangolo 2008: un anno di Oncologia, Genova, 1-2 Dicembre 2008
Relazione: «Rene»

136. Convegno: Le metastasi ossee nei pazienti con tumori solidi: ottimizzazione del trattamento, Pavia, 20 Febbraio 2009
Relazione: «Rene»

137. Clinical Share in Kidney Cancer: esperienze teorico-pratiche, Milano, 20 Aprile 2009
Moderazione dell'intera giornata (con: G. Procopio)

138. Clinical Share in Kidney Cancer: esperienze teorico-pratiche, Milano, 20 Aprile 2009
Relazione: «Strategie terapeutiche nel carcinoma renale»

139. Clinical Share in Kidney Cancer: esperienze teorico-pratiche, Padova, 24 Aprile 2009
Moderazione dell'intera giornata (con: E. Galligioni)

140. Corso: Special Ca.Re. (Specialisti in carcinoma renale), edizione 2009, Milano, 21-22 Maggio 2009
Relazione: «Fattori prognostici e predittivi nel trattamento del carcinoma renale»

141. Expert Summit 2009: Innovazione in Oncologia, Baveno (VB), 1-13 Giugno 2009
Relazione: «Carcinoma del rene»

142. Convegno: Bersagli e terapie mirate in Oncologia. Il contributo del Laboratorio nell'ottimizzazione del trattamento Medico, Pavia, 23-24 Ottobre 2009
Relazione: «Carcinoma del rene»

143. III Corso Annuale Residenziale: nuovi farmaci, nuove indicazioni, nuove tossicità, nuove problematiche, Bergamo, 28 Ottobre 2009
Sessione: Nuovi farmaci: indicazioni e selezione dei pazienti. Relazione: «Inibitori multi target e di mTOR nel carcinoma renale»

144. Corso interattivo: Therapy management nel carcinoma renale, Pollenzo (CN), 6 Novembre 2009
Relazione: «Gestione degli eventi avversi»

145. V Congresso nazionale Approccio globale al paziente Oncologico e I Congresso Nazionale della Società Italiana di Osteoncologia, Forlì, 25-27 Novembre 2009
Sessione: Farmaci orali nel trattamento delle neoplasie. Relazione: «Le target-therapy nel carcinoma renale»

146. Grandangolo 2009: un anno di Oncologia, Genova, 30 Novembre-1 Dicembre 2009
Relazione: «Vescica e rene»

147. Meeting: Renal Study Cooperative Unit (RESCUe), Bagno a Ripoli, 26-27 Marzo 2010
Moderazione dell'intero meeting (con C. Ortega)

148. Meeting: Renal Study Cooperative Unit (RESCUe), Bagno a Ripoli, 26-27 Marzo 2010
Relazione: «Fattori prognostici e predittivi nel trattamento del carcinoma renale: i fattori prognostici molecolari»

149. Meeting: Renal Study Cooperative Unit (RESCUe), Bagno a Ripoli, 26-27 Marzo 2010
Relazione: «E' la Progression-Free Survival un adeguato endpoint per gli studi clinici futuri?»

150. Meeting: Renal Study Cooperative Unit (RESCUe), Bagno a Ripoli, 26-27 Marzo 2010
Relazione: «Quale terapia per quale paziente?»

151. XX Congresso Nazionale della Società Italiana di Urologia Oncologica (SIUrO), Roma, 23-25 Giugno 2010
Sessione: Focus on: Terapia Medica del carcinoma renale metastatico. Relazione: «Trattamento di prima linea: Sunitinib o Bevacizumab + Interferone?»

152. Congresso: RCC – Renal Cancer Conference, Istituto Nazionale Tumori Regina Elena, Roma, 16-17 Settembre 2010
Sessione: Gestione del trattamento con le terapie target. Relazione: «Ottimizzare i benefici clinici delle terapie target: l'importanza del therapy management»

153. 83° Congresso Nazionale della Società Italiana di Urologia (SIU), Milano, 17-20 Ottobre 2010
Lettura: «La terapia sistemica del carcinoma renale»

154. Convegno: dalla prima linea alla strategia terapeutica, Treviglio, 28 Ottobre 2010
Relazione: «Il tumore del rene: dal nulla al dubbio … e poi?»

155. Convegno: dalla Letteratura alla pratica clinica nel carcinoma renale metastatico, Bologna, 29 Ottobre 2010
Relazione: «Quali sequenze terapeutiche sono ipotizzabili?»

156. XII Congresso Nazionale dell'Associazione Italiana di Oncologia Medica (AIOM), Roma, 6-8 Novembre 2010
Relazione: «Nuove tossicità: tossicità cardiovascolari»

157. IV Consensus Conference CIPOMO (Collegio Italiano Primari Oncologia Medica Ospedalieri), Matera, 19-20 Novembre 2010

Relazione: «Il Bevacizumab come terapia di prima linea per il carcinoma renale metastatico»

158. Corso: Carcinoma renale: le nuove sfide nell'era delle terapie biologiche, Serralunga d'Alba (CN), 26-27 Novembre 2010
Relazione: «Fattori predittivi molecolari»

159. Grandangolo 2010: un anno di Oncologia, Genova, 15-16 Dicembre 2010
Relazione: «Rene»

160. Convegno: Quarto Hot topics in Urologia, Genova, 10-11 Febbraio 2011
Relazione: «Trials clinici sulla terapia neoadiuvante ed adiuvante del carcinoma renale: up to date»

161. Convegno: La valutazione della risposta in Oncologia, Candiolo (TO), 11 Febbraio 2011
Discussant della sessione: Tumori del rene

162. Corso: Special Ca.Re. (Specialisti in carcinoma renale), edizione 2011, Firenze, 24-25 Marzo 2011
Discussant della I Sessione plenaria

163. Corso: Special Ca.Re. (Specialisti in carcinoma renale), edizione 2011, Firenze, 24-25 Marzo 2011
Relazione: «Il futuro del trattamento del carcinoma renale»

164. XIX Conferenza Nazionale AIOM sui Tumori Urologici, Torino, 7-9 Aprile 2011
VI Sessione: Le neoplasie renali. Relazione: «Seconda linea e sequenze»

165. Expert Meeting su Health Technology Assessment nel carcinoma renale, Milano, 23 Maggio 2011
Relazione: «L'evidenza clinica di Pazopanib: efficacia, sicurezza, tollerabilità»

166. Convegno: La sostenibilità economica dei farmaci Oncologici, Milano, 5 Ottobre 2011
Relazione: «Le valutazioni economiche: il punto di vista dell'Oncologo»

167. V Corso Annuale Residenziale: Nuovi farmaci, nuove indicazioni, nuove tossicità, nuove problematiche, Bergamo, 10 Ottobre 2011
Sessione: «Nuovi farmaci e gestione del paziente. Relazione: Sunitinib»

168. Congresso: Virus e tumori solidi, Pavia, 20-21 Ottobre 2011
Relazione: «Nuovi farmaci per l'HCC»

169. Convegno: Approccio multidisciplinare al carcinoma renale nell'era delle target therapies, Camogli, 21-22 Ottobre 2011
Relazione: «La terapia di seconda linea del carcinoma renale metastatico»

170. XIII Congresso Nazionale di Oncologia Medica (AIOM), Bologna, 5-7 Novembre 2011
Moderazione della sessione di comunicazioni orali sulle neoplasie Genito-Urinarie (con: R. Passalacqua)

171. XXXVII Congresso Nazionale della Società Italiana Tumori (SIT), Bologna, 24-26 Novembre 2011
Relazione: «L'epatocarcinoma: terapia a bersaglio molecolare»

172. Grandangolo 2011: un anno di Oncologia, Genova, 15-16 Dicembre 2011
Relazione: «Rene»

173. Corso residenziale della Mediterranean School of Oncology (MSO) e del Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO): Highlights in advanced renal cell carcinoma management, Roma, 24 Febbraio 2012
Direzione Scientifica dell'intero corso

174. Terza Edizione del corso residenziale della Società Italiana di Urologia Oncologica (SIUrO): Core Curriculum Uro-Oncologico, Bertinoro (BO), 8-10 Marzo 2012
Relazione: «Il trattamento della malattia metastatica ed il follow-up»

175. Special CaRe (SPECIAListi in CArcinoma Renale), edizione 2012, Firenze, 29-30 Marzo 2012
Discussant: Highlights dall'ASCO GU

176. X Seminario ITMO: Neoplasie a bassa incidenza, Monza, 7 Maggio 2012
Relazione: «Tumori rari del rene: trattamento per stadio ed istologia»

177. Meeting: Sharing experiences in RCC, Venezia, 25-26 Maggio 2012
Relazione: «Stato dell'arte nel trattamento del carcinoma renale metastatico … al Maggio 2012 (pre-ASCO)»

178. XXII Congresso Nazionale della Società Italiana di Urologia Oncologica (SIUrO), Bologna, 13-15 Giugno 2012
Moderazione (con F. Bergamaschi, G. Frezza e B. Fossa-Jereczeck) della Sessione di Comunicazioni orali su: Prognosi/qualità della vita/sorveglianza attiva

179. XXII Congresso Nazionale della Società Italiana di Urologia Oncologica (SIUrO), Bologna, 13-15 Giugno 2012
Relazione: «Trattamento di seconda linea del carcinoma renale avanzato»

180. Convegno: Il carcinoma renale a 360°: approccio multidisciplinare, Moltrasio (CO), 12-13 Ottobre 2012
Presidenza del Convegno (insieme a Sandro Barni)

181. Convegno: Il carcinoma renale a 360°: approccio multidisciplinare, Moltrasio (CO), 12-13 Ottobre 2012
Relazione: «Meccanismi di resistenza ai farmaci a bersaglio molecolare»

182. XIV Congresso Nazionale dell'Associazione Italiana di Oncologia Medica (AIOM), Roma, 27-29 Ottobre 2012
Discussant: Comunicazioni orali in Oncologia Genito-Urinaria

183. Corso residenziale della Mediterranean School of Oncology (MSO) e del Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO): Highlights in the management of advanced renal cell carcinoma, Roma, 22 Febbraio 2013
Relazione: «How to select among available options for the treatment of advanced RCC: favorable and intermediate risk patients»

184. Corso della Società Italiana di Urologia Oncologica (SIUrO): Oncoforum Urology, Napoli, 26 Febbraio 2013
Relazione: «Novità nella terapia medica del RCC»

185. Corso di Management in Oncologia, Mantova, 24-25 Maggio 2013
Relazione: «Gestione personalizzata delle nuove terapie biologiche orali»

186. XXIII Congresso Nazionale della Società Italiana di Urologia Oncologica (SIUrO), Firenze, 9-11 Giugno 2013
Sessione: Le possibili scelte terapeutiche della prima e seconda linea del carcinoma renale avanzato. Relazione: «Prima linea di trattamento: tra scelta del medico e scelta del paziente – in favore della scelta del paziente»

187. XXIII Congresso Nazionale della Società Italiana di Urologia Oncologica (SIUrO), Firenze, 9-11 Giugno 2013
Corso ECM: Shoot the Pathologist – novità in uropatologia e relativo impatto clinico (con E. Bollito, R. Montironi, M. Fiorentino, A. Lopez Beltran, G. Martignoni, F. Porpiglia, M.R. Raspollini, M. Tucci). Relazione: «Rene – impatto clinico-terapeutico»

188. 15° Congresso Nazionale del Gruppo Oncologico dell'Italia Meridionale (GOIM): Il team multidisciplinare nella Medicina Oncologica, Napoli, 17-19 Giugno 2013
Relazione: «Le nuove terapie mediche nel carcinoma renale: ASCO 2013»

189. Scuola di Uro-Oncologia – Il tumore del rene, Roma, 12-13 Luglio 2013
Relazione: «Platinum Series (best papers on renal cancer) – in Oncologia»

190. Scuola di Uro-Oncologia – Il tumore del rene, Roma, 12-13 Luglio 2013
Moderazione della sessione: Le domande degli Oncologi agli Urologi (con G. Cartenì)

191. Scuola di Uro-Oncologia – Il tumore del rene, Roma, 12-13 Luglio 2013
Sessione: Le domande degli Urologi agli Oncologi. Relazione: «Terapia neo-adiuvante ed adiuvante»

192. Scuola di Uro-Oncologia – Il tumore del rene, Roma, 12-13 Luglio 2013
Sessione: Le domande degli Urologi agli Oncologi. Relazione: «Oltre la prima linea»

193. Scuola di Uro-Oncologia – Il tumore del rene, Roma, 12-13 Luglio 2013
Sessione: Le domande degli Urologi agli Oncologi. Relazione: «Follow-up e valutazione della risposta»

194. Quarta Edizione del corso residenziale della Società Italiana di Urologia Oncologica (SIUrO): Core Curriculum Uro-Oncologico, Bertinoro (BO), 12-14 Settembre 2013
Relazione: «Rene – trattamento della malattia non metastatica»

195. Quarta Edizione del corso residenziale della Società Italiana di Urologia Oncologica (SIUrO): Core Curriculum Uro-Oncologico, Bertinoro (BO), 12-14 Settembre 2013
Relazione: «Rene – trattamento della malattia metastatica»

196. Quarta Edizione del corso residenziale della Società Italiana di Urologia Oncologica (SIUrO): Core Curriculum Uro-Oncologico, Bertinoro (BO), 12-14 Settembre 2013
Relazione: «Rene – Biomarcatori predittivi, valutazione della risposta, attività, tollerabilità e scelta terapeutica»

197. Quarta Edizione del corso residenziale della Società Italiana di Urologia Oncologica (SIUrO): Core Curriculum Uro-Oncologico, Bertinoro (BO), 12-14 Settembre 2013
Relazione: «Pene – Chirurgia dei linfonodi, chemioterapia, sexual sparing»

198. Convegno: Update in Genitourinary tumors, Milano, 17 Settembre 2013
Moderazione della sessione: Sessione interattiva con casi clinici

199. 54° Congresso Nazionale della Società Italiana di Nefrologia (SIN), Firenze, 25-28 Settembre 2013
Joint Symposium SIN/AIOM: Clinical decisions in ESRD patients with cancer. Relazione: «Kidney transplantation in patients with previous cancer» (con S. Sandrini)

200. XV Congresso Nazionale dell'Associazione Italiana di Oncologia Medica (AIOM), Milano, 11-13 Ottobre 2013
Sessione Educazionale: Tumori Genito-Urinari. Relazione: «La seconda linea nel carcinoma renale»

201. Convegno: Il trattamento del carcinoma renale metastatico, Santa Margherita Ligure, 18-19 Ottobre 2013
Relazione: «Una poltrona per due» (botta e risposta con G. Pappagallo)

202. Corso della Società Italiana di Urologia Oncologica (SIUrO): Oncoforum Urology, Milano, 5 Novembre 2013
Relazione: «Carcinoma renale – what's in, what's new»

203. Hot topics in Oncologia Urologica, Bergamo, 16 Novembre 2013
Lettura magistrale: «Carcinoma renale, strategie per il futuro»

204. VII Meeting: Il trattamento del carcinoma renale metastatico: risultati clinici, evidenze e linee guida, Bologna, 28 Novembre 2013
Relazione: «Il trattamento di prima linea: pro Sunitinib»

205. Convegno: Terapie innovative in Oncologia: farmaci a bersaglio molecolare e farmaci da nano-biotecnologie, Castelfranco Veneto (TV), 14-15 Febbraio 2014
Relazione: «Carcinoma renale – algoritmo decisionale nella scelta della terapia»

206. Meeting: Reset Study & Castration-Resistant Prostate Cancer, Mestre, 19 Febbraio 2014
Relazione: «Sorafenib: il pulcino è veramente nero?»

207. Special Care (SPECIAListi in CArcinoma Renale) 2014, VIII edizione, Firenze, 20-21 Febbraio 2014
Relazione: «Novità nel RCC nell'ultimo anno»

208. Special Care (SPECIAListi in CArcinoma Renale) 2014, VIII edizione, Firenze, 20-21 Febbraio 2014
Tavola rotonda (con S. Bracarda, G. Procopio, C.N. Sternberg e R. Sabbatini): Massimizzare il trattamento di seconda linea

209. Special Care (SPECIAListi in CArcinoma Renale) 2014, VIII edizione, Firenze, 20-21 Febbraio 2014
Tutor percorsi interattivi Med-to-Med

210. Presentazione delle Linee Guida della Associazione Italiana di Oncologia Medica (AIOM) sui tumori del rene: Condividere per aderire, Roma, 2 Aprile 2014
Relazione: «Prospettive future: non clear cell RCC ed immunoterapia»

211. XXI Riunione Nazionale ITMO (Italian Trials in Medical Oncology): Evoluzione delle conoscenze, Monza, 8-9 Maggio 2014
Relazione: «Nuovi farmaci: corretto uso e sostenibilità»

212. XXIV Congresso Nazionale SIUrO (Società Italiana di Urologia Oncologica), Corso interattivo multidisciplinare: Qualità dell'evidenza e pratica clinica nei tumori del rene, Bologna, 22 Giugno 2014
Moderazione (con T. Prayer-Galetti) dell'intero corso

213. Scuola di Uro-Oncologia – Il tumore del rene, Roma, 19 Settembre 2014
Moderazione (con G. Cartenì) della sessione: Controversie Chirurgiche

214. Scuola di Uro-Oncologia – Il tumore del rene, Roma, 19 Settembre 2014
Sessione: Controversie Oncologiche. Relazione: «Oltre la prima linea»

215. Scuola di Uro-Oncologia – Il tumore del rene, Roma, 19 Settembre 2014
Tavola Rotonda (con M. Battaglia e B. Corcioni): Valutazione della risposta

216. Scuola di Uro-Oncologia – Il tumore del rene, Roma, 19 Settembre 2014
Moderazione (con M. Battaglia) della sessione: Follow-up: a chi compete?

217. 87° Congresso Nazionale della Società Italiana di Urologia (SIU), Corso multidiscplinare: Cosa c'è di nuovo in Oncologia renale?, Firenze, 29 Settembre 2014
Relazione: «Cosa c'è di nuovo nel trattamento della malattia avanzata/metastatica?»

218. 87° Congresso Nazionale della Società Italiana di Urologia (SIU), Tavola rotonda: La qualità in Uro-Oncologia: oltre l'autoreferenzialità, Firenze, 29 Settembre 2014
Moderazione della sessione

219. XVI Congresso Nazionale dell'Associazione Italiana di Oncologia Medica (AIOM), Roma, 24-26 Ottobre 2014
Sessione Educazionale: AIOM incontra SIN. Relazione: «Pazienti neoplastici e trapianto di rene: il punto di vista dell'Oncologo»

220. 115° Congresso Nazionale della Società Italiana di Medicina Interna (SIMI), Roma, 25-27 Ottobre 2014
Poster discussant (per quanto attiene ai posters di argomento Oncologico)

221. Grandangolo 2014: un anno di Oncologia, Genova, 1-2 Dicembre 2014
Relazione: «Rene»

222. Special Care (SPECIAListi in CArcinoma Renale), edizione 2015, Roma, 22-23 Gennaio 2015
Relazione: «Nuove prospettive nel carcinoma renale metastatico»

223. AIOM post ASCO GU, Milano, 27 Marzo 2015
Relazione: «Cancro del rene: *highlights*»

224. VII Congresso del Gruppo Oncologico Chirurgico Cooperativo Italiano (GOCCI): Terapie mediche innovative in Oncologia, Firenze, 7 e 8 Maggio 2015
Relazione: «Farmaci a bersaglio molecolare nella terapia del carcinoma renale»

225. Hot topics in Oncologia Urologica 2015, Bergamo, 9 Maggio 2015
Moderazione (con G. Procopio) della Sessione: Tumore renale

226. XXV Congresso Nazionale SIUrO (Società Italiana di Urologia Oncologica), Corso interattivo multidisciplinare: Il trattamento delle metastasi ossee da tumori urologici, Roma, 22 Giugno 2015
Relazione: «Le metastasi ossee non da prostata – terapia sistemica ed associazioni: quando e perché»

227. Convegno: Genitourinary tumors – update and clinical trials, Milano, 17 Settembre 2015
Sessione: News on the corner. Relazione: «Immunotherapy»

228. Grandangolo 2015: un anno di Oncologia, Genova, 30 Novembre-1 Dicembre 2015
Relazione: «Rene»

229. RCC Conference: recoding, conversation, contents, Napoli, 15-16 Gennaio 2016
Relazione: «Pazopanib: le opportunità future»

230. RCC Conference: recoding, conversation, contents, Napoli, 15-16 Gennaio 2016
Talk show (con S. Bracarda, G. Cartenì e C. Ortega): riflessioni sulla seconda linea di trattamento

231. Corso: Gestione del paziente Uro-Oncologico, Modena, 20 Gennaio 2016
Relazione: «Il trattamento di prima linea del carcinoma renale metastatico: quale futuro per l'immunoterapia?»

232. Convegno AIOM post-ASCO GU, Milano, 22 Gennaio 2016
Moderazione (con F. Calabrò) della sessione: Rene II (malattia metastatica)

233. Convegno AIOM post-ASCO GU, Milano, 22 Gennaio 2016
Sessione: Rene II (malattia metastatica). Relazione: «Come cambia la pratica

clinica?»

234. 51° Convegno multidisciplinare di Oncologia: L'immunoterapia dei tumori solidi – quale integrazione con i trattamenti convenzionali? e XXIX Riunione dei Ricercatori del Gruppo Oncologico dell'Italia Meridionale (GOIM), Bari, 26 Febbraio 2016
Relazione: «Immunoterapia e target therapy»

235. VIII Congresso del Gruppo Oncologico Chirurgico Cooperativo Italiano (GOCCI): Terapie mediche innovative in Oncologia, Firenze, 12 e 13 Maggio 2016
Relazione: «Farmaci a bersaglio molecolare nella terapia del carcinoma renale»

236. XXVI Congresso Nazionale SIUrO (Società Italiana di Urologia Oncologica), Corso interattivo multidisciplinare: Immunoterapia oggi, Firenze, 9 Giugno 2016
Relazione: «Lettura critica sui dati dell'immunoterapia nel rene (Checkmate 025 e studi ongoing in prima linea)»

237. Convegno: Trattamento del mCRPC: identificazione del paziente ed outcomes del pecorso di cura, Milano, 6 Luglio 2016
Relazione: «Definizione di criteri nella strategia terapeutica del mCRPC: il paziente ideale candidabile a trattamento con Abiraterone»

238. Convegno: Advances in genitourinary tumors: evidence and trials in progress, Milano, 15 Settembre 2016
Sessione: Treatment strategies for renal cell carcinoma and prostate cancer. Relazione: «Open issues»

239. iGrandangolo: focus in Immuno-Oncologia, Roma, 20-21 Settembre 2016
Moderazione (con G. Procopio) della sessione: dalle immunoterapie all'immunoterapia – il carcinoma del rene

240. iGrandangolo: focus in Immuno-Oncologia, Roma, 20-21 Settembre 2016
Sessione: dalle immunoterapie all'immunoterapia – il carcinoma del rene. Relazione: «Take home messages»

241. 57° Congresso Nazionale della Società Italiana di Nefrologia (SIN), Milano, 12-15 Ottobre 2016
Tavola Rotonda: Onconefrologia. Relazione: diagnosi e terapia della lisi tumorale

242. 89° Congresso Nazionale della Società Italiana di Urologia (SIU), Venezia, 15-18 Ottobre 2016
Corso: Trattamento multidisciplinate delle neoplasie renali: dal caso clinico alle raccomandazioni – Tavola Rotonda con: A. Volpe, A. Antonelli, N. Longo, L. Masieri, R. Montironi, A. Veltri

243. 89° Congresso Nazionale della Società Italiana di Urologia (SIU), Venezia, 15-18 Ottobre 2016
Sessione: Carcinoma del rene con trombosi cavale. Relazione: «Terapia neoadiuvante o a progressione sistemica?»

244. XVIII Congresso Nazionale dell'Associazione Italiana di Oncologia Medica (AIOM), Roma, 28-30 Ottobre 2016
Sessione Educazionale Tumori dell'Apparato Genito-Urinario. Relazione: «Cosa c'è dietro l'angolo?»

245. Grandangolo 2016: un anno di Oncologia, Genova, 15-16 Dicembre 2016
Relazione: «Rene»

246. AIOM post ASCO GU, Milano, 3 Febbraio 2017
Relazione: «Carcinoma renale metastatico: cambia la pratica clinica?»

247. AIOM incontra SIN, Milano, 9 Marzo 2017
Relazione: «Take home messages»

248. Corso: Gestione del paziente Uro-Oncologico, Modena, 24 Marzo 2017
Relazione: «mRCC: a glowing glance into the crystal ball»

249. Convegno promosso dalla Federazione Italiana delle Associazioni di Volontariato in Oncologia (FAVO): Il carcinoma renale, dalla diagnosi precoce alla definizione del migliore approccio integrato. Pazienti, clinici, Istituzioni e accademici a confronto, Roma (Senato della Repubblica), 29 Marzo 2017
Relazione: «Il carcinoma renale: stato dell'arte e nuove modalità di approccio clinico»

250. Expert Symposium sul carcinoma prostatico 'CA.P. days', Baveno (VB), 7-8 Aprile 2017
Moderazione della sessione: Restituzione dei lavori dei Workshop e condivisione dei risultati (con E.M. Ruggeri, G.N. Conti e S.M. Magrini)

251. Conferenza Stampa in Senato per la Giornata Mondiale contro il tumore del rene (con: M. Ripa di Meana, E. Iannelli, M. Gallucci, G. Procopio, F. Cognetti), Roma, 22 Giugno 2017

252. Corso Residenziale: Masterclass su targeted therapies in Oncologia, Milano, 26-27 Giugno 2017
Relazione: «Carcinoma renale»

253. 58° Congresso Nazionale della Società Italiana di Nefrologia (SIN), Rimini, 4-7 Ottobre 2017
Relazione (con M. Foramitti): «Nefrotossicità dei farmaci a bersaglio molecolare: antiangiogenici, inibitori di EGFR, HER2, e bone-targeting agents»

254. 58° Congresso Nazionale della Società Italiana di Nefrologia (SIN), Rimini, 4-7 Ottobre 2017
Moderazione (con L. Romanini) della Tavola Rotonda SIN, AIOM; SIRM: Utilizzo dei mezzi di contrasto nel paziente Oncologico

255. 90° Congresso Nazionale della Società Italiana di Urologia (SIU), Napoli, 7-10 Ottobre 2017
Discussant (con G. Martignoni, A. Volpe e F. Stacul) della Sessione: Il tumore del rene nel giovane adulto

256. 90° Congresso Nazionale della Società Italiana di Urologia (SIU), Napoli, 7-10 Ottobre 2017
Discussant (con G. Martignoni e F. Stacul) del Corso tematico di Oncologia renale Trattamento multidisciplinare delle neoplasie renali: dal caso clinico alle raccomandazioni

257. Corso: Landscapes in Immuno-Oncologia, Milano, 13 Ottobre 2017
Relazione: «Le certezze: carcinoma renale»

258. I Master sul carcinoma renale, Modena, 17-18 Ottobre 2017
Relazione: «Uno sguardo al futuro»

259. XIX Congresso dell'Associazione Italiana di Oncologia Medica (AIOM), Roma, 27-29 Ottobre 2017
Incontro con l'esperto (con L. Cosmai): Gestire i trattamenti nel paziente con insufficienza renale

260. Convegno: Le neoplasie Urologiche, Brescia, 9 Novembre 2017
Relazione: «Carcinoma renale – L'uso dei TKIs: quale ruolo?»

261. Convegno: Immunoterapia dei tumori: prospettive cliniche, ricadute organizzative, sostenibilità, Udine, 23 Novembre 2017
Relazione: «Tumori urogenitali»

262. Corso Residenziale di Accademia Nazionale di Medicina: Farmaci Oncologici: sviluppo pre-clinico, clinico, sostenibilità ed oltre (I Edizione), Genova, 27 Novembre 2017
Direzione del Corso

263. Convegno: Targets molecolari, immunoterapia e Precision Medicine, Roma, 16 Febbraio 2018
Relazione: «Terapia personalizzata nel carcinoma renale»

264. Convegno AIOM post-ASCO GU, Milano, 2 Marzo 2018
Keynote Lecture: «Immunotherapy in GU cancers: where are we, and where are we going?»

265. Corso Residenziale: Landscapes in Oncologia – la Precision Medicine tra targeted therapy ed immunoterapia, Milano, 24-25 Settembre 2018
Relazione: «Il carcinoma renale»

266. 7th Controversies in Genitourinary tumors, Milano, 4 Ottobre 2018
Relazione: «Hot topics in RCC: targeted therapies»

267. XX Congresso dell'Associazione Italiana di Oncologia Medica (AIOM), Roma, 16-18 Novembre 2018
Moderazione (con G. Cartenì) della prima parte della Sessione sulle neoplasie Genito-Urinarie

268. XX Congresso dell'Associazione Italiana di Oncologia Medica (AIOM), Roma, 16-18 Novembre 2018

Relazione: «Novità nel trattamento delle neoplasie renali»

269. Grandangolo 2018: un anno di Oncologia, Genova, 13-15 Dicembre 2018
Relazione: «Carcinoma del rene»

270. AIOM post ASCO GU, Milano, 2 Marzo 2019
Relazione: «Carcinoma renale metastatico: come cambia la pratica clinica?»

271. II SIU (Società Italiana di Urologia) updates on ASCO GU, Roma, 16 Maggio 2019
Relazione: «Update on systemic treatment of metastatic RCC»

272. V Riunione Nazionale del Gruppo Meet-Uro, Milano, 23-24 Maggio 2019
Relazione: «Renal carcinoma: hot topics in advanced disease»

273. Congresso: Multidisciplinarietà in Uro-Oncologia: quale ruolo nell'epoca dell'Oncologia di precisione e dell'immunoterapia, Aosta, 15-16 Novembre 2019
Sessione: Tumori del rene; Relazione: «Evoluzione del trattamento medico di prima linea»

274. Corso Residenziale di Accademia Nazionale di Medicina: Farmaci Oncologici: sviluppo pre-clinico, clinico, sostenibilità ed oltre (II Edizione), Genova, 18 Novembre 2019
Direzione del Corso

275. Convegno: Le neoplasie genito-urinarie tra pratica clinica ed innovazione, Brescia, 4 Dicembre 2019
Moderazione (con R. Sabbatini) della sessione: Rene – quale ruolo per le terapie locali: dalle small renal masses alla metastasectomia

276. Grandangolo 2019: un anno di Oncologia, Genova, 18-20 Dicembre 2022
Relazione: «Carcinoma del rene»

277. III Società Italiana di Urologia (SIU) updates on ASCO GU and ASCO 2020, 19 Giugno 2020 (virtual)
Relazione: «Il tumore del rene»

278. Corso Webinar "La prevenzione del danno renale acuto da procedure TC con mezzo di contrasto in pazienti con cancro", 13 Luglio 2020 (virtual)
Relazione: «L'Oncologo ed i suoi needs»

279. XXX Congresso Nazionale della Società Italiana di Urologia Oncologica (SIUrO), 26-29 Settembre 2020 (virtual)
Relazione: «Quali dati di efficacia e tossicità sui farmaci immunologici per il trattamento dei tumori renali?»

280. XXII Congresso Nazionale di Oncologia Medica (AIOM), 30 Ottobre/1 Novembre 2020 (virtual)
Relazione: «Controversial – Pro e contro: iper-progressors con immunoterapia, mito o realtà? Mito»

281. 22° Congresso Nazionale del Gruppo Oncologico dell'Italia Meridionale (GOIM): La cura dei tumori: attualità e prospettive, 13-15 Ottobre 2020 (virtual)
Relazione: «Novità nel trattamento delle neoplasie renali»

282. IV Convegno Nazionale della Società Italiana di Farmacia Clinica e Terapia (SIFACT): Pillole virtuali in Oncologia: tra real practice a sfide future, 22, 24, 29 e 31 Ottobre 2020 (virtual)
1° Modulo – Area Precision Medicine (22 Ottobre 2020); Relazione: «Target therapies: news from ASCO»

283. L'insolito Grandangolo in Oncologia, Genova, 11-17 Dicembre 2020 (virtual)
Relazione: «Carcinoma del rene e vescica»

284. Congresso: La Medicina di precisione: tra targeted therapy ed immunoterapia, 3 Settembre 2021 (virtual)
Moderazione della Sessione I: Nuovi spazi all'immunoterapia – in quali neoplasie?

285. Congresso: La Medicina di precisione: tra targeted therapy ed immunoterapia, 3 Settembre 2021 (virtual)
Relazione «Il carcinoma renale. Siamo di fronte ad un bivio: target therapy o immunoterapia?»

286. Nephrology Weekly Webinar Series della Società Italiana di Nefrologia (SIN) – 2° Webinar di Onco-Nefrologia: Nefrotossicità delle terapie oncologiche e gestione dei protocolli terapeutici nella popolazione nefrologica, 27 Aprile 2021 (virtual)
Relazione «Chemioterapia citotossica: il punto di vista dell'Oncologo»

287. Nephrology Weekly Webinar Series della Società Italiana di Nefrologia (SIN) – 3° Webinar di Onco-Nefrologia: La gestione multidisciplinare del paziente oncologico: neoplasia renale, glomerulopatie e screening oncologico, 16 Marzo 2021 (virtual)
Moderazione (con L. Cosmai) di tutto il Webinar

288. Nephrology Weekly Webinar Series della Società Italiana di Nefrologia (SIN) – 3° Webinar di Onco-Nefrologia: La gestione multidisciplinare del paziente oncologico: neoplasia renale, glomerulopatie e screening oncologico, 16 Marzo 2021 (virtual)
Relazione: «Lo screening oncologico nel paziente con glomerulopatia secondaria»

289. Digital Event: Landscapes in Oncologia 2021 – Precision Medicine: targeted therapy e immunoterapia, 15, 17, 21 e 22 Giugno 2021 (virtual)
Moderazione (con P. Zucali) della Sessione: Tumori genito-urinari

290. 20° Congresso Nazionale dell'Associazione Italiana di Endourologia (IEA), Bari, 6-8 Settembre 2021
Lettura: «Medical treatment of renal carcinoma: what's new?»

291. Convegno: Nuove strategie in immunoncologia: quali evidenze, Bologna, 1 Ottobre 2021
Relazione: «Il carcinoma renale»

292. 62° Congresso Nazionale della Società Italiana di Nefrologia (SIN), Rimini, 6-9 Ottobre 2021

Moderazione (con L. Cosmai) del Workshop di Nefro-Oncologia Anemia, insufficienza renale e cancro. Chi beneficia dell'uso dell'eritropietina: la neoplasia o il paziente?

293. Evento ibrido (in presenza + Webinar): Decameroom: focus group on prostate cancer, Bari, 29 Ottobre 2021
Coordinazione del gruppo di Bari (con P. Ditonno)

294. VII Congresso Nazionale del Gruppo Italiano di Oncologia Geriatrica (GIOGer) e X Convegno Oncologia Geriatrica Salentina, 3-4 Dicembre 2021 (virtual)
Presidenza della IV sessione: Hot topics

295. V Congresso Osteoporosi e alterazioni del metabolismo osseo nella malattia renale cronica, Padova, 6-7 Aprile 2022
Membro del Comitato Scientifico del Congresso (con M.C. Mereu, M. Ravera, L. Cosmai, M. Foramitti, S. Giannini, M. Gallieni, F. Locatelli, A. Aghi e C. Politi)

296. V Congresso Osteoporosi e alterazioni del metabolismo osseo nella malattia renale cronica, Padova, 6-7 Aprile 2022
Moderatore (con M. Gallieni) della Sessione III: Osso, rene e cancro

297. Masterclass in Uro-Oncologia della Società Italiana di Urologia (SIU): tumore del parenchima renale, 9 Giugno 2022 (virtual)
Panel Discussion (con A. Antonelli, R. Campi, A. Veltri, A. Volpe, F. Alongi)

298. Webinar: I tumori renali e della vescica, 16 Giugno 2022
Relazione: «Terapia medica del paziente con tumore renale»

299. VI Convegno Nazionale della Società Italiana di Farmacia Clinica e Terapia (SIFACT): Presente e futuro della farmacia clinica oncologica tra innovazioni terapeutiche e nuovi modelli organizzativi, Bari, 17-18 Giugno 2022
Relazione: «Nuove combo-therapies nei tumori solidi»

300. Corso COMU (Collegio degli Oncologi Medici Universitari) e confronto con i Giornalisti, Palermo, 18-19 Novembre 2022
Sessione: News in Oncology: l'Oncologo incontra il giornalista
Relazione: «Neoplasie genito-urinarie»

301. Corso ibrido: Check-point inhibitors – focus on combinations, Milano, 28 Novembre 2022
Relazione: «Scelta delle migliori opzioni terapeutiche proponibili in base a caratteristiche del paziente, modalità di presentazione della malattia ed evidenza scientifiche disponibili»

302. Webinar della Società Italiana di Urologia Oncologica (SIUrO): Tutto quello che avreste voluto sapere su … un approccio ragionato al carcinoma renale metastatico, 14 Dicembre 2022
Relazione: «L'esempio del tumore del rene»

303. Webinar della Società Italiana di Urologia (SIU): Approccio multidisciplinare al trattamento della neoplasia renale, 14 Dicembre 2022
Relazione: «Terapia peri-operatoria: update e linee di ricerca»

304. Grandangolo 2022: un anno di Oncologia, Genova, 15-16 Dicembre 2022
Relazione: «Carcinoma del rene»

305. Convegno: News in GU Oncology 2023, Bari, 10-11 Marzo 2023
Presidenza di tutto il convegno (con S. Cinieri e M. Tucci)

306. Convegno: News in GU Oncology 2023, Bari, 10-11 Marzo 2023
Moderazione della Sessione: Carcinoma Renale (con C. Ortega)

307. Webinar della Società Italiana di Urologia Oncologica (SIUrO): ReLive: Genitourinary Cancers Symposium, 23 Marzo 2023
Sessione: Renal cancer
Relazione: «Highlights»

308. XXII Congresso della Società Urologia Nuova (SUN), Firenze, 31 Marzo-1 Aprile 2023
Sessione: Oncologia nel carcinoma renale
Moderazione della sessione (con G. Carrieri, V. Ficarra & B. Rocco)

309. Webinar: Renal Cancer Think Tank 2023, 28 Aprile 2023 (virtual)
Relazione: «Il trattamento adiuvante del tumore del rene»

310. 2023 Cancer Research: from Orlando to Palermo – news from AACR Annual Meeting, Palermo, 5-6 Maggio 2023
Sessione: Le tematiche emergenti: scienze della popolazione e delle disparità
Moderazione della sessione (con R. Berardi)

311. Convegno: Young Onco-GU 2023, Verbania, 18-19 Maggio 2023
Sessione: Neoplasie renali avanzate e metastatiche
Moderazione della sessione (con G. Procopio e A. Volpe)

312. Convegno: Onconephrology – the new challenge for Nephrologists and Oncologists, Torino, 25-26 Maggio 2023
Lettura Magistrale: «Update on the antineoplastic treatment of patients affected by renal cell carcinoma»

313. Webinar dell'Associazione Italiana Radioterapia ed Oncologia Clinica (AIRO): La gestione integrata dei pazienti affetti da tumore renale oligometastatico, 26 Maggio 2023 (virtual)
Relazione: «Quali novità nella terapia sistemica di prima linea per il tumore renale?»

Congressi internazionali

314. 1st Italy-U.S.A. Conference on Malignant Mesothelioma and other Asbestos-related Neoplasms, Belgirate (Novara, Italy), May 29th-30th, 1997
Panel Discussion: What is the optimal therapy for mesothelioma? Could molecular and immunologic approaches lead to new therapies to mesothelioma?

315. 6th World Congress on Advances in Oncology and 4th International Symposium on Molecular Medicine, Hersonissos, Creta (Grecia), 18-20 Ottobre 2001

Relazione: «Eosinophils and macrophages in advanced Renal Cell Carcinoma. Why do these blood cells predict a poor outcome of IL-2-based immunotherapy?»

316. 7th World Congress on Advances in Oncology and 5th International Symposium on Molecular Medicine, Hersonissos, Creta (Grecia), 10-12 Ottobre 2002
Relazione: «Anti-angiogenetic drugs and malignant mesothelioma: an act of faith or a rational consequence of our increasing knowledge?»

317. The 20th IATMO (International Academy of Tumor Marker in Oncology) Conference, Siena (Italy), 21-25 Giugno 2003
Relazione: «Circulating Interleukin-6 (IL-6): is it a marker for hepatocellular carcinoma?»

318. VII Meeting of the International Mesothelioma Interest Group (IMIG), Brescia (Italy), 24-26 Giugno 2004
Moderazione della sessione: Experimental Approaches - part I (con: A. Ardizzoni)

319. 4th Symposium on New Molecules in Cancer Therapeutics, Athens (Hellas), 21-23 October 2005
Relazione: «Sorafenib (BAY 43-9006): a novel oral multi-kinase inhibitor»

320. 1er Congreso Internacional de Terapias Biológicas en México, Ciudad de México (México), 7-8 April 2006
Relazione: «Sorafenib (BAY 43-9006): a novel oral multi-kinase inhibitor»

321. International Workshop on Intra-Arterial Chemotherapy for Head and Neck Cancer, Springfield, Ill. (USA), August 20-22, 2006
Relazione: «Intra-arterial chemotherapy trials in Europe: the Italian experience»

322. Korean Association of Clinical Oncology (KACO) ASCO Review Meeting, Seoul (Korea), August 26th, 2006
Relazione: «Updates on Targeted Agents. Sorafenib: a novel, broadly-active, multi-kinase inhibitor for cancer treatment»

323. 19th Meeting of The Korean Urological Oncology Society (KUOS), Seoul (Korea), 2 September 2006
Relazione: «Targeted Therapy in Renal Cell Carcinoma. Sorafenib: increased molecular knowledge of renal cell cancer leads to active targeted treatments»

324. BESTT: The first Bayer Expert Symposium on Targeted Therapies, Praha (Czech Republic), 10-12 November 2006
Relazione: «Sorafenib: preclinical and phase I data»

325. BESTT: The first Bayer Expert Symposium on Targeted Therapies, Praha (Czech Republic), 10-12 November 2006
Moderazione della sessione: Optimising care with Sorafenib (con: C. Szczylik)

326. 3rd International Symposium on Angiogenesis and Cancer, Malaga (España), 16-17 November 2006
Relazione: «Sorafenib: present and future in cancer. A clinical review»

327. XVII Congreso Brasileiro de Cancerologia, Belo Horizonte (Brasil), 23 November 2006
Relazione: «Nexavar™: results and clinical practice»

328. International Conference of Oncology, El Ain (United Arab Emirates), 22 February 2007
Relazione: «Recent advances in metastatic renal cell carcinoma management»

329. The second European International Kidney Cancer Symposium (EIKCS), Rome (Italy), 4-5 May 2007
Relazione: «Algorythm for systemic therapies in metastatic kidney cancer: the role of targeted therapies»

330. 10th Annual Meeting of the Chinese Society of Clinical Oncology (CSCO), Harbin (China), September 20th, 2007
Relazione: «Targeted Therapy in Hepatocellular Carcinoma (HCC): an informative update»

331. 1st Pavia Symposium on kidney cancer, Cervesina, PV (Italy), 4-5 October 2007
Presidenza del Congresso

332. 1st Pavia Symposium on kidney cancer, Cervesina, PV (Italy), 4-5 October 2007
Relazione: «Tyrosine kinase inhibitors and immune system: friend or foe?»

333. Annual Meeting of the Thai Society of Clinical Oncology (TSCO), Huain (Thailand), October 13th, 2007
Relazione: «Sorafenib: a multi-kinase inhibitor in cancer treatment»

334. BESTT '07: Bayer-Schering Expert Symposium on Targeted Therapies, Vienna (Austria), 16-18 November 2007
Relazione: «Drugs in development for HCC: ongoing programmes»

335. World Congress on Controversies in Urology (CURy), Barcelona (España), January 31-February 3, 2008
Relazione: «Defining patient populations: how can we effectively integrate targeted therapies into urological practice?»

336. 23rd Annual Meeting of the European Association of Urology (EAU), Milan (Italy), 26-29 March 2008
Relazione: «Sorafenib in advanced renal cell carcinoma (RCC): survival and biomarker results form a phase III trial»

337. 3rd European International Kidney Cancer Symposium (EIKCS), Paris (France), 2-3 May 2008
Relazione: «Sorafenib»

338. 1st International Conference on Translational Research in Oncology (ICTRO), Forlì (Italy), 14-16 May 2008
Relazione: «Sunitinib»

339. Annual Symposium of the Catholic University of Korea: Hepatocellular Carcinoma, Seoul (Korea), July 19th, 2008

Relazione: «Targeted therapies for HCC: opportunities and challenges»

340. 2nd Slovenian Congress of Gastroenterology and Hepatology, Bled (Slovenija), 1-4 October 2008
Relazione: «New developments in management of patients with hepatocellular carcinoma (HCC)»

341. RCC Scientific Forum: Optimizing patient outcomes with Sorafenib: a patient-focused approach to treatment, Madrid (España), 12-13 November 2008
Moderazione di tutto il Convegno (con: P. Mulders)

342. RCC Scientific Forum: Optimizing patient outcomes with Sorafenib: a patient-focused approach to treatment, Madrid (España), 12-13 November 2008
Relazione: «Developing a patient-focused approach to RCC»

343. RCC Connections 2008: an Oncologist Leadership Forum, Vienna (Austria), 11-12 December 2008
Relazione: «Integrating Bevacizumab + IFN into first-line therapy for metastatic RCC»

344. RCC Connections 2008: an Oncologist Leadership Forum, Vienna (Austria), 11-12 December 2008
Relazione: «Tolerability in RCC: an unmet need?»

345. 3rd Caribbean Association of Oncology & Haematology Conference, Paradise island (The Bahamas), March 5th-7th, 2009
Relazione: «Hepatocellular carcinoma: an overview focused on treatment»

346. 3rd Caribbean Association of Oncology & Haematology Conference, Paradise island (The Bahamas), March 5th-7th, 2009
Relazione: «Renal cell cancer: an overview focused on treatment»

347. Bayer Schering Academy of Oncology, Sofia (Bulgaria), March 27th, 2009
Relazione: «Current treatment options in renal cell carcinoma: targeted therapies. Patient-focused approach in the treatment of metastatic renal cell carcinoma»

348. Meeting: Behandling af RCC, Copenhagen (Denmark), May 6th, 2009
Relazione: «How to rationally position Sorafenib in the treatment algorithm for advanced RCC patients»

349. 2nd Pavia International Symposium on Advanced Kidney Cancer. The 3rd Perugia-Pavia post-ASCO Kidney Cancer Meeting, Pavia (Italy), June 26-27, 2009
Presidenza del Congresso (con: S. Bracarda)

350. 2nd Pavia International Symposium on Advanced Kidney Cancer. The 3rd Perugia-Pavia post-ASCO Kidney Cancer Meeting, Pavia (Italy), June 26-27, 2009
Relazione: «Controversial – Clinical or molecular prognostic/predictive factors to guide treatment choices in kidney cancer. Clinical»

351. 2nd Pavia International Symposium on Advanced Kidney Cancer. The 3rd Perugia-Pavia post-ASCO Kidney Cancer Meeting, Pavia (Italy), June 26-27, 2009

Relazione: «Controversial – Multikinase inhibitors and cytokines: to combine or not? Contra»

352. 1st Congress of the Mediterranean Multidisciplinary Oncology Forum, Athens (Hellas), 10-13 September, 2009
Relazione: «Everolimus (RAD001) in advanced RCC»

353. Joint ECCO 15-ESMO 34th Multidisciplinary Congress, Berlin (Germany), 20-24 September 2009
Scientific Symposium: What are the side-effects of therapy in metastatic RCC and how to handle them? Relazione: «Do combination and sequential therapies have increased side-effects?»

354. Expert Practice in Genitourinary Malignancy, Bruxelles (Belgium), 9-10 October 2009
Relazione: «Intermediate-risk renal cell carcinoma: best choice and sequencing of therapy»

355. Expert Practice in Genitourinary Malignancy, Bruxelles (Belgium), 9-10 October 2009
Discussant sulla relazione: «Nonseminomatous germ cell tumor of the testis. A multidisciplinary approach» (effettuata dal Dr. K. Miller)

356. Expert Practice in Genitourinary Malignancy, Bruxelles (Belgium), 9-10 October 2009
Relazione: «Castration-resistant prostate cancer: optimal management of a patient with a good Performance Status»

357. 4th Oncology Workshop, Pissouri (Cyprus), 24-25 October 2009
Relazione: «Afinitor™: a new treatment option for RCC»

358. CME-certified course: Angiogenesis: a key target in Oncology, Barcelona (España), October 30-31, 2009
Relazione: «Angiogenesis inhibition in RCC»

359. XII Workshop de Urologia Oncológica (25° Aniversário do Grupo Português Genito-Urinário), Carvoeiro (Portugal), 20-21 November, 2009
Relazione: «Bevacizumab as first-line therapy of metastatic renal cell cancer»

360. Conference Of Renal cancer Experts (CORE) meeting, Istanbul (Turkey), 12-13 March, 2010
Relazione: «How can biomarkers better guide treatment decisions in mRCC?»

361. Conference Of Renal cancer Experts (CORE) meeting, Istanbul (Turkey), 12-13 March, 2010
Relazione: «AE management of mTOR inhibitors: management and awareness»

362. 5th European International Kidney Cancer Symposium (EIKCS), London (UK), 7-8 May 2010
Relazione: «Debate on maintenance therapy after complete remission – Pro»

363. Meeting of the Polish Renal Cell Carcinoma Cooperative Group, Wierzba (Poland), June 17th and 18 th, 2010

Relazione: «Role of cytokines in modern treatment of metastatic RCC. Pros and cons»

364. Conference Of Renal cancer Experts extended (CORE-X 2010) meeting, Dubai (United Arab Emirates), 24 September 2010
Relazione: «mTOR inhibitor safety: characterisation, management and awareness»

365. Conference Of Renal cancer Experts extended (CORE-X 2010) meeting, Moscow (Russia), 25 September 2010
Relazione: «mTOR inhibitor safety: characterisation, management and awareness»

366. Conference Of Renal cancer Experts extended (CORE-X 2010) meeting, Seoul (Korea), 23 October 2010
Relazione: «mTOR inhibitor safety: characterisation, management and awareness»

367. Conference Of Renal cancer Experts extended (CORE-X 2010) meeting, Tokyo (Japan), 25 October 2010
Relazione: «mTOR inhibitor safety: characterisation, management and awareness»

368. Simposio Cientifico SOGUG (Spanish Oncololy Genito-Urinary Group), Madrid (España), 19-20 November 2010
Relazione: «Beyond the first-line: the role of Sorafenib»

369. III International Conference on angiogenesis in memory of Judah Folkman, Rome (Italy), 14-15 January 2011
Session IV: Clinical Research. Relazione: «Rene»

370. Meeting: Maximizing the duration of disease stabilization with targeted agents: can we predict an optimal sequence? Bruxelles (Belgium), 20 January 2011
Chairmanship dell'intero meeting

371. Meeting: 'Dare to compare' in kidney cancer, Zürich (Switzerland), 27 January 2011
Chairmanship (con F. Stenner) dell'intero meeting

372. Meeting: 'Dare to compare' in kidney cancer, Zürich (Switzerland), 27 January 2011
Relazione: «Tolerability of substances according to data and personal experience»

373. Meeting: Dare to compare in kidney cancer, Zürich (Switzerland), 27 January 2011
Relazione: «As of today, what do we know about sequences?»

374. Middle East 3rd Hematology & Oncology Summit, Dubai (United Arab Emirates), 25-26 February 2011
Round table (with B. Escudier and V. Grünwald): mTOR pathway

375. Middle East 3rd Hematology & Oncology Summit, Dubai (United Arab Emirates), 25-26 February 2011
Session: mTOR pathway & development of Everolimus in renal cell carcinoma (RCC).
Relazione: «Case council: efficacy and tolerability»

376. 5th Post-Graduate Seminar on Urological Cancers, Athens (Hellas), 10-12 March 2011

Relazione: «Mechanisms of resistance to anti-angiogenic therapies in renal cell carcinoma»

377. 4th ATST Meeting "Autologous and allogeneic cell therapy in solid tumors", Venice (Italy), March 31-April 1, 2011
Relazione: «Immunological effects of molecularly targeted agents for kidney cancer: a clue for integration with cellular therapies?»

378. 13th Course: Advances in Urological Oncology – Focus on renal cancer, Erice (Italy), April 27-May 1, 2011
Relazione: «Neo-adjuvant and adjuvant treatments: today and tomorrow»

379. 24th Meeting of The Korean Urological Oncology Society (KUOS), KwangJu (Korea), 27 Agosto 2011
Relazione: «Considerations in RCC treatment selection: progress and challenges to date»

380. Roundtable: RCC treatment with targeted agents in a changing therapeutic environment – what do the new data for 2011 tell us? Barcellona (España), 2 Settembre 2011
Relazione: «VEGF inhibitors in sequential therapy: focus on AXIS»

381. Roundtable: RCC treatment with targeted agents in a changing therapeutic environment – what do the new data for 2011 tell us? Barcellona (España), 2 Settembre 2011
Relazione: «Treatment sequence strategies: latest data and ongoing studies»

382. Convegno: Osteotropic cancers: new pathogenetic and clinical aspects, Bari (Italy), 23-24 Settembre 2011
Relazione: «Bone metastatic tumors: role of TKR inhibitors»

383. Corso: Expert Practice in Genitourinary malignancies, Paris (France), 12 Novembre 2011
Relazione: «What's hot in Genitourinary Oncology?»

384. Corso: Expert Practice in Genitourinary malignancies, Paris (France), 12 Novembre 2011
Relazione: «Renal cell carcinoma (RCC): what's the status of adjuvant or neoadjuvant therapies?»

385. Roundtable: Temsirolimus in clinical practice, Frankfürt (Germany), 16 Novembre 2011
Chairmanship dell'intero meeting

386. Roundtable: Temsirolimus in clinical practice, Frankfürt (Germany), 16 Novembre 2011
Relazione: «Temsirolimus for the treatment of poor-prognosis patients with mRCC: an overview»

387. Roundtable: Temsirolimus in clinical practice, Frankfürt (Germany), 16 Novembre 2011
Relazione: «New opportunities for Temsirolimus in mRCC»

388. 2nd Congress of the Mediterranean Multidisciplinary Oncology Forum (MMOF), Istanbul (Turkey), 17-19 Novembre 2011

Relazione: «Treatment of mRCC beyond TKI/VEGF targeted therapies»

389. IV International Conference on angiogenesis in memory of Judah Folkman, Rome (Italy), 13-14 January 2012
Roundtable: «New therapeutic strategies for antiangiogenic therapy» (con A. Vacca e M. D'Incalci)

390. 1st Milan Conference on Urologic Tumors – Pathology or rare tumors and pseudotumors, Milan (Italy), 27-28 January 2012
Moderazione della sessione: Rare tumors and pseudotumors of the kidney (con C. Doglioni e F. De Braud)

391. Expert Roundtable: RCC treatment with targeted agents in a changing therapeutic environment – what do the new data for 2011/2012 tell us?
A roundtable discussion, Frankfurt (Germany), 16 March 2012
Chairmanship dell'intero meeting

392. Workshop on Kidney Cancer, Tallinn (Estonia), April 13th, 2012
Relazione: «1st line treatment of metastatic renal cell carcinoma (mRCC)»

393. Workshop on Kidney Cancer, Tallinn (Estonia), April 13th, 2012
Relazione: «Sequential treatment of metastatic renal cell carcinoma (mRCC)»

394. RCC Workshop, Helsinki (Finland), April 16th, 2012
Relazione: «Overview of the latest data on 1st line treatment of mRCC»

395. RCC Workshop, Helsinki (Finland), April 16th, 2012
Relazione: «Overview of the latest data on sequential treatment of mRCC»

396. XXI Porto Cancer Meeting, Porto (Portugal), 19-20 April, 2012
Relazione: «mTOR inhibition in kidney cancer and beyond: a crossroad between metabolism and angiogenesis»

397. 3rd annual COnference of Renal cancer Experts – CORE 2012, Munich (Germany), 19-21 April, 2012
Relazione: «Novel agents on the horizon»

398. Seventh European International Kidney Cancer Symposium (EIKCS), Vienna (Austria), 4-5 May, 2012
Relazione: «Should response to 1st-line agents guide the choice of treatment in 2nd-line?»

399. 2nd Oncology Symposium – Konstelacje, Kraków (Poland), 11-12 May 2012
Relazione: «The need for a patient-focused approach in mRCC: the role of Sorafenib»

400. European Cancer Congress (ECCO 17, ESMO 38, ESTRO 32), Vienna (Austria), 28 September-2 October 2012
Debate: «This house believes there is no need for more VEGFR TKIs to treat renal cancer. Contra» (con B. Escudier)

401. Meet the Investigators – Renal Cell Carcinoma (RCC) – at the European Society of Medical Oncology (ESMO) 2012 Annual Conference, Vienna (Austria), 30th September 2012. Roundtable discussion: TIVO-1 study (con M. Schmidinger, T. Eisen e M. Holmes)

402. Eleventh International Kidney Cancer Symposium (IKCS), Chicago, Ill. (USA), October 5-6, 2012
Relazione: «How recent Pazopanib data impact our treatment paradigm?»

403. Convegno: Sequential treatment of metastatic renal cell carcinoma – where are we today? Stockholm (Sweden), 17 October 2012
Relazione: «Overview of targeted therapies and treatment algorithm. What are the evidences?»

404. Congresso: 1st World Top Communications of the Year in Genitourinary Oncology, Arezzo (Italy), 18-19 October 2012
Relazione: «RCC debate – In favour of a TKI-TKI sequence»

405. Congresso: Insight on Genitourinary Cancers: new pathogenetic and clinical aspects, Bari (Italy), November 30th-December 1st, 2012
Relazione: «Update on mRCC treatment with TKIs»

406. V International Conference on angiogenesis in memory of Judah Folkman, Rome (Italy), January 19th, 2013
Relazione: «Translational studies by tumor type. The model of renal cancer»

407. Africa-Middle East (AfME) mRCC Workshop, Doha (Qatar), February 28-March 1, 2013
Relazione: «1st line therapy in mRCC: using evidence-based data to guide clinical decision making»

408. Africa-Middle East (AfME) mRCC Workshop, Doha (Qatar), February 28-March 1, 2013
Relazione: «Sequential therapy with targeted agents: defining the optimal treatment algorithm»

409. Congresso: Renal Horizons 2013, Berlin (Germany), March 22-23, 2013
Panel Discussion: Achieving a continuum of care in mRCC: the Physicians' field of view (con M. Schmidinger e A. Bex)

410. Congresso: Renal Horizons 2013, Berlin (Germany), March 22-23, 2013
Parallel Case Study Workshop 1: Achieving a continuum of care (con M. Schmidinger e L. Leon)

411. Congresso: Renal Horizons 2013, Berlin (Germany), March 22-23, 2013
Parallel Case Study Workshop 2: Achieving a continuum of care (con T. Powles e L. Leon)

412. Congresso: Renal Horizons 2013, Berlin (Germany), March 22-23, 2013
Ask the Experts Session (con M. Aitchinson)

413. Scientific Conference: Topical questions on diagnosis and treatment of malignant tumors: breast cancer, renal cell carcinoma and neuroendocrine tumors, Irkutsk (Russia), March 28-30, 2013
Relazione: «Targeted therapy of metastatic RCC»

414. 4th Annual Conference Of Renal cancer Experts (CORE) Meeting, Vienna (Austria), 11-13 April, 2013
Relazione: «Expanding the armamentarium: novel agents and approaches to the systemic treatment of mRCC»

415. 4th Annual Conference Of Renal cancer Experts (CORE) Meeting, Vienna (Austria), 11-13 April, 2013
Breakout Session (con D.Y.C. Heng): Immunotherapy

416. 4th Annual Conference Of Renal cancer Experts (CORE) Meeting, Vienna (Austria), 11-13 April, 2013
Meet the Experts breakfast Session (con V. Grünwald)

417. Eight European International Kidney Cancer Symposium (EIKCS), Budapest (Hungary), 3-4 May, 2013
Relazione: «Sunitinib remains the best choice in first-line»

418. 49th Annual Meeting of the American Society of Clinical Oncology (ASCO 2013), Chicago, Ill. (USA), May 31-June 4, 2013
Co-Chair (con E.M. Posadas) della Sessione: Genitourinary (non prostate) Poster Discussion Session

419. Conferinta Societatii Române de Radioterapie si Zilele Medicale ale Institutului Oncologic Prof. Dr. Alexandru Trestioreanu, Bucuresti, Bucharest (Romania), 31 Octombrie-2 Noiembrie, 2013
Relazione: «Clinical advances in the treatment of metastatic renal cell carcinoma and patient preference insights»

420. Congresso: 2nd World Top Communications of the Year in Genitourinary Oncology, Arezzo (Italy), 7-8 November 2013
Relazione: «RCC debate – 1st line treatment: patient preference or physician choice? In favor of patient preference and why»

421. RCC Roadshow, Bucharest (Romania), 13 November, 2013
Relazione: «How to select first-line treatment for mRCC: an evidence-based approach»

422. RCC Roadshow, Bucharest (Romania), 13 November, 2013
Relazione: «Sequencing therapy in mRCC: what should drive 2nd-line treatment decisions?»

423. IV Simposio Cientìfico SOGUG (Spanish Oncology Genitourinary Group), Madrid (España), 20-22 Noviembre, 2013
Relazione: «Individualized treatment in advanced RCC: how to incorporate the available options»

424. Roszsiany Rak Nerkowokomorkowy, Serock (Poland), 28-30 November, 2013
Relazione: «mRCC treatment – the role of sequencing»

425. 2nd Milan Conference on Urologic tumors – pathology of kidney and testis tumors, Milan (Italy), 23-24 January, 2014
Moderazione (con Giuseppe Viale) della sessione Tumori del rene I

426. VI International Conference on angiogenesis in memory of Judah Folkman, Rome (Italy), January 25, 2014
Relazione: «New translational acquisitions in the pathogenesis of renal cancer and therapeutic implications»

427. 5th Annual Conference Of Renal cancer Experts (CORE) meeting, Prague (Czech Republic), 3-5 April, 2014
Moderatore dell'Audience Breakout Session: Sequencing strategies for maximizing benefit in mRCC (insieme a I. Davis)

428. 5th Annual Conference Of Renal cancer Experts (CORE) meeting, Prague (Czech Republic), 3-5 April, 2014
Relazione: «Recent progress in the systemic treatment of non-clear cell mRCC»

429. Workshop: Non clear cell RCC (nccRCC): current trends in management and treatment, Paris (France), 26 June 2014
Relazione: «nccRCC management and treatment: current status»

430. 4th International Pavia Kidney Cancer Symposium, Pavia (Italy), 11 September 2014
Presidenza del Congresso

431. 4th International Pavia Kidney Cancer Symposium, Pavia (Italy), 11 September 2014
Relazione: «New genes and new targets towards a personalized treatment for advanced RCC»

432. 4th International Pavia Kidney Cancer Symposium, Pavia (Italy), 11 September 2014
Moderazione (con G. Pappagallo) della Sessione: Controversials

433. 4th International Pavia Kidney Cancer Symposium, Pavia (Italy), 11 September 2014
Moderazione (con R. Sabbatini) della Sessione: Shedding a different light on toxicities

434. Meeting: Nierenzellkarzinom, Frankfurt (Germany), 17 September 2014
Relazione: «Afinitor 10 mg in 2nd line after initial TKI 1st line»

435. CORE (Conference Of Renal cancer Experts) Speaker Tour Meeting, Helsinki (Finland), 18 September 2014
Relazione: «The second-line dilemma: analysing sequencing strategies for optimal treatment in progressive RCC»

436. CORE (Conference Of Renal cancer Experts) Speaker Tour Meeting, Helsinki (Finland), 18 September 2014
Relazione: «Managing VEGFR-TKIs and mTOR inhibitors-related toxicities»

437. Ninth International Conference of the International Institute of Anticancer Research (IIAR), Sithonia (Hellas), October 6-10, 2014
Relazione: «First-line medical therapy in advanced metastatic RCC»

438. Congresso: 3rd World Top Communications of the Year in Genitourinary Oncology, Arezzo (Italy), 9-10 October 2014
Relazione: «If starting with Pazo, which 2nd line?»

439. 15th Course: Kidney Cancer: innovations in Surgery and Oncology, Erice (Italy), November 28th-December 1st, 2014
Relazione: «Neo-adjuvant targeted therapies»

440. VII International Conference on angiogenesis in memory of Judah Folkman, Rome (Italy), January 23-24, 2015
Relazione: «Antiangiogenetic therapy in renal cancer»

441. 10th European International Kidney Cancer Symposium (EIKCS), Lyon (France), 24-25 April, 2015
Relazione: «Treatment beyond second-line»

442. 10th European International Kidney Cancer Symposium, Lyon (France), 24-25 April, 2015
Moderazione (con L. Albiges) della sessione: Open questions/Controversies

443. V Sympozjum Naukowe Onkologia "Konstellacje 2015", Kraców (Poland), 22-23 May 2015
Relazione: «How RCC targeted treatment optimization impacts patients' survival»

444. 6th Annual Conference Of Renal cancer Experts (CORE) meeting, Berlin (Germany), 27-28 June, 2015
Relazione: «Mechanisms of resistance to targeted therapies in mRCC»

445. 6th Annual Conference Of Renal cancer Experts (CORE) meeting, Berlin (Germany), 27-28 June, 2015
Breakout Session (presentazione con discussione interattiva): Immunotherapy (vaccines) and other novel emerging agents

446. 2nd Renal Cell Carcinoma Symposium of the RCCNET.CH, Zürich (Switzerland), 10 September, 2015
Relazione: «Best use of registered treatments»

447. European Cancer Congress 2015 (ECCO 18, ESMO 40, ESSO 35), Vienna (Austria), 25-29 September 2015
Sessione: Proffered paper session: Genitourinary malignancies – prostate and nonprostate.
Discussant dell'abstract n. 2509, presentato da Tom Hutson «Overall survival analysis from a randomized phase III trial of axitinib vs sorafenib as first-line therapy in patients with metastatic renal cell carcinoma»

448. Congresso: 4th World Top Communications of the Year in Genitourinary Oncology, Arezzo (Italy), 8-9 October 2015
RCC theatre – New limes in RCC: only one definition of "progression" after TKI-mTORI and anti-PD1/PD-L1 agents? Relazione: «In favour of a previous treatment maintenance and why»

449. 4th Techno-Urology Meeting (TUM): from pre-clinical setting to the operating room, Orbassano (Italy), 27-29 January, 2016
Relazione: «Chemotherapy for renal cancer: which benefit for whom?»

450. RCC Tour 2016, St. Petersburg (Russia), 15 April, 2016
Debate: «Targeted therapies in renal cell carcinoma»

451. Eleventh European International Kidney Cancer Symposium (EIKCS), Barcelona (España), 29-30 April, 2016
Relazione: «First line treatment: what it will look like in 2020»

452. Convegno "Innovation in Clinical Oncology: Oncogenomics for diagnosis and treatment, Bari (Italy), 23-24 June, 2016
Relazione: «TKIs in renal cell carcinoma: what can we expect from the future? »

453. European Society of Medical Oncology (ESMO) Academy 2016, Oxford (UK), 26-28 August, 2016
Relazione: «Treatment of clear cell RCC»

454. Congresso: 5th World Top Communications of the Year in Genitourinary Oncology, Arezzo (Italy), November 16-18, 2016
RCC theatre – Moving from 1st line to following treatment options. Relazione: «The best candidate to a TK inhibitor, and why»

455. Congresso: 5th Pavia International Symposium on Advanced Kidney Cancer, Pavia (Italy), November 24th, 2016
Presidenza dell'intero congresso

456. Congresso: 5th Pavia International Symposium on Advanced Kidney Cancer, Pavia (Italy), November 24th, 2016
Relazione: «Are we close or not to Precision Medicine in kidney cancer?»

457. 12th European International Kidney Cancer Symposium (EIKCS), München (Germany), April 21-22, 2017
Chair (con M. Staehler): Interdisciplinary Discussions in advanced RCC: lymph-node disease

458. 12th European International Kidney Cancer Symposium (EIKCS), München (Germany), April 21-22, 2017
Relazione: «How should the next generation trials address the question of sequence?»

459. The Fourth International Renal Meeting with Mayo Clinic in Sardinia, Cagliari (Italy), 30 April-3 May, 2017
Moderazione (con B. Basolo) della sessione: Onco-Nephrology

460. 51st Annual Scientific Meeting of the European Society for Clinical Investigation (ESCI), Genoa (Italy), May 17-19, 2017
Relazione: «New cancer immunotherapy indications: renal, bladder, and head and neck cancer»

461. National Immuno-Oncology Forum, Bucharest (Romania), May 25, 2017
Relazione: «Adding value in mRCC – focus on overall survival»

462. European Society of Medical Oncology (ESMO) Academy 2017, Oxford (UK), 4-6 August, 2017
Relazione: «Treatment of clear cell renal cell carcinoma»

463. 42nd European Society of Medical Oncology Congress (ESMO 2017), Madrid (Spain), 8-12 September, 2017
Discussant della Sessione: Genitourinary tumours, non prostate, poster discussion session (9 September 2017)

464. 42nd European Society of Medical Oncology Congress (ESMO 2017), Madrid (Spain), 8-12 September, 2017
Moderazione (con L. Albiges) dello Special Symposium: Impact of tumour heterogeneity on precision medicine in kidney and bladder cancer (11 September 2017)

465. XX Kongres Polskiego Towarzystwa Onkologii Klinicznej (PTOK – Polish Society of Medical Oncology), Krakow (Poland), 15 September, 2017
Relazione: «METEOR study: transferring triple mechanism of action into the clinical practice»

466. Controversies on GU tumors, 6th edition, Milan (Italy), 21 September 2017
Relazione: «Hot topics in advanced renal cell carcinoma»

467. XII International Conference on Biologic Therapy, Vilnius (Lithuania), 24 November 2017
Relazione: «New highlights in the treatment of renal and bladder (urothelial) carcinoma»

468. Symposium: Revolutionary treatments for renal cell carcinoma, prostate cancer, and bladder carcinoma, Serock (Poland), 24-25 November 2017
Relazione: «mTOR inhibitors in mRCC: saving private Ryan»

469. International Conference on Onco-Nephrology: an emerging field in Medicine, Naples (Italy), 7-9 December 2017
Session IV – «Clinical efficacy of novel molecular therapies; relazione: Agents targeting VEGF»

470. International Conference on Onco-Nephrology: an emerging field in Medicine, Naples (Italy), 7-9 December 2017
Session V – «Renal cell cancer update; relazione: Which recommendations for first-line treatment in metastatic renal cell carcinoma»

471. Pfizer Oncology Academy, Zagreb (Croatia), 16-17 December 2017
Relazione: «Emerging clinical evidence»

472. Pfizer Oncology Academy, Zagreb (Croatia), 16-17 December 2017
Moderazione della sessione: mRCC: real-life case discussion

473. 6th Techno-Urology Meeting (TUM): new technologies for a more precise surgery, Orbassano (Italy), 24-26 January, 2018
Relazione: «Immunotherapy for kidney cancer: current outcomes»

474. Africa-Middle East (AfME) Oncology Forum, Abu Dhabi (UAE), 13-14 April 2018
Relazione: «Towards optimising the mRCC treatment outcomes: how can we optimise each treatment line?»

475. 13th European International Kidney Cancer Symposium (EIKCS), Prague (Czech Republic), 27-28 April 2018
Moderazione (con L. Albiges) della sessione Revolution in 1st line

476. 13th European International Kidney Cancer Symposium (EIKCS), Prague (Czech Republic), 27-28 April 2018
Panel Discussion (con K. Bensalah, V. Grunwald e V, Matveev) della sessione 'Complex case discussion', condotta da C.G. Wood

477. 4th Ελληνικο Συνεδριο Ογκολογιασ (4th Pan-Hellenic Oncology Congress – EOPE), Thessaloniki (Hellas), 3-5 May 2018
Relazione: «Immunotherapy changes first-line treatment paradigm in advanced RCC»

478. European Society of Medical Oncology (ESMO) Academy 2017, Oxford (UK), 1-3 September, 2018
Relazione: «Treatment of clear cell renal cell carcinoma»

479. III Simposio Oncopromesas vs Oncosauros – asimilando los progresos en Oncologia, Santander (España), 4-6 July 2018
Relazione: «Redefinición del tratamiento de primera línea del carcinoma metastásico de células renales:¿Cómo aplicamos las pruebas más recientes?»

480. Oncoforum, Krakow (Poland), 5-6 October, 2018
Relazione: «The evolving treatment landscape of metastatic renal cell carcinoma»

481. Current trends in Immuno-Oncology: urothelial carcinoma, Milan (Italy), 6-7 November, 2018
Moderazione (con G. Cartenì) della Sessione Workshops

482. Current trends in Immuno-Oncology: urothelial carcinoma, Milan (Italy), 6-7 November, 2018
Relazione: «Immuno-Oncology beyond urothelial carcinoma»

483. European School of Oncology (ESO)/American Society of Clinical Oncology (ASCO) Masterclass in Clinical Oncology, Yerevan (Armenia), 9-13 November, 2018
Moderazione (con V. Badeyan) della Clinical Session – Prostate Cancer

484. European School of Oncology (ESO)/American Society of Clinical Oncology (ASCO) Masterclass in Clinical Oncology, Yerevan (Armenia), 9-13 November, 2018
Relazione: «Management of early and metastatic prostate cancer»

485. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Zürich (Switzerland), 23-24 November 2018
Direzione del corso (con A. Bamias)

486. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Zürich (Switzerland), 23-24 November 2018
Relazione: «mRCC: antiangiogenic therapy»

487. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Zürich (Switzerland), 23-24 November 2018
Debate (vs Viktor Grünwald): «Immunotherapy is the standard first-line therapy in mRCC? No»

488. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Zürich (Switzerland), 23-24 November 2018
Relazione: «Side effects of TKIs amd mTOR inhibitors»

489. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Zürich (Switzerland), 23-24 November 2018
Relazione: «Side effects of immunotherapy»

490. "Around the kidney" International Surgery, Knowledge and Technology, Milan (Italy), 28-30 November 2018
Relazione: «Cytoreductive nephrectomy: is it dead?»

491. Congresso: 6th Pavia International Symposium on Advanced Kidney Cancer, Pavia (Italy), November 30th, 2018
Presidenza dell'intero congresso

492. Congresso: 6th Pavia International Symposium on Advanced Kidney Cancer, Pavia (Italy), November 30th, 2018
Moderazione (con R. Sabbatini) della I Sessione: Il carcinoma renale a cellule chiare; basi biologiche

493. Congresso: 6th Pavia International Symposium on Advanced Kidney Cancer, Pavia (Italy), November 30th, 2018
Moderazione (con G. Procopio) della II Sessione: Il carcinoma renale a cellule chiare; evoluzione terapeutica

494. Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference on Onco-Nephrology, Milan (Italy), 13-16 December 2018
Conference Co-Chairmanship (con J. Malyszko)

495. 40th European Organization for the Research and Treatment of Cancer (EORTC) Pharmacology and Molecular Mechanisms Group (PAMM) Winter Meeting, Verona (Italy), 8 February 2019

Relazione: «New paradigms in the treatment of advanced renal cell carcinoma»

496. 14th European International Kidney Cancer Symposium (EIKCS), Dubrovnik (Croatia), 29-30 March 2019
Moderazione della sessione Abstracts

497. European Society of Medical Oncology (ESMO) preceptorship on Immuno-Oncology, Zürich (Switzerland), 10-11 May 2019
Relazione: «Bladder and renal cell cancer»

498. Congresso: 7th Pavia International Symposium on Advanced Kidney Cancer, Pavia (Italy), November 8th, 2019
Presidenza dell'intero congresso

499. Congresso: 7th Pavia International Symposium on Advanced Kidney Cancer, Pavia (Italy), November 8th, 2019
Relazione: «Carcinoma renale e risposta immune: basi biologiche»

500. Congresso: 7th Pavia International Symposium on Advanced Kidney Cancer, Pavia (Italy), November 8th, 2019
Moderazione (con S. Bracarda) della Sessione: Carcinoma renale: nuove strategie

501. 4th International Congress on Clinical needs and translational research in Oncology, Reggio Emilia (Italy), November 21-22, 2019
Lettura: «Biological evidence and strategy of care in advanced renal cancer»

502. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Lugano (Switzerland), 29-30 November 2019
Direzione del corso (con A. Bamias)

503. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Lugano (Switzerland), 29-30 November 2019
Relazione: «mRCC: antiangiogenic therapy»

504. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Lugano (Switzerland), 29-30 November 2019
Debate (vs Aristotelis Bamias): «Systemic chemotherapy is the standard of care for metastatic urothelial cancer? No»

505. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Lugano (Switzerland), 29-30 November 2019
Debate (vs Viktor Grünwald): «Which immunotherapy is the standard first-line therapy for mRCC? Immune combos with a TKI»

506. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Lugano (Switzerland), 29-30 November 2019
Relazione: «Side effects of TKIs and mTOR inhibitors»

507. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, Lugano (Switzerland), 29-30 November 2019

Relazione: «Side effects of immunotherapy»

508. Immuno-Oncology Forum, Warsaw (Poland), 6-7 December 2019
Relazione: «Immunotherapy in 2nd line of renal cell carcinoma»

509. Immuno-Oncology Forum, Warsaw (Poland), 6-7 December 2019
Relazione: «Immune-based combinations for metastatic kidney cancer»

510. European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19-21 Settembre 2020
Sessione: Presidential Symposium I. Discussant dell'abstract n. 696O, presentato da Toni K. Choueiri: «Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial»

511. Congresso: 8th New Generation World Top Communications of the Year in Genitourinary Oncology (WTC-GU), 1-2 October 2020 (virtual)
Relazione: «Optimal candidates to different approaches in the 1st line setting»

512. 11th East European Regional Oncology Forum "Aspiring to regional advancements in cancer care in the new decade", 23-24 October 2020 (virtual)
Session: Novel clinical perspectives in treating mRCC; Relazione: «Applying evidence in clinical practice: decision-making in mRCC»

513. Menarini Symposium on Onconephrology, an evolving field in Medicine, 29th October, 4th & 11th November 2020 (virtual)
Moderazione (con M.H. Rosner) della prima giornata

514. IV Conference of Pulmonary Oncology: from prevention to advanced disease (despite COVID-19), 9-10 November 2020 (virtual)
Moderazione (con S. Cinieri & A. Catino) della Session III

515. Live Webinar The current landscape of renal cancer management, 24 November 2020 (virtual)
Moderazione dell'intero Webinar

516. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, 27-28 November 2020 (virtual)
Direzione del corso (con A. Bamias)

517. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, 27-28 November 2020 (virtual)
Relazione: «1st line treatment for clear-cell mRCC»

518. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, 27-28 November 2020 (virtual)
Relazione: «Personalized therapy in metastatic bladder cancer and RCC: RCC»

519. 1° Conferenza Italo-Russa: esperienze Oncologiche a confronto, 30 Novembre-1 Dicembre 2020 (virtual)

Relazione: «Kidney cancer biomarkers: from discovery to treatment»

520. Immunotherapy Bridge 2020, December 2nd-3rd, 2020 (virtual)
Session: «Trends in immunotherapy; Relazione: Kidney cancer»

521. Congresso: 8th International Symposium on Advanced Kidney Cancer, 11 December 2020 (virtual)
Presidenza dell'intero congresso

522. European Society of Medical Oncology (ESMO) preceptorship on Immuno-Oncology, 16-17 December 2020 (virtual)
Relazione: «Bladder and renal cell cancer»

523. GU Cancer Forum, organizzato dallo Swiss Group for Clinical Cancer Research (SAKK) e dall'Istituto Oncologico della Svizzera Italiana (IOSI), 24 Febbraio 2021 (virtual)
Relazione: «Highlights carcinoma a cellule renali metastatico – Terapia sistemica»

524. GU Academy, 30 March April 2021 (virtual)
Relazione: «Overview of the RCC treatment landscape»

525. 15th European International Kidney Cancer Symposium (EIKCS), 23-24 April 2021 (virtual)
Relazione: «Modern therapeutic approaches in second-line and later therapies»

526. Pan-Asia adapted ESMO clinical consensus guidelines for the management of patients with renal cell carcinoma meeting, 14-15 May 2021 (virtual)
Relazione: «ESMO clinical practice guidelines for renal cell carcinoma»

527. 58th ERA-EDTA (European Renal Association/European Dialysis and Transplantation Association) Congress, June 5-8, 2021 (virtual)
Chairmanship (with M. Simeoni) of the Symposium 3.4 Onconephrology

528. Webinar Linking GU Experts from Brasil, 19 July, 2021 (virtual)
Relazione: «First-line treatment of mRCC: decision-making process in the real world»

529. ESMO Academy Virtual Meeting, 20-21 August, 2021 (virtual)
Relazione: «Renal cancer»

530. European Society of Medical Oncology (ESMO) Virtual Congress 2021, 16-21 Settembre 2021
Special session: Management of a clinical challenging patient with clear cell RCC.
Relazione: «Treatment for disease that has progressed on first-line treatment»

531. The National Romanian Society of Medical Oncology annual meeting, 7-9 October, 2021 (hybrid format)
Relazione: «Evolution of immunotherapy in the management of 1st-line advanced RCC: latest updates & clinical practice»

532. Congresso: 9th World Top Communications of the Year in Genitourinary Oncology (WTC-GU), 14 October 2021 (evento ibrido: in presenza – Terni [Italy] + Webinar)

Relazione: «My opinion on the 1st line combination data in ccmRCC, state of the art»

533. 1st International Genitourinary Cancer Conference (IGCC) (hybrid event: in presence – Jeddah [Saudi Arabia] + Webinar), 5-6 November 2021
Relazione: «Sequencing in mRCC»

534. 6th International Congress on "Clinical needs and translational research in Oncology", Reggio Emilia (Italy), November 18-19, 2021
3rd needs: «New biological and clinical evidences on therapy sequences in advanced disease. Lettura: Renal cancer».

535. Immunotherapy Bridge 2021 (hybrid event: in presence – Naples [Italy] + Webinar), December 1st-2nd, 2021
Symposium: Combination therapies across cancers
Relazione: «RCC»

536. ESMO Immuno-Oncology, 8-11 December 2021 (virtual)
Educational session: New developments in genitourinary tumors. Relazione: «Immunotherapy combinations in renal cancer»

537. International Kidney Cancer Symposium (ICKS) Europe, 22-23 April 2022 (hybrid event: in presence – Antwerp [Belgium] + Webinar)
Session 6: Systemic therapy debate: later-line therapy. Relazione: «What do we know from evidence-based 2nd line treatment»

538. International School of Clinical Oncology (ISCO) Annual Congress, 12-13 May 2022, Cairo (Egypt)
Relazione: «State of the art in first-line treatment of metastatic RCC»

539. Middle East and Africa Oncology Summit, 27-28 May 2022, (hybrid event: in presence – Dubai [United Arab Emirates] + Webinar)
Relazione: «1st line treatment in RCC»

540. Middle East and Africa Oncology Summit, 27-28 May 2022, (hybrid event: in presence – Dubai [United Arab Emirates] + Webinar)
Panel Discussion (with M. Schmidinger, H. Jafaar, I. Duran

541. European Society of Medical Oncology (ESMO) preceptorship on Immuno-Oncology, 26-27 June 2022, Zurich (Switzerland)
Relazione: «Clinical development: bladder cancer»

542. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, 11-12 July 2022, Lugano (Switzerland)
Relazione: «1st line treatment for clear-cell mRCC»

543. European Society of Medical Oncology (ESMO) preceptorship on metastatic bladder and kidney cancer, 11-12 July 2022, Lugano (Switzerland)
Relazione: «Side effects management – IO/IO and IO single agent»

544. European Society of Medical Oncology (ESMO) Academy 2022, Dublin (Ireland), 19-21 August, 2022
Relazione: «Renal cancer»

545. 2022 European Society of Medical Oncology (ESMO) Annual Congress, Paris (France), 9-12 Settembre 2022
ESMO Colloquia: The emerging continuum of care in advanced RCC". Relazione: «2nd line and beyond»

546. 2022 European Society of Medical Oncology (ESMO) Annual Congress, Paris (France), 9-12 Settembre 2022
Mini oral presentation: «Updated efficacy of Lenvatinib plus pembrolizumab versus sunitinib in patients with advanced renal cell carcinoma in the CLEAR study»

547. Congresso: 10th World Top Communications of the Year in Genitourinary Oncology & Genomic Oncology (WTC-GU&GO), September 22-23, 2022 (evento ibrido: in presenza – Terni [Italy] + Webinar)
Tumor Board discussion and round table – The first (line), the best (results): which combo for any patient?
Relazione: «CLEAR»

548. National Oncology Congress of Bulgaria (hybrid event: in presence – Sofia [Bulgaria] + Webinar), 30th September-1st October 2022
Relazione: «Long-term efficacy of dual checkpoint inhibition in Renal Cell Carcinoma»

549. Congresul National de Oncologie (hybrid event: in presence – Poiana Brasov [Romania] + Webinar), 5-8 October 2022
Relazione: «Angiogenesis inhibitors for the treatment of metastatic renal cell carcinoma in the era of immune-based combination»

550. Virtual Meeting – Renal talks: leveraging discussions in RCC, 26 October 2022
Relazione: «Revision del algoritmo de tratamiento en CCR avanzado»

551. Virtual Meeting – Renal talks: leveraging discussions in RCC, 26 October 2022
Relazione: «Experiencia clinica en el manejo de las combinaciones en 1L»

552. 14th European Multidisciplinary Congress on Urological Cancer (EMUC), Budapest (Hungary), 10-13 November 2022
Discussant: «Adjuvant therapies in high-risk RCC»

553. 2nd International Genitourinary Cancer Conference (IGCC) (hybrid event: in presence – Jeddah [Saudi Arabia] + Webinar), 18-19 November 2022
Relazione: «RCC genetic syndromes»

554. 7th International Congress on Clinical needs and translational research in Oncology (hybrid event: in presence – Reggio Emilia [Italy] + Webinar), November 24-25, 2022
Sessione: The biological and clinical "value" of first-line therapy choice in advanced cancer disease
Lettura: «Kidney cancer»

555. Immunotherapy Bridge 2022 (hybrid event: in presence – Naples [Italy] + Webinar), November 30th-December 1st, 2022
Symposium: What's new in immunotherapy
Relazione: «Renal Cell Carcinoma»

556. China-Europe Medical Forum on Gynecology, February 4th, 2023 (virtual)
Relazione: «Progress in immunotherapy of cervical cancer: rationale and mechanisms»

557. International Kidney Cancer Symposium: Europe, Edinburgh (Scotland), 21-22 April, 2023
Relazione: «Optimizing later line therapy selection»

558. ReIn CaRe 2023 – Réunion Interdisciplinaire Cancer du Rein, Nice (France), 10-12 Mai, 2023
Relazione: «RCC treatment: actuality and vision for the future»

559. International School of Clinical Oncology (ISCO) Annual Congress, 11-12 May 2023, Cairo (Egypt)
Relazione: «Factors to inform 1st line decision in mRCC: IO-TKI vs IO-IO, the debate»

Seminari

560. Seminario su invito presso l'IRCCS Fondazione 'Salvatore Maugeri' di Pavia: Tossicologia Cardiaca, Pavia, 20 Maggio 2003
Relazione: «Tossicità cardiaca da chemioterapici»

561. Seminario su invito presso il Department of Clinical Pharmacology, Rhode Island Hospital e Brown University, Providence, RI (USA), 15 Luglio 2003
Relazione: «Oxidative DNA damage induced by high-dose chemotherapy: clinical implications for high-dose regimens with peripheral blood stem cell support in the treatment of solid and hematologic malignancies»

562. Seminario su invito presso il Nerviano Medical Sciences (NMS), Nerviano, 1 Febbraio 2005
Relazione: «Malignant Mesothelioma: from pathogenesis to targeted-treatments»

563. Seminario su invito presso la Divisione di Oncologia Medica 'Falck' dell'Ospedale di Niguarda Cà Granda: Avanzamenti nella terapia medica del carcinoma renale, Milano, 4 Luglio 2006
Relazione: «Advances in the treatment of RCC: anti-angiogenic drugs and multi-kinase inhibitors»

564. Seminario su invito presso la Divisione di Oncologia Medica dell'Ospedale 'SS. Antonio e Biagio e Carlo Arrigo' di Alessandria, Alessandria, 16 Novembre 2006
Relazione: «Advances in the treatment of RCC: anti-angiogenic drugs and multi-kinase inhibitors»

565. Seminario su invito presso l'Ospedale di Bolzano, Bolzano/Bözen, 10 Settembre 2007
Relazione: «Nuove strategie terapeutiche per il carcinoma renale metastatico»

566. ECM at home: carcinoma del rene, Biella, 30 Settembre 2009

Relazione: «Trattamento medico del carcinoma renale avanzato: stato dell'arte e problematiche aperte»

567. Seminario su invito presso Divisione di Oncologia Medica dell'Ospedale Civile Sant'Andrea, La Spezia, 1 Ottobre 2009
Relazione: «Il trattamento dei tumori del rene»

568. Seminario su invito presso Divisione di Oncologia Medica dell'Ospedale della Versilia, Lido di Camaiore (LU), 20 Ottobre 2009
Relazione: «Il trattamento dei tumori del rene»

569. ECM at home: carcinoma del rene, Brescia, 17 Novembre 2009
Relazione: «Il trattamento dei tumori del rene»

570. ECM at home: carcinoma del rene, Pisa, 2 Marzo 2010
Relazione: «Il trattamento dei tumori del rene»

571. ECM at home: carcinoma del rene, Firenze, 20 Marzo 2010
Relazione: «Il trattamento dei tumori del rene»

572. Seminario su invito presso l'Universitätsspital Zürich, Zürich (Switzerland), 29 Aprile 2010
Relazione: «Systemic therapy of renal cell cancer»

573. ECM at home: Focus on: carcinoma del polmone e carcinoma del rene, Busto Arsizio (VA), 11 Maggio 2010
Relazione: «La terapia medica del carcinoma renale: stato attuale»

574. ECM at home: Aggiornamenti in tema di carcinoma del rene, Mantova, 28 Giugno 2010
Relazione: «Gestione ottimale del paziente affetto da carcinoma renale»

575. Seminario su invito presso la Divisione di Oncologia Medica 'Falck' dell'Ospedale Niguarda Cà Granda, Milano, 5 Ottobre 2010
Relazione: «Everolimus: una nuova opzione terapeutica per il carcinoma renale»

576. Seminario su invito presso l'Inselspital, Bern (Switzerland), 20 Ottobre 2010
Relazione: «Systemic therapy of renal cell cancer»

577. Seminario su invito presso il Bundang Seoul National University Hospital, Seoul (Korea), 25 Agosto 2011
Relazione: «Considerations in RCC treatment selection: progress and challenges to date»

578. Seminario su invito presso il Samsung Cancer Center, Seoul (Korea), 26 Agosto 2011
Relazione: «Considerations in RCC treatment selection: progress and challenges to date»

579. Seminario su invito presso la Divisione di Oncologia Medica dell'Azienda Ospedaliera-Universitaria Maggiore della Carità, Novara, 23 Novembre 2011

Relazione: «Mi viene il dubbio che …; qualcosa che nessuno – di solito – vi dice sul trattamento del carcinoma renale avanzato»

580. Seminario su invito presso la Divisione di Oncologia Medica dell'Ospedale San Carlo Borromeo, Milano, 28 Novembre 2011
Relazione: «Il trattamento sistemico del carcinoma renale avanzato»

581. Workshop congiunto Fondazione Smith Kline/AIOM: "PROs in Oncologia", Milano, 10 Ottobre 2013
Relazione: «Quando la QoL diventa un fattore di scelta terapeutica»

582. Webinar: Highlights 2014 nel carcinoma renale avanzato, 13 Ottobre 2014

583. Seminario su invito presso l'Ospedale Umberto I, Roma, 5 Novembre 2014
Relazione: «Optimizing the use of targeted therapies in metastatic renal cell carcinoma»

584. Seminario su invito presso il Department of Urology, Semmelweis University, Budapest (Hungary), December 11-12, 2015
Relazione: «The treatment of advanced RCC: from first-line to ...»

585. Seminario su invito presso il Department of Urology, Semmelweis University, Budapest (Hungary), December 11-12, 2015
Relazione: «Novelties in the pathogenesis of RCC leading to new therapeutic approaches: a glowing glance into the crystal ball»

586. Seminario su invito presso il Department of Urology, Semmelweis University, Budapest (Hungary), December 11-12, 2015
Relazione: «Adjuvant and neo-adjuvant treatment for RCC»

587. Seminario su invito presso la Divisione di Oncologia Medica dell'Ospedale Galliera di Genova, Genova, 15 Giugno 2016
Relazione: «Trattamenti farmacologici di 1° e 2° linea nel carcinoma renale metastatico: cosa è cambiato»

588. Seminario su invito presso la Divisione di Oncologia Medica dell'Ospedale "Guglielmo da Saliceto" di Piacenza, Piacenza, 20 Giugno 2016
Relazione: Trattamenti farmacologici di 1° e 2° linea nel carcinoma renale metastatico: cosa è cambiato»

589. Seminario su invito presso il Princess Margaret Cancer Center/University Hospitals Network, Toronto (Canada), 18 August 2016
Relazione: «Are we close or not to Precision Medicine in kidney cancer?»

590. Seminario per Oncologi Medici Egiziani nell'ambito del progetto "Perceptorship in Medical Oncology", svoltosi presso l'IRCCS Policlinico San Matteo di Pavia, Pavia, 11-13 Gennaio 2017
Relazione: «How to design a clinical protocol in my hospital»

591. Seminario presso il Dipartimento di Medicina Molecolare dell'Università degli Studi di Pavia, Pavia, 8 Giugno 2017

Relazione: «Precision medicine and kidney cancer: a glowing glance to what should be, or just another politicians' promise?»

592. Seminario su invito presso la Divisione di Oncologia Medica dell'Ospedale SS. Annunziata di Sassari, Sassari, 20 Giugno 2017
Relazione: «Lo stato dell'arte del trattamento medico del mRCC»

593. Seminario su invito presso l'Università degli Studi di Palermo, Palermo, 11 Maggio 2018
Relazione: «Renal cell cancer treatment: focus on immunotherapy»

594. Seminario su invito presso la Divisione di Oncologia Medica della Poliambulanza di Brescia, Brescia, 21 Maggio 2018
Relazione: «La terapia del tumore renale metastatico: l'oggi è già domani»

595. Seminario su invito presso l'Antoni Van Leeuwenhoek Hospital/The Netherlands Cancer Center, Amsterdam (The Netherlands), 1 Febbraio 2019
Relazione: «Medical treatment of kidney cancer»

596. Seminario su invito al 18° Corso di Formazione Avanzata della Fondazione Ghislieri Immunoterapia, Pavia, 22-24 Maggio 2019
Relazione: «Immunology in Clinical Oncology: open questions»

597. Seminario su invito presso la Divisione di Oncologia Medica dell'Ospedale Giovanni Paolo XXIII di Bergamo, Bergamo, 30 Ottobre 2019
Relazione: «Terapie in associazione e/o sequenze: il punto di vista dell'Oncologo»

598. N. 5 seminari locali ed un seminario nazionale presso Ospedali Canadesi (Halifax, Montreal, Quebec City, Ottawa, Toronto, Hamilton), organizzati da OncologyEducation, Dicembre 2020-Febbraio 2021 (virtual)
Relazione: «Individualizing renal cancer care: from biology to treatment approaches»

599. Seminario alle Scuole di Specializzazione in Urologia delle Università di Firenze e Genova, 6 Febbraio 2023 (virtual)
Relazione: «Advanced kidney cancer: the Oncologist's viewpoint»

Simposi satellite, Seminari e Corsi di Aggiornamento per Industrie Farmaceutiche

600. Janssen-Cilag First European Sales Training Meeting, Baveno (Italy), 28-29 April 1998
Relazione: Biology and treatment of lung cancer.
Relazione: «Lo stato dell'arte nel trattamento del mRCC»

601. Sorafenib Slide Development Workshop, Madrid (España), 27 April 2006
Relazione: «Clinical experience with Sorafenib»

602. Web seminar: Recap & Impact - ESMO 2006
Relazione: «Sorafenib: data presented at the European Society of Medical Oncology (ESMO)»

603. Convention di lancio del Sutent™, Verona, 10 Gennaio 2007
Relazione: «Esperienza personale con il Sutent»

604. Nexavar™ Launch Symposium, Seoul (Korea), 27 April 2007
Relazione: «Nexavar in hepatocellular carcinoma»

605. Nexavar™ Launch Symposium, Seoul (Korea), 27 April 2007
Relazione: «Overview of other development areas for Nexavar (malignant melanoma, NSCLC, etc.)»

606. Nexavar™ Launch Symposium, Ljubljana (Slovenia), 14 June 2007
Relazione: «Novel therapies in HCC»

607. Official Satellite Symposium of the 10th Annual Meeting of the Chinese Society of Clinical Oncology (CSCO), Harbin (China), September 20th, 2007
Relazione: «Recent advances with Sorafenib in the treatment of Hepatocellular Carcinoma (HCC)»

608. Official ECCO 14 Sponsored Satellite Symposium: Towards a treatment algorithm for advanced renal cell carcinoma (RCC): the role of targeted therapies, Barcelona (España), 26 September 2007
Relazione: «Defining the current role of targeted therapies in the treatment of renal cell carcinoma»

609. Nexavar™ Launch Symposium, Singapore (Singapore), 10 October 2007
Relazione: «Sorafenib: multikinase inhibition in kidney and lung cancer»

610. Nexavar™ Launch Symposium, Canacona, Goa (India), 23-24 February 2008
Relazione: «Making history: Nexavar in RCC»

611. Nexavar™ Launch Symposium, Canacona, Goa (India), 23-24 February 2008
Relazione: «Beyond RCC: progress with Nexavar in HCC»

612. Official Joint ECCO (European Cancer Conference) 15-34th ESMO (European Society of Medical Oncology) Satellite Symposium, Berlin (Germany), 20-24 September 2009
Relazione: «Bevacizumab plus IFN: delivering clinical benefit in mRCC»

613. Simposio Satellite Bayer nel corso del 11° Congresso Nazionale di Oncologia Medica (AIOM), Milano, 10-13 Ottobre 2009
Relazione: «Beyond RCC: progress with Nexavar in HCC»

614. Afinitor™ Launch Symposium, Oslo (Norway), 18 November 2009
Relazione: «mTOR: a critical pathway for RCC»

615. Official GSK sponsored European Association of Urology Satellite Symposium: Time for change: optimizing treatment for metastatic renal cell carcinoma, Barcelona (España), 19 April 2010
Relazione: «Evolution of systemic treatments for metastatic RCC»

616. Simposio Satellite Pfizer nel corso del 12° Congresso Nazionale di Oncologia Medica (AIOM), Roma, 6-8 Novembre 2010
Relazione: «Il trattamento di prima linea nel paziente *poor-risk*: considerazioni ed esperienze»

617. Pfizer Oncology Europe – Year Beginning Meeting, Lisbon (Portugal), 2 December 2010
Relazione: «Treatment of patients with metastatic renal cell carcinoma according to risk status: considerations and experiences»

618. GSK Oncology Event, Siena, 16-19 Maggio 2011
Relazione: «Pazopanib nel RCC»

619. Simposio Satellite Pfizer nel corso del XIII Congresso Nazionale di Oncologia Medica (AIOM), Bologna, 5-8 Novembre 2011
Chairmanship dell'intero Simposio (con C.N. Sternberg)

620. Simposio Satellite Pfizer nel corso del XIII Congresso Nazionale di Oncologia Medica (AIOM), Bologna, 5-8 Novembre 2011
Relazione: «Considerazioni conclusive: take home messages»

621. Pfizer Satellite Symposium at the Seventh European International Kidney Cancer Symposium (EIKCS): Long-term management of mRCC: recent advances and ongoing debates, Vienna (Austria), 4 May 2012
Relazione: «Difficult-to-treat mRCC patients: available first-line options and remaining questions»

622. American Society of Clinical Oncology (ASCO) 2012 Annual Meeting Official Symposium: Emerging therapies for metastatic Renal Cell Carcinoma: improving the current treatment landscape, Chicago, Ill. (USA), 2 June 2012
Relazione: «Improving patient outcomes in Renal Cell Carcinoma (RCC) through management of Adverse Events (AEs)»

623. Simposio Satellite GSK nel corso del XIV Congresso Nazionale di Oncologia Medica (AIOM), Roma, 27-29 Ottobre 2012
Relazione: «Il punto di vista dell'Oncologo: lo studio PISCES»

624. Simposio Satellite Pfizer nel corso del XIV Congresso Nazionale di Oncologia Medica (AIOM), Roma, 27-29 Ottobre 2012
Relazione: «Quali trattamenti successivi? Considerazioni sulle strategie di sequencing»

625. Novartis Pharma Sponsored Symposium at the 27th Annual Congress of the European Association of Urology (EAU): Sifting through the evidence in GU malignancies: A day in the clinic, Paris (France), 3-4 November 2012
Relazione: «Treating with TKIs in mRCC: from resistance to resensitization»

626. Bayer-Schering Pharma Joint RCC/HCC EMEA/Region Europe & Canada Meeting: Sharing real-world experience with sorafenib in RCC and HCC: where are we now? Kyiv (Ukraine), 3-4 November 2012
Chairmanship dell'intero Meeting (con M. Peck-Radosavljevic)

627. Bayer-Schering Pharma Joint RCC/HCC EMEA/Region Europe & Canada Meeting: Sharing real-world experience with sorafenib in RCC and HCC: where are we now? Kyiv (Ukraine), 3-4 November 2012
Relazione: «Sorafenib in RCC: where are we now?»

628. Bayer-Schering Pharma Joint RCC/HCC EMEA/Region Europe & Canada Meeting: Sharing real-world experience with sorafenib in RCC and HCC: where are we now? Kyiv (Ukraine), 3-4 November 2012
Relazione: «Primary and secondary end-points: OS and surrogate end-points for clinical trials in RCC»

629. Bayer-Schering Pharma Joint RCC/HCC EMEA/Region Europe & Canada Meeting: Sharing real-world experience with sorafenib in RCC and HCC: where are we now? Kyiv (Ukraine), 3-4 November 2012
Relazione: «Patient-focused approach in RCC: an update»

630. Astellas Sponsored Symposium at the 4th European Multidisciplinary Meeting on Urological Cancers (EMUC): Is there a need for a new TKI in advanced RCC?, Barcelona (España), 19 November 2012
Relazione: «Case history: the physician and patient experience»

631. Bayer-Schering Pharma Sponsored Symposium at the 4th European Multidisciplinary Meeting on Urological Cancers (EMUC): Extending survival for patients with RCC and CRPC: new hope in advanced disease, Barcelona (España), 19 November 2012
Relazione: «Building the optimal sequence in metastatic RCC to maximize survival benefit»

632. Bayer-Schering Pharma Sponsored Symposium at the 28th Annual European Association of Urology (EAU) Congress: Extending survival in RCC and CRPC: current evidences and future horizons, Milan (Italy), 15 March 2013
Relazione: «How should we tailor the RCC treatment strategy for individual patients?»

633. Pfizer Oncology Sponsored Symposium at the Eight European International Kidney Cancer Symposium (EIKCS): The evolving mRCC landscape: building on evidence and experience, Budapest (Hungary), 3 May 2013
Relazione: «First-line treatment of mRCC: providing context»

634. Pfizer Oncology Sponsored 'Meet the Experts' Dinner at the Eight European International Kidney Cancer Symposium (EIKCS), Budapest (Hungary), 3 May 2013
Relazione: «Evidence to support the use of sunitinib as first-line treatment for mRCC»

635. Astellas Oncology Sponsored Symposium at the Eight European International Kidney Cancer Symposium (EIKCS), Budapest (Hungary), 4 May 2013
Relazione: «Is there a need for a new TKI in advanced RCC?»

636. Simposio Satellite Pfizer nel corso del XV Congresso Nazionale di Oncologia Medica (AIOM), Milano, 11-13 Ottobre 2013
Moderazione dell'intero simposio (con G. Cartenì)

637. Simposio Satellite Pfizer nel corso del XV Congresso Nazionale di Oncologia Medica (AIOM), Milano, 11-13 Ottobre 2013
Relazione: «Take Home Messages»

638. Seminario in Astellas, Milano, 14 Novembre 2013

Relazione: «Farmaci antitumorali ad alto costo: aspetti di economia sanitaria»

639. Pfizer Oncology Modified Schedule Expert Roundtable, Frankfurt (Germany), 12 September 2014
Relazione: «Overview of Sutent schedule modification data and RAINBOW study»

640. Official ESMO 2014 Sponsored Satellite Symposium: Immuno-Oncology: a potential new approach in genitourinary cancers, Madrid (España), 26 September 2014
Relazione: «Biomarkers in Immuno-Oncology: expectations and challenges»

641. Simposio Satellite Pfizer nel corso del XVI Congresso Nazionale di Oncologia Medica (AIOM), Roma, 24-26 Ottobre 2014
Relazione: «Axitinib: la nuova opzione nel trattamento di seconda linea»

642. Pfizer Oncology Sponsored Symposium (Practical approach to optimising therapy in mRCC) at the 10th European International Kidney Cancer Symposium (EIKCS), Lyon (France), 24 April 2015
Relazione: «Selecting the most appropriate treatment»

643. Novartis Oncology Sponsored Symposium (Understanding therapeutic options across several lines of therapy for aRCC) at the 10th European International Kidney Cancer Symposium (EIKCS), Lyon (France), 25 April 2015
Relazione: «Second-line therapy after VEGFR TKIs»

644. Novartis Oncology: 2nd European Scientific Seminar (NOESS), Berlin (Germany), 27-28 June 2016
Panel Discussion: solid tumors

645. ESMO 2016 Industry Satellite Symposium: Management of advanced renal cell carcinoma in the spotlight: important changes are occurring, Copenhagen (Denmark), October 8th, 2016
Relazione: «Tyrosine kinase inhibition for advanced RCC: what's changed?»

646. Simposio Satellite Novartis nel corso del XVIII Congresso Nazionale di Oncologia Medica (AIOM), Roma, 28-30 Ottobre 2016
Tavola rotonda (con: L. Del Mastro, M. De Laurentis, R, Iacovelli, V. Gregorc e A. Ardizzoni)

647. Simposio Satellite Eisai nel corso del XVIII Congresso Nazionale di Oncologia Medica (AIOM), Roma, 28-30 Ottobre 2016
Relazione: «Lenvatinib più Everolimus nel carcinoma renale avanzato»

648. ECCO 2017 Industry Satellite Symposium: Raising the bar in the management of advanced renal cell carcinoma, Amsterdam (The Netherlands), 29 January 2017
Relazione: «New expectations in first-line therapy for advanced RCC»

649. Astra Zeneca One4U Scientific Exchange Meeting, Roma, 9-10 Febbraio 2017
Panelist (con: E. Pujade-Lauraine, A. Sobrero, M. Perol e S. Dahlberg) nella Breakout Session #7: Duration and sequencing of treatment to optimise outcome

650. Meeting: Nivolution – raising the bar in Oncology, Roma, 24-25 Febbraio 2017
Chairmanship (con G. Procopio) della Tavola Rotonda: Tollerabilità e qualità della vita (Panel: U. Basso, L. Galli, M. Milella e P.A. Zucali)

651. Training alle Direzioni Meciche di BMS (Worldwide Field Medical Oncology Training), Praga (Repubblica Ceca), 15 Marzo 2017
Relazione: «Bladder cancer overview»

652. Pfizer RCC Balkan Summit, Belgrade (Serbija), 1 April 2017
Relazione: «Real world practice: what have we learned over the past 10 years of sunitinib in mRCC?»

653. Pfizer RCC Balkan Summit, Belgrade (Serbija), 1 April 2017
Co-Chairing (con M. Schmidinger) del Workshop: Exchange of clinical excellence – How would you treat this patient?

654. Pfizer RCC Balkan Summit, Belgrade (Serbija), 1 April 2017
Relazione: «Summary and take home messages»

655. Workshop Nivolution: first in class in RCC, Milano, 7 Luglio 2017
Relazione: «Conferma ed innovazione: l'immuno-oncologia nel carcinoma renale»

656. Workshop Nivolution: first in class in RCC, Milano, 7 Luglio 2017
Chairmanship (con G. Procopio) della sessione: Efficacia

657. Workshop Nivolution: first in class in RCC, Milano, 7 Luglio 2017
Chairmanship (con G. Procopio) della sessione: Popolazioni speciali

658. Workshop Nivolution: first in class in RCC, Milano, 7 Luglio 2017
Chairmanship (con G. Procopio) della sessione: Tollerabilità e qualità della vita

659. Simposio Satellite Pfizer nel corso del XIX Congresso Nazionale di Oncologia Medica (AIOM), Roma, 27-29 Ottobre 2017
Moderazione dell'intero simposio (27 Ottobre 2017)

660. Simposio Satellite Ipsen nel corso del XIX Congresso Nazionale di Oncologia Medica (AIOM), Roma, 27-29 Ottobre 2017
Relazione: «Superare le resistenze alle terapie di I linea: nuove strategie terapeutiche in seconda linea»

661. CA.RE 3.0 – Evento di lancio del Cabometyx, Milano, 26-27 Gennaio 2018
Terza Sessione: METEOR: approfondimenti sullo studio registrativo di Cabozantinib in mRCC. Relazione: «Evidence to Decision» (con G. Pappagallo)

662. EUSA Pharma Symposium at the 13th European International Kidney Cancer Symposium (EIKCS), Prague (Czech Republic), 27 April 2018
Relazione: «Selective VEGFR inhibition: introducing Tivozanib»

663. Novartis Symposium at the 13th European International Kidney Cancer Symposium (EIKCS), Prague (Czech Republic), 28 April 2018

Relazione: «Looking ahead: unmet needs and novel mechanisms of action»

664. Simposio General Electrics (GE) Healthcare: Paziente Oncologico ed oltre: primum non nocere. Esperti a confronto, nel corso del Congresso Nazionale della Società Italiana di Radiologia Medica (SIRM), Genova, 9 Novembre 2018
Talk Show con: C. Privitera, L. Gesualdo, A. Laghi e L. Cosmai

665. Simposio Satellite EUSA Pharma nel corso del XX Congresso Nazionale di Oncologia Medica (AIOM), Roma, 16-18 Novembre 2018
Relazione: «La patogenesi molecolare del carcinoma renale»

666. Simposio Satellite Pfizer Oncology nel corso del XX Congresso Nazionale di Oncologia Medica (AIOM), Roma, 16-18 Novembre 2018
Moderazione del Simposio

667. Simposio Satellite Pfizer Oncology nel corso del XX Congresso Nazionale di Oncologia Medica (AIOM), Roma, 16-18 Novembre 2018
Relazione: «Axitinib: protagonista di nuove strategie di combinazione»

668. EUSA Pharma Symposium at the 14th European International Kidney Cancer Symposium (EIKCS), Dubrovnik (Croatia), 30 March 2019
Relazione: «First-line advanced RCC management: what does tivozanib offer?»

669. Ipsen Symposium at the European Society of Medical Oncology (ESMO) virtual congress 2020, 22 September 2020
Relazione: «Personalizing treatment approaches in clinical practice. Part 1 – Sequencing of treatment in aRCC following progression»

670. EUSA University Fotivda™ Webinar: Renal cell carcinoma in the age of immunotherapy (virtual), 16 October 2020
Relazione: «State of the art advances in RCC: treatment in the age of immunotherapy»

671. EUSA Pharma post-ESMO Webinar: Looking to the future in managing patients with mRCC: ESMO 2020 (virtual), 19 October 2020
Relazione: «Which treatment for which patient? What we have learned from ESMO 2020»

672. Simposio Satellite MSD al XXII Congresso Nazionale dell'Associazione Italiana di Oncologia Medica (AIOM) 2020: Digital Keynotes 2020: nuove opportunità di cura nel trattamento del NSCLC, del tumore renale, del distretto testa-collo e del melanoma (virtual), 30 Ottobre 2020
Relazione: «La prima linea nel tumore del rene: dal TKI alla terapia di combinazione, nuove opportunità di cura»

673. Simposio Satellite BMS al XXII Congresso Nazionale dell'Associazione Italiana di Oncologia Medica (AIOM) 2020 – virtual, 1 Novembre 2020
Relazione: «RCC: a powerful beginning to obtain the best disease control outcomes»

674. Angelini Pharma Fotivda Kick-Off Meeting, 4th March 2021 (virtual)
Relazione: «Tivozanib: from the bench to the bedside»

675. Angelini Pharma Medical Training Session on aRCC treatment: the role of TKIs, 4th February 2021 (virtual)
Relazione: «State of the art advances in renal cell carcinoma»

676. Angelini Pharma Medical Training Session on aRCC treatment: the role of TKIs, 4th February 2021 (virtual)
Relazione: «Tivozanib and TKIs as 1L treatment in renal cell carcinoma»

677. Meeting: Nivolution – Leading the next revolution, Roma, 24-25 Marzo 2022
Partecipazione alla Tavola Rotonda Tavola Rotonda: «L'immunoterapia nella pratica clinica: la visione italiana» (con: A. Santoro, F. De Braud, M. Maio, F. Capuzzo, F. De Vita)

678. Simposio Satellite Eisai al XXIV Congresso Nazionale dell'Associazione Italiana di Oncologia Medica (AIOM) 2022: Immunoterapia e TKIs: dal razionale biologico alla pratica clinica. Focus sul carcinoma dell'endometrio e del rene, 3 Ottobre 2022
Relazione: «Focus sul carcinoma del rene»

679. Satellite Symposium Angelini at the Congresul National de Oncologie (hybrid event: in presence – Poiana Brasov [Romania] + Webinar), 5-8 October 2022
Relazione: «How to optimize first-line systemic therapy selection in the treatment of metastatic renal cell carcinoma»

Migliori 5 relazioni/moderazioni

1. 49th Annual Meeting of the American Society of Clinical Oncology (ASCO 2013), Chicago, Ill. (USA), May 31-June 4, 2013
   Co-Chair (con E.M. Posadas) della Sessione: Genitourinary (non prostate) Poster Discussion Session

2. European Cancer Congress (ECCO 17, ESMO 38, ESTRO 32), Amsterdam (The Netherlands), 27 September-1 October 2012
   Debate: «This house believes there is no need for more VEGFR TKIs to treat renal cancer. Contra» (con B. Escudier)

3. Joint ECCO 15-ESMO 34th Multidisciplinary Congress, Berlin (Germany), 20-24 September 2009
   Scientific Symposium: What are the side-effects of therapy in metastatic RCC and how to handle them? Relazione: «Do combination and sequential therapies have increased side-effects?»

4. 10th Annual Meeting of the Chinese Society of Clinical Oncology (CSCO), Harbin (China), September 20th, 2007
   Relazione: «Targeted Therapy in Hepatocellular Carcinoma (HCC): an informative update»

5. European Society of Medical Oncology (ESMO) Virtual Congress 2020, 19-21 Settembre 2020
   Sessione: Presidential Symposium I. Discussant dell'abstract n. 696O, presentato da Toni K. Choueiri «Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial»

PUBBLICAZIONI SCIENTIFICHE DEL Prof. CAMILLO PORTA

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1. Bobbio-Pallavicini E, **Porta C**, Anselmetti L, Viarengo GL, Nastasi G, Notario A. Acute promyelocytic leukaemia (APL): chemotherapy or bone marrow transplantation? *Bone Marrow Transpl* 1989;4(Suppl. 3):102.

SUMMARY - We studied 24 patients affected by Acute Promyelocytic Leukemia (APL) treated according to the original Jean Bernard's protocol (an induction phase with high doses of DNR, followed by a manteinance phase with MTX and 6-MP, and periodic reinduction cycles with DNR and Methyl-GAG). We obtained 21 CR (87.5%), while 3 patients died during the induction treatment. The 5-year mortality rate of all the patients was 46.1%; 12 patients are still alive and 9 (37.5%) relapsed at different times from the first remission. From the accurate analysis of these cases we concluded that the microgranular variant of the disease and the impossibility to perform a correct maintenance therapy are negative prognostic indexes and, ultimately, a possible indication to BMT in adult patients affected by APL.
I.F. = 1,995
N. citazioni = 1

2. Nastasi G, Spaghi A, Costa D, Albergati MG, Moroni M, **Porta C**, Bobbio-Pallavicini E, Notario A. Infiltrazione eosinofila del tratto gastro-enterico: descrizione di un caso clinico simulante un processo linfoproliferativo. *Medicina-rivista EMI* 1990;10:27-9.

SUMMARY - A case of diffuse eosinophilic infiltration of the gastroenteric tract which involved a large portion of the small intestine is discussed. It arose in a patient not previously affected with allergic traits and without eosinophilia in peripheral blood. Problems of differential diagnosis and clinical-therapeutic implications are reported.
I.F. = n.r.

3. **Porta C**, Nastasi G, Spaghi A, Moroni M. Doxorubicin/methotrexate/fluorouracil in advanced pancreatic cancer. *Lancet* 1990;i(336):1454-5 [Letter].

SUMMARY - We report our discouraging preliminary data relative to an ongoing phase-II trial aimed at evaluating Doxorubicin, Methotrexate and Fluorouracil (AMF) in advanced pancreatic cancer patients. Our data are clearly in contrast with those recently reported by other Authors. In conclusion, we quote Brennan and colleagues' words: "a more thorough understanding of the cellular biology of this tumor is needed", since there have been "insufficient effort(s) to correlate laboratory insights with clinical outcome".
I.F. = 15,940
N. citazioni = 1

4. **Porta C**, Moroni M, Nastasi G, Invernizzi R, Bobbio-Pallavicini E. Hypocholesterolemia and acute myeloid leukemia (AML). *Haematologica* 1991;76:348 [Letter].

SUMMARY - We investigated total blood cholesterolemia values at onset in 182 patients affected with AML (30 M1, 26 M2, 25 M3, 52 M4, 20 M5a, 8 M5b, 8 M6 and 13 M0). The mean cholesterolemia values observed in our series were compared with the average normal values of a control group reported in literature. In our series 83.5% of the patients presented with hypocholesterolemia, cholesterol values being significantly lower then the mean values observed in the control group with homologous sex and age ($p < 0.005$); The highest hypocholesterolemia values were observed in the most undifferentiated subtypes of AML: AMyL, FAB M1 (99 mg/dL) and AMoL, FAB M5a (97.5 mg/dL), while hypocholesterolemia was lower in the remaining groups. Hypocholesterolemia in AML patients may be referred to proliferating leukemic blasts stealing endogenous cholesterol for the synthesis of new cell membranes.
I.F. = 0,562
N. citazioni = 8

5. Gioglio L, **Porta C**, Moroni M, Nastasi G, Gangarossa I. Scrotal angiokeratoma (Fordyce): histopathological and ultrastructural findings. *Histol Histopathol* 1992;7 47-55.

SUMMARY - Bioptic findings related to four cases of scrotal angiokeratoma-Fordyce, were studied under light and electron microscopy. A particular heterogeneity of the structural and ultrastructural patterns typical of this lesion was thus observed. Light microscopy study pointed out, in particular, different degrees of dilation of papillary vessels, whereas ultrastructural study highlighted marked alterations of endothelial cells with structural and quantitative modifications of cytoplasmic organelles.
I.F. = 0,486
N. citazioni = 10

6. Caporali R, Choucair J, Bobbio-Pallavicini E, **Porta C**, Montecucco C. Autoantibody profile in thrombotic thrombocytopenic purpura. *Transfus Sci* 1992;13:33-6.

SUMMARY - Patients with Systemic Lupus Erythematosus (SLE) and related autoimmune disorders may develop disturbances in blood coagulation characterized by coexistent thrombosis and thrombocytopenia, as always occurs in Thrombotic Thrombocytopenic Purpura (TTP) patients. These abnormalities are associated with antiphospholipid antibodies, usually responsible for LAC, BFP-STS, and positive ACA-tests. Present study deals with the measurement of circulating antiphospholipid antibodies and other SLE-associated circulating antibodies in 9 patients with active TTP, including one case with TTP "secondary" to SLE. In conclusion, we can confirm that antiphospholipid antibodies do not have a role in TTP. No patient with TTP had either IgG-ACA, BFP-STS, or LAC. This suggest that the mechanisms underlying thrombotic events and thrombocytopenia are quite different in TTP and the so-called "antiphospholipid antibodies syndrome", despite the cited clinical similarities.
I.F. = 0,438
N. citazioni = 2

7. Bobbio-Pallavicini E, **Porta C**, Fornasari PM, Viarengo GL, Ascari E. Thrombotic thrombocytopenic purpura (TTP): retrospective study on 84 patients and therapeutical prospects. *Transfus Sci* 1992;13:39-44.

SUMMARY - We analyzed clinical features and therapeutical options in 84 patients affected with TTP, gathered from 1970 to the present by centers adhering to the "Italian Cooperative Group for the study and treatment of TTP". We highlighted the effectiveness of plasma-exchange in the acute phase of the disease, effectiveness which was found to be directly proportional to the number of sessions and to the method and frequency of its execution. We also confirmed the correlation between neurological damage at onset and resulting survival. Therapeutical prospects were also reported and a new therapy protocol, which is now in progress, was presented and discussed.
I.F. = 0,438
N. citazioni = 19

8. Casagranda I, Beltrame M, Cosimi MF, Tommaselli F, Nastasi G, Moroni M, **Porta C**. Orbital involvement in multiple myeloma. *Pathologica* 1992;84:1-5.

SUMMARY - Orbital involvement is a rare manifestation of Multiple Myeloma. The initial clinical sign of the disease is often proptosis. The Authors report on a new case and emphasize the diagnostic procedures which led to a correct diagnosis.
I.F. = n.r.

9. Bobbio-Pallavicini E, Brambilla G, **Porta C**, Cannatelli G, Battistini E, Gorini M. Chronic Epstein-Barr virus infection. *Haematologica* 1992;77:359-60.

SUMMARY - To date, EBV has been associated with 3 types of clinical manifestations: infectious mononucleosis, Burkitt's lymphoma and nasopharyngeal carcinoma. Thanks to recent advances in the study of this virus, serological profiles can now be traced which are typical of both the first infection, and the reactivation of a latent infection. Strauss and Coll. have described the clinical and the serological features of recurrent EBV infection, a syndrome which other Authors have identified with the Chronic Asthenia Syndrome, even if the exact etiology of this condition has, at times, proved to be different. We report the case of a 30 years old male whose serological profile was demonstrated to be consistent with that observed in the reactivation of latent EBV infection. Differential diagnosis with other conditions, such as the Chronic Asthenia Syndrome or even psychiatric disorders, is discussed.
I.F. = 0,562

10. Casagranda I, Davio P, Moroni M, Nastasi G, **Porta C**. Infusione di immunoglobuline ad alte dosi in un caso di porpora trombocitopenica idiopatica. *Minerva Med* 1992;83:1-4.

RIASSUNTO - La Porpora Trombocitopenica Idiopatica (PTI) è una patologia caratterizzata dalla presenza in circolo di autoanticorpi piastrinici che provocano la distruzione prematura delle piastrine da parte del sistema reticoloendoteliale. Riportiamo un caso di PTI insensibile alla terapia steroidea, trattamento di prima scelta per questa malattia, risoltosi completamente con l'infusione di immunoglobuline (400 mg/Kg/die per 5 giorni) in associazione a dosi decrescenti di steroide. Al termine del trattamento con HDIgG, il paziente presentava normali valori piastrinici e, a tutt'oggi, a 5 mesi di distanza dalla sospensione di ogni trattamento, gode di buone condizioni di salute e presenta valori piastrinici nella norma.
I.F. = 0,065

11. Santagati G, Nastasi G, **Porta C**, Moroni M, Santagati C, Casagranda I, Bobbio-Pallavicini E, Cosimi MF. Low doses of α-2b interferon in the treatment of hairy cell leukemia: results of treatment and mean follow-up at 18 months in 13 patients. *Pathologica* 1992;84:1-6.

SUMMARY - We treated 13 Hairy Cell Leukemia patients with rIFN α-2b. In case of complete/partial response, the patients were submitted to maintenance treatment, while, in case of minimal/no response, a second induction cycle was administered, followed by a manteinance one. The patients were followed, on an outpatient basis, for 18 months at least, obtaining a 100% overall response rate; one patient had compete response, 7 had partial response, and 5 only minimal response. Six patients (46%) relapsed an average of 13 months after the end of the treatment. The utitlity of a manteinance therapy is discussed.
I.F. = n.r.

12. Cosimi MF, Casagranda I, **Porta C**, Moroni M, Orsi R, Nastasi G. Correlación entre el grado de malignidad histológica y la positividad nuclear con la técnica de AgNOR en 6 casos de LNH óseos monolocalizados. *Sangre* 1992;37:399-402.

RESUMEN - Numerosos estudios han indicado que la puesta in evidencia de las regiones organizadores nucleolares (NORs) mediante la técnica argiròfila AgNOR puede ser ùtil en la evaluaciòn del grado de malignidad del tejido neoplasico, por ser indicativa del aumento de la síntesis proteica. Hemos aplicado esta tècnica a seis casos de linfoma no Hodgkin òseos monolocalizados (cuatro linfomas de grado intermedio de malignidad, dos de tipo difuso de celulas pequeña hendida y dos de tipo difuso de celulas pequeña hendida y non hendida, y dos linfomas de alto grado, variedad inmunoblàstica) con el fin de evaluar la correlaciòn entre el grado de malignidad histològica de la lesiòn y el número de regiones positivas para el AgNOR. Hemos constatado que la malignidad de la poblaciòn neoplasica, reflejada en el periodo de supervivencia y la tendencia a la infiltraciòn de partes blandas, se correlacionan con el nùmero de gràanulos AgNOR (sin olvidar la positividad para el anticuerpo monoclonal Ki-67), màs que con las características histològicas evaluadas clàsicamente mediante los criterios de la Working Formulation, por ser los primeros ìndices màs directamente relacionados con el ciclo (proliferaciòn) celular.
I.F. = n.r.
N. citazioni = 3

13. **Porta C**, Moroni M, Nastasi G, Ricci G, Casagranda I. Anti-HCV antibodies and hepatocellular carcinoma. Relationship in a medium-risk population. *Upsala J Med Sci* 1992;97:261-6.

SUMMARY - By means of an accurate immunoenzymatic assay, the prevalence was studied of antibodies to hepatitis C virus (HCV) in three different populations: 74 patients affected with Hepatocellular Carcinoma (HCC) on preexisting cirrhosis, 82 patients with liver cirrhosis but with no apparent neoplasm, and 70 control subjects, hospitalized for various conditions of internal medicine or geriatric interest. 70.2% of HCC patients exhibited anti-HCV antibodies, versus 47.5% of cirrhotic subjects with no tumor and 7.1% of controls. Such results suggested the possible role of HCV in the etiopathogenesis of HCC, and its possible synergy with other agents - e.g., hepatitis B virus, alcohol - in causing chronically injured hepatocytes to become neoplastic.
I.F. = 0,174
N. citazioni = 2

14. **Porta C**, Casagranda I, Semino G, Moroni M, Ratto C. Chronic myeloid leukaemia following cyclophosphamide-containing chemotherapy in a breast cancer patient. *Haematologica* 1993;78:56-7.

SUMMARY - Cyclophosphamide is not only an antineoplastic compound highly recommended as a component of post-operative adjuvant chemotherapy for breast cancer, but also a well-known carcinogenic agent, both in animals and in man. Indeed, bladder and renal tumors and non-lymphocytic acute leukaemias have been reported in patients receiving long-term cyclophosphamide therapy for both neoplastic and non-neoplastic diseases. We report on a rare case of Ph+ chronic myeloid leukaemia that developed after the administration of cyclophosphamide for a breast carcinoma, with enphasis on the relationship exhisting between cumulative dose and relative risk, clearly evidenced by other Authors and also present in the case of our patient.

I.F. = 1,000

N. citazioni = 6

15. Bobbio-Pallavicini E, **Porta C**, Moroni M, Spaghi A, Casagranda I, Nastasi G. Folinic acid does improve 5-FU activity *in vivo*. Results of a phase-III study comparing 5-FU to 5-FU and folinic acid in advanced colon cancer patients. *J Chemother* 1993;5:52-5.

SUMMARY - We report the results of a phase-III trial in which we compared 5-FU to 5-FU and FA in 150 previously untreated metastatic colon cancer patients. Patients were randomized in the ratio of 1:2 to receive 5-FU (370 mg/m^2, i.v., for 5 days) in arm A or equidose 5-FU plus FA (200 mg/m^2, i.v., for 5 days) for arm B, each cycle being repeated every 4 weeks. Five of 49 evaluable arm A patients (10.2%) and 31 of arm B (31.9%) achieved a complete or partial response ($p \leq 0.01$). Median survival time of arm A patients was 6 months (mean: 6.18), while it was 8 months (mean: 9.01) for arm B cases ($p \leq 0.05$). In conclusion, our data indicate that FA can enhance 5-FU activity and that this combination is an effective palliative treatment for metastatic colon cancer patients.

I.F. = 0,327

N. citazioni = 30

16. **Porta C**, Bobbio-Pallavicini E, Centurioni R, Tacconi F, Caporali R, Montecucco CM. Thrombotic thrombocytopenic purpura in systemic lupus erythematosus. *J Rheumatol* 1993;20:1625 [Letter].

SUMMARY - Systemic Lupus Erythematosus (SLE) and Thrombotic Thrombocytopenic Purpura (TTP) are two separate well-defined diseases which can share common clinical and pathologic findings. Within 103 TTP cases recently reviewed by the Italian Cooperative Group for TTP, we found only 4 patients (3.8%) with a known SLE who subsequently developed TTP, once more underlining the rarity of such association. Different from what observed by other Authors, the outcome of our patients was extremely unsatisfactory. In conclusion, the concomitant occurrence of SLE and TTP in the same patient is certainly rare, but it is probably underestimated and should be carefully considered, especially in patients with SLE presenting with thrombocytopenia and neurological symptoms, and differentiated from the so-called antiphospholipid antibodies syndrome, since mechanisms underlying thrombotic events and thrombocytopenia in these two conditions are quite different. Medical treatment should include plasma-exchange, which is undoubtedly the treatment of choice for this disease, and eventually, in the absence of clinical response, also other treatment modalities, such as immunosuppressant agents, antiplatelets drugs, staph-A column, and high doses of IgG.

I.F. = 2,276

N. citazioni = 31

17. **Porta C**, Bobbio-Pallavicini E, Centurioni R, Tacconi F, and the Italian Cooperative Group for TTP. Thrombotic thrombocytopenic purpura resistant to plasma-exchange: salvage treatment with high-dose IgG or vincristine. *Int J Artif Organs* 1993;16(S5):201-4.

SUMMARY - Even though plasma-exchange (PE), either alone or combined with cortisone or platelet anti-aggregating substances is the treatment of choice for TTP, 10-15% of patients is resistant to treatment. Since immunoglobulin (IgG) infusion was reported to cure the clinical symptoms of PE-resistant TTP, and vincristine (VCR) has been recently successful to treat TTP, we revised the results obtained with both drugs in 20 PE-resistant patients. Of 12 patients receiving IgG and 8 receiving VCR, 3 (25%) and 4 (50%), respectively, achieved complete remission. Even though no conclusions can be drawn from such results, if complete remission can be achieved in a however small number of PE-resistant patients, the use of these drugs is suggested as a salvage treatment for TTP.

I.F. = 0,743

N. citazioni = 6

18. Davio P, Casagranda I, Moroni M, **Porta C**, Ratto C, Cosimi MF, Bobbio-Pallavicini E. Difficoltà diagnostiche in un caso di malattia di Behçet. *Rec Progr Med* 1993;84:850-4.

RIASSUNTO - La Malattia di Behçet è un disordine multisistemico cronico determinato da un processo vasculitico che coinvolge vasi, sia venosi che arteriosi, di ogni calibro. Nel 1990 sono stati proposti una serie di criteri necessari per porre diagnosi di Malattia di Behçet: presenza di ulcere orali più almeno due dei seguenti sintomi o segni: ulcere genitali, caratteristiche lesioni oculari, tipiche lesioni cutanee, positività al pathergy test. Nonostante tali raccomandazioni, la diagnosi di Malattia di Behçet rimane a volte estremamente complessa, sia dal punto di vista clinico che da quello anatomopatologico. Riportiamo un caso di malattia di Behçet significativo a tal proposito.

I.F. = n.r.

N. citazioni = 2

19. **Porta C**, Bobbio-Pallavicini E. High-dose human immunoglobulins in thrombotic thrombocytopenic purpura. *Am J Hematol* 1994;45:99-100 [Letter].

SUMMARY - Even though plasma-exchange (PE) is nowadays widely recognized as the therapy of choice in the treatment of Thrombotic Thrombocytopenic Purpura (TTP), the role is still to be defined of the various drugs which are usually combined with PE - i.e., cortisone, platelet anti-aggregating substances, and vincristine. The inhibitory effect of human immunoglobulins on platelet aggregation which was observed in vitro has been considered as the rationale of their use in vivo in the treatment of TTP. However, only few reports seem to suggest that human immunoglobulins are effective to treat TTP, at least in the rare cases not responding to more conventional therapy. We briefly report on a recent case which was treated and cured by means of high-dose immunoglobulins administration, after the failure of combined apheretic therapy, cortisone and platelet anti-aggregating substances.

I.F. = 1,744

N. citazioni = 3

20. Bobbio-Pallavicini E, **Porta C**, Centurioni R, Gugliotta G, Vianelli N, Tacconi F, Billio A, Ascari E and the Italian

Cooperative Group for TTP. Vincristine sulfate for the treatment of thrombotic thrombocytopenic purpura refractory to plasma-exchange. *Eur J Haematol* 1994;52:222-6.

SUMMARY - Among all the patients treated by the Italian Cooperative Group for TTP, we retrospectively reviewed the results obtained using vincristine (VCR) in 8 TTP patients (4 men and 4 women, average age: 39.25 years, range: 23-48) who did not respond to combined apheretic and pharmacologic treatment. All patients, after failing to respond to treatment, were started on VCR at the dose of 2 mg, i.v., once a week. Despite this treatment, 4 patients (50%) died 1, 7, 12 and 25 days after the first VCR dose, respectively. The other 4 patients who received VCR achieved complete remission 24, 30, 40 and 50 days from the beginning of the treatment. Total doses of VCR ranged from 2 to 6 mg in the deceased group, and from 6 to 14 mg in the cured patients. In our experience, VCR is a promising agent to treat TTP patients resistant to conventional plasma-exchange and pharmacologic therapy.
I.F. = 1,836
N. citazioni = 62

21. **Porta C**, Moroni M, Nastasi G. Allopurinol mouthwashes in the treatment of 5-Fluorouracil-induced stomatitis. *Am J Clin Oncol (CCT)* 1994;17: 246-7.

SUMMARY - This study was aimed at assessing the efficacy of allopurinol mouthwashes in the treatment of 5-fluorouracil-induced stomatitis. A randomized double-blind, placebo-controlled trial was thus designed to tests its efficacy to treat oral mucositis in advanced cancer patients receiving 5-fluorouracil-containing chemotherapy. There were 44 patients randomized to receive allopurinol mouthwashes, or placebo, as soon as mucosal lesions were observed during any treatment cycle. Stomatitis was evaluated at the end of each 5-day treatment cycle. Allopurinol mouthwashes resolved stomatitis in 9 of 22 treated patients (40.9%), and diminished its intensity in 10 more patients (45.4%); stomatitis resolved completely in none of the 22 patients and partially in 3 patients in the placebo group ($p < .001$ by χ^2 test). Duration of symptoms was also significantly different between the two groups (median: 4 days for the allopurinol group, 7.5 days for the control group; $p < .0005$ by Student's t-test). In conclusion, our results suggest that allopurinol mouthwashes can be effective to treat 5-fluorouracil-induced stomatitis.
I.F. = 0,737
N. citazioni = 39

22. Montecucco CM, Caporali R, Rossi S, **Porta C**. Allopurinol mouthwashes in methotrexate-induced stomatitis. *Arthr Rheum* 1994;37:777-8.

SUMMARY - Some preliminary studies have shown that allopurinol mouthwashes are an effective treatment for 5-FU-induced stomatitis. Since the systemic administration of allopurinol does not improve the therapeutic ratio of 5-FU, a local action seems likely, possibly related to the anti-oxidant properties of this drug. Oral ulcers are among the commonest side effects of methotrexate (MTX) and represents a frequent adverse experience in rheumatoid arthritis (RA) patients receiving weekly low doses of this drug. We have therefore activated a pilot study to test the efficacy of allopurinol mouthwashes for the treatment of MTX-induced oral mucositis. Our preliminary data on 6 patients suggest that allopurinol mouthwashes may be effective in reducing oral discomfort in MTX-treated RA patients; it is well tolerated and does not affect the underlying disease.
I.F. = 6,298
N. citazioni = 13

23. Nastasi G, **Porta C**, Moroni M, Bobbio-Pallavicini E, Santagati G, Santagati C, Alessiani M. Nephrectomy as a component of systemic treatment for renal cell carcinoma patients. *J Surg Oncol* 1994;56:81-2 [Letter].

SUMMARY - Analyzing our personal experience on 62 patients with advanced renal cell cancer, observed over a period of 5 years, who underwent nephrectomy and then were recruited into three clinical trials of systemic therapy (vinblastine + IFN α2b, IL-2 + IFN α2b and Floxuridine alone), we concluded that nephrectomy should be routinely offered as a step of a more complex therapeutic approach to advanced renal cell cancer patients, which should include also systemic treatment.
I.F. = 0,443

24. **Porta C**, Moroni M, Nastasi G. Metachronous occurrence of seminoma and Hodgkin's lymphoma in the same patient with the late onset of colon cancer. *J Intern Med* 1994;236:1444-5.

SUMMARY - Testicular cancer and Hodgkin's disease are two malignancies sharing a lot of epidemiological similarities, including age classes and geographic distribution. However, the association of these tumours in the same patient is an exceptional event; to date, only 14 metachronous and 3 synchronous cases have been described in the literature. We report on a case of testicular seminoma and Hodgkin's lymphoma association, with the additional occurrence, near 20 years later, of a colon carcinoma.
I.F. = 1,622
N. citazioni = 6

25. Bobbio-Pallavicini E, **Porta C**, Tacconi F, Gugliotta L, Centurioni R, Vianelli N, Billio A, Ascari E and the Italian Cooperative Group for Thrombotic Thrombocytopenic Purpura. Intravenous Prostacyclin (as Epoprostenol) infusion in thrombotic thrombocytopenic purpura. Four case reports and review of the literature. *Haematologica* 1994;79: 429-37.

SUMMARY - Background: The enhanced platelet aggregation which is observed in TTP was suggested to be due to an unbalance between unknown agents insulting endothelial wall and defense factors, such as Prostacyclin (PGI_2). Several reports suggested an aberration of PGI_2 activity as a critical step in the pathogenesis of TTP. Therefore, PGI_2 was proposed as an alternative treatment for TTP patients. Methods: We report the results obtained with growing doses (from 2 ng/Kg/min to 10 ng/Kg/min in 5 days) of PGI_2 - as Epoprostenol - in 4 TTP patients from the retrospective series of the Italian Cooperative Group who were considered as resistant to conventional plasma-exchange (PE)-based treatments. Results: Despite PGI_2 infusion, 2 patients died, while the extant 2 achieved stable complete remission. Noteworthy, the only patient whose PE was administered with adequate frequency and for an adequate period of time, and thus the only unquestionably PE-resistant patient, was also resistant to PGI_2 infusion. Major side-effects were few and observed at the highest doses. Comments: In our personal experience and from the analysis of the literature, which, as far as we know, includes only 23 patients treated with PGI_2-like substances, the role of PGI_2 in the treatment of TTP appears to be modest. Maybe the identification of subgroups of TTP patients exhibiting some defects in PGI_2 metabolism, together with the use of more manageable PGI_2 analogs, such as Iloprost, could revive the interest in these molecules in the future.
I.F. = 1,090
N. citazioni = 15

26. **Porta C**, Moroni M, Nastasi G. 5-fluorouracil combined with the pure *l*-stereoisomer of leucovorin calcium to treat

advanced colon cancer patients: a phase-II study. *Oncol Rep* 1995;2:73-6.

SUMMARY - A theoretical superiority of 5-Fluorouracil (FUra) activity when combined with l-Leucovorin (LV) might be postulated on the basis of a possible interference of the inactive d-stereoisomer of LV with the active l-form. We treated 47 patients by means of FUra (370 mg/m²/day), and l-LV (100 mg/m²/day), for 5 consecutive days, every 4 weeks. An objective response was observed in 12 patients (25.5%, ninety-five percent confidence interval: 12.5-38.5%), with 2 complete responses. As regards toxicity, 53.1% of the patients experienced mucositis, 51% diarrhea, 31.9% nausea and vomiting, 12.7% leukocytopenia, 8.5% cutaneous toxicity, 4.25% neurotoxicity, conjunctivitis and phlebitis. This regimen appears to be substantially superimposible to the classic FUra/d,l-LV combination. Therefore, the use of l-LV, in those countries where this compound is commercially available, should not be discouraged.
I.F. = 0,421
N. citazioni = 1

27. Confalonieri M, Tacconi F, De Amici M, Maccario R, **Porta C**, Gioglio L, Bobbio-Pallavicini E. Benign idiopathic hypereosinophilia: a feeble masquerader or a smoldering form of the hypereosinophilic syndrome? *Haematologica* 1995;80:50-53.

SUMMARY - In a patients with long-standing idiopathic hypereosinophilia with no apparent organ damage we measured serum eosinophil cationic protein (ECP) and eosinophil protein X (EPX) titers, activated circulating eosinophils rates (by means of monoclonal antibodies EG2) and the release of ECP and EPX in vitro by leukocytes at different culture stages, to detect possible functional abnormalities associated with hypereosinophilia. Our patient had high serum levels of both ECP and EPX, together with a high EG2 count, which would suggest eosinophil activation. However, serum levels of ECP and EPX were not significantly high relative to the total number of eosinophil cells, although higher than in healthy controls. Moreover, the release of intracytoplasmatic basic proteins by the patient's eosinophils was poor even after in vitro stimulation. Since hypereosinophilic syndrome (HES) with organ damage can actually appear even after 8-9 years after hypereosinophilic state, the absolutely benign nature of our patient's condition cannot be defined yet. Thus, the possibility could be of slow-onset or smoldering HES.
I.F. = 1,200
N. citazioni = 8

28. Bobbio-Pallavicini E, **Porta C**, Brocchieri A, Saporiti A, Tacconi F. Ocular involvement in acute thrombotic thrombocytopenic purpura. *Haematologica* 1995;80:194-5.

SUMMARY - Ocular involvement in TTP is usually an underestimated, though far from uncommon, event which is mainly detectable in the preterminal stage of the disease. We briefly reported on a TTP patient who developed ocular lesions during the acute phase of the disease. This case must remind us that: a) the eye may be damaged in the course of TTP; b) such damage may occur even in the early phases of the disease, with possible subsequent diagnostic implications; c) such symptoms can be cured, even in the short term, with adequate treatment, and d) this kind of ocular involvement may represent another prognostic factor in TTP patients, adding to and completing the classic score system by Eldor and Rose.
I.F. = 1,200
N. citazioni = 10

29. Girola SS, Mazzone A, Moroni M, **Porta C**, Nastasi G, Notario A. Rabdomiolisi ipopotassiemica e diuretici tiazidici. Tre casi clinici. *Ann Ital Med Int* 1995;10:134-7.

RIASSUNTO - La rabdomiolisi, patologia acuta del muscolo scheletrico, è caratterizzata da un'alterata integrità delle membrane delle fibrocellule muscolari e può essere causata da svariati fattori di natura non necessariamente traumatica. L'ipopotassiemia ne rappresenta una delle più frequenti cause metaboliche (14-28% di tutte le sindromi rabdomiolitiche). Riportiamo di seguito tre casi di ipopotassiemia causata da terapia diuretica con idroclorotiazide, caratterizzati da una sintomatologia prevalentemente a carico dell'apparato muscolare, conseguente ad una massiva rabdomiolisi.
I.F. = n.r.
N. citazioni = 4

30. Moroni M, Tommaselli F, Casagranda I, Rizzi E, **Porta C**. Methimazole agranulocytosis treated with recombinant human granulocyte colony stimulating factor. *Rec Progr Med* 1995;86:241.

ABSTRACT - Methimazole agranulocytosis represents the most severe and potentially fatal side-effect of this antithyroid drug. We have succesfully treated a patient suffering from methimazole agranulocytosis by mean of the recombinant human granulocyte colony stimulating factor (rHuG-CSF). According to both our experience and literature data, and considering the potential severe consequences of agranulocytosis together with the good tolerance to rHuG-CSF, the use of this drug in the above condition appears to be justified.
I.F. = n.r.
N. citazioni = 1

31. **Porta C**, Moroni M, Nastasi G, Bobbio-Pallavicini E, Barazzoni GC. Utility of embolization or chemoembolization as second-line treatment in patients with advanced or recurrent colorectal carcinoma. *Cancer* 1995;75:2782-3 [Letter].

SUMMARY - Finding effective second-line therapies for metastatic colorectal cancer is actually mandatory. Transarterial chemioembolization (TACE) has been investigated in the past few years in our Institution as front-line therapy for colorectal cancer patients with the liver as the only site of metastatic disease. TACE consisted of the monthly intrahepatic administration of Mitomycin C (MM-C), followed by an emulsion of Gelfoam powder and Doxorubicin, and was combined with systemic 5-Fluorouracil (5-FU) and Leucovorin (LV) chemotherapy. The rate of objective responses we obtained was in agreement with those reported in patients treated with systemic 5-FU and LV alone. Moreover, the poor tolerability of repeated sessions of transfemoral catheterization of the hepatic artery seemed not to justify further and wider applications of this treatment. For these reasons and for the poor results we obtained, we closed another phase II trial of TACE efficacy, where TACE was administered as above, but with no combined systemic chemotherapy, as second-line treatment of patients with hepatic metastases resistant to fluoro-folates. A recent report by Martinelli et Al., suggests that TACE, with 5-FU and interferon-α (IFN), have anticancer activity as second-line therapy in patients with hepatic metastases from colorectal cancer. The use of only one TACE session, thanks to the utilization of Ivalon particles, whose degradation rate is lower than Gelfoam's, together with the locoregional administration of both 5-FU and IFN, may account for the differences between ours and Martinelli's experience. To conclude, TACE in this setting still deserves further investigation, possibly in clinical trials aimed at assessing its impact on patients' survival.
I.F. = 2,864
N. citazioni = 5

32. Centurioni R, Bobbio-Pallavicini E, **Porta C**, Rodeghiero

F, Gugliotta L, Billio A, Tacconi F, Ascari E and the Italian Cooperative Group for Thrombotic Thrombocytopenic Purpura. Treatment of thrombotic thrombocytopenic purpura with high-dose immunoglobulins. Results in 17 patients. *Haematologica* 1995;80:325-31.

SUMMARY - Background: The experimental observation that plasma from TTP patients sometimes exhibits a protein which can cause platelet agglutination, and that such agglutination can be inhibited in vitro by the use of IgG, led some Authors to treat plasma exchange-resistant TTP patients with high-dose IgG (HDIgG). Methods: We report the results obtained with HDIgG treatment in 17 patients retrospectively examined by the Italian Cooperative Group for the study of TTP: 6 males and 11 females, mean age was 31.7 years for the women (range: 20-65) and 44.6 for the men (range: 26-66). In all cases HDIgG administration was combined with other treatment modalities. Results: Of the 17 patients, 7 died from disease progression (41.1%), 2 achieved partial remission (11.7%) and the remaining 8 achieved complete remission (47%). Of the 10 cases (58.8%) with a positive response, only in 4 did the addition of HDIgG seem to produce significant improvement. All efforts made to characterize the subgroup of patients who responded to HDIgG and compare them with the non responders failed. Conclusions: Although our results do not unquestionably demonstrate the role of HDIgG in the treatment of TTP, they suggest a possible role for HDIgG in the treatment of those rare plasma exchange-resistant TTP cases.
I.F. = 1,200
N. citazioni = 29

33. Saporiti A, Brocchieri A, **Porta C**, Moroni M, Grignani G. Effect of different platelet agonists on intracellular free Ca^{++} concentrations in human tumor cells: possible role in tumor growth. *Int J Cancer* 1995;62:291-6.

ABSTRACT - Modulation of cytoplasmic Ca^{++} concentration is a mechanism common to signal transduction pathways regulating many cellular phenomena, including the interactions of tumors with the hemostatic system. We have investigated the pro-aggregating and pro-coagulant activities of human tumor cell lines cultured in vitro and the ability of different platelet agonists to induce Ca^{++} transients in these cells. Cells of a malignant mesothelioma line activated platelets by a thrombin-dependent mechanism; on the contrary, HeLa cells, derived from a uterine cervical cancer, possessed ADP-dependent pro-aggregating activity, and DND-1A melanoma cells did not stimulate platelet aggregation. All cell lines showed a tissue-factor-like pro-coagulant property, more pronounced in mesothelioma cells. Furthermore, ADP was able to induce a transient increase in cytoplasmic Ca^{++} concentration in tumor cells from all lines; collagen showed this effect in mesothelioma cells and in HeLa cells, and thrombin was effective only in mesothelioma cells. PAF never induced Ca^{++} fluxes in any of the cell lines investigated. Finally, the calcium-channel blocker verapamil inhibited agonist-induced Ca^{++} transients in tumor cells and in vitro tumor-cell growth. These data may help to identify new possible mechanisms of the 2-way interaction of tumors with the hemostatic system.
I.F. = 3,403
N. citazioni = 9

34. Nastasi G, **Porta C**, Moroni M, Riso S, Sesana G. Inadequacy of combined 5-fluorouracil, very-high-dose leucovorin, mitomycin-C and cisplatin as second-line therapy for advanced colon cancer. *Oncol Rep* 1995;2:815-8.

ABSTRACT - Fourteen patients with metastatic colon cancer which had progressed under fluoro-folates chemotherapy were treated with MM-C (10 mg/m^2 on day 1), 5-FU (370 mg/m^2 for 5 consecutive days), l-LV (500 mg/m^2 for 5 consecutive days) and CDDP (70 mg/m^2 on day 4), every 29th day till further disease progression. Neither CR nor PR were observed; 3 patients only had stable disease, while the extant 11 patients progressed. Resulting toxicity was severe. Since no antitumor effects were evidenced in the first 14 patients, the study was discontinued according to commonly accepted criteria.
I.F. = 0,421

35. Bobbio-Pallavicini E, Valsecchi C, Tacconi F, Moroni M, **Porta C**. Sarcoidosis following beta-interferon therapy for multiple myeloma. *Sarcoidosis* 1995;12:140-2.

ABSTRACT - Some reports correlate the administration of all forms of interferon with the development or exacerbation of autoimmune phenomena and diseases, including sarcoidosis, because of the strong and complex immune action of interferons. We report on a case of sarcoidosis following β-interferon treatment for multiple myeloma. Differently from what observed in all the 8 previously reported cases of associated multiple myeloma and sarcoidosis, where the plasmacellular malignancy followed the onset of the respiratory disease, in the case of our patient, sarcoidosis arose after multiple myeloma was first diagnosed.
I.F. = 0,135
N. citazioni = 61

36. **Porta C**, Moroni M, Nastasi G, Arcangeli G. 5-fluorouracil and *d,l*-leucovorin calcium are active to treat unresectable hepatocellular carcinoma patients: preliminary results of a phase II study. *Oncology* 1995;52:487-91.

ABSTRACT - Twenty-five patients affected with unresectable hepatocellular carcinomas (HCCs) were treated with 370 mg/m^2 5-fluorouracil (5-FU) plus 200 mg/m^2 racemic leucovorin both for 5 consecutive days. The chemotherapy cycle was repeated every 4 weeks until disease progression. One complete remission (4%) and 6 partial responses (24%) were obtained, that is 7 objective responses in all (28%, ninety-five confidence interval: 10.1-45.9%). All responders had a good PS and only 1 of them presented with bulky disease. Five patients (20%) exhibited stable disease, while the remaining 13 patients (52%) progressed. Toxicity was mild: 11 patients (44%) had grade II/III mucositis, 10 patients (40%) grade II diarrhea, 7 patients (28%) grade II nausea, 2 patients (8%) grade III granulocytopenia and 1 patient only (4%) grade I skin toxicity. This regimen made it possible to obtain a high rate of objective responses even in inoperable HCCs which are commonly considered as chemoresistant lesions.
I.F. = 1,857
N. citazioni = 38

37. Ricci G, Colombo C, Ghiazza B, **Porta C**, Moroni M, Illeni MT. HLA-A, B, C, DR and DQ expression and hepatocellular carcinoma: study of 205 Italian subjects. *Cancer Letters* 1995;98:121-5.

ABSTRACT - We have evaluated the frequence of HLA class I and II antigens in 205 Italian patients with hepatocellular carcinoma (HCC) and 749 blood donors (controls). Moreover, we have looked for correlations between HLA antigen frequencies and HBV and/or HCV infections in HCC patients. We found great differences in HLA antigen frequencies considering only two groups: HCC patients and controls. The polymorphism is smaller when we consider the different groups of HCC patients in regard to previous viral infections (HBV and/or HCV). The most interesting finding is the higher frequency of Cw7, B8 and DR3 in almost all groups of HCC patients. It is well known that the HLA A1, Cw7, B8, DR3 antigen haplotype is associated with a rapid decline of CD4 cells, and HLA B8, DR3 positive subjects may display some changes in immune parameters and are prone to develop several immuno-

logic diseases. Thus, HCC might be the result of a lower sensitivity (genetically given) to mitogenic stimuli of HBV and HCV.
I.F. = 1,219
N. citazioni = 9

38. **Porta C**, Moroni M, Epis O, Nastasi G. 5-methyltetrahydrofolate or 5-formyltetrahydrofolic acid to modulate 5-fluorouracil's cytotoxic activity *in vivo*? A phase II study in patients with advanced colon cancer. *Cancer Chemother Pharmacol* 1996;38:195-7.

ABSTRACT - The purpose of this study was to test the hypothesis that 5-methyltetrahydrofolate (Me-THF), a source of reduced folates alternative to leucovorin, could effectively modulate 5-fluorouracil's (5-FU) cytotoxic activity in patients with advanced colon cancer. A total of 23 patients were enrolled in a phase II trial; they received 5-FU as a 30-min infusion at a dose of 370 mg/m^2 following a rapid i.v. push of 200 mg/m^2 Me-THF, both drugs being given for 5 consecutive days. Cycles were repeated every 4 weeks until disease progression. No patient achieved a complete response. In all, 4 patients showed a partial response (17.4%), 7 developed stable disease (30.4%), and the remaining 12 (52.2%) progressed. Toxicity was acceptable and never exceeded WHO grade III intensity. According to our experience, the Me-THF/5-FU combination does not appear to be an effective treatment for advanced colon cancer. Despite its low toxic profile, in our opinion, its wider use should be discouraged.
I.F. = 1,261
N. citazioni = 1

39. **Porta C**, Caporali R, Montecucco C, Bobbio-Pallavicini E on behalf of the Italian Cooperative Group for TTP. Lack of evidence of antineutrophil cytoplasmic antibodies involvement in the acute phase of thrombotic thrombocytopenic purpura. *Nephron* 1996;73:352-3 [Letter].

ABSTRACT - A consistent amount of experimental data suggest the hypothesis that neutrophils participate in the pathophysiology of the hemolytic-uremic syndrome (HUS); furthermore, a partecipation of antineutrophil cytoplasmic antibodies (ANCA) in the pathophysiology of HUS, at least in certain patients, has been recently postulated. Thrombotic thrombocytopenic purpura (TTP) is a rare hematological disorder closely related to HUS. Therefore, despite the microthrombi found in the microcirculation of TTP patients usually lacks polymorphonuclear cells, we looked for the eventual presence of ANCA in sera of 29 acute-phase TTP patients. A completely negative ANCA assay was found in all TTP patients tested. The absence of ANCA in the sera of our 29 acute-phase TTP patients, seems to exclude the involvement of these autoantibodies in the pathogenesis of TTP.
I.F. = 1,938
N. citazioni = 3

40. Brocchieri A, Saporiti A, Moroni M, **Porta C**, Tua A, Grignani G. Verapamil inhibits to different extents agonist-induced Ca^{++} transients in human tumor cells and *in vitro* tumor cell growth. *Invas Metast* 1996;16:56-64.

ABSTRACTS - Platelet agonists are known to contribute to regulation of cytoplasmic Ca^{++} levels in tumor cells and this property could be relevant in the stimulation of cell proliferation. In the present study we have investigated the ability of ADP, collagen and thrombin to increase cytoplasmic Ca^{++} levels in different human tumor cell lines (mesothelioma, DND-1A melanoma, HeLa uterine carcinoma) and we have analysed the effect of the calcium channel blocker verapamil on Ca^{++} fluxes and on in vitro tumor cell growth. ADP was able to induce a transient increase in cytoplasmic Ca^{++} concentration in tumor cells from all lines; collagen showed this effect in mesothelioma cells and in HeLa cells, and thrombin was effective only in mesothelioma cells. Verapamil inhibited Ca^{++} fluxes induced by the effective agonists in a dose-dependent manner. Values of IC_{50} for inhibition of ADP induced Ca^{++} transients were 63.5 mM in mesothelioma cells, 97.3 mM in DND-1A cells and 93.5 mM in HeLa cells, while those for inhibition of collagen-induced Ca^{++} movements were slightly higher (170.2 mM in mesothelioma cells and 112.3 mM in HeLa cells) and the value of IC_{50} for inhibition of thrombin-induced Ca^{++} fluxes (evaluated only in mesothelioma cells) was lower (22.5 mM). The drug dose-dependently inhibited also the in vitro growth of tumor cells; values of IC_{50} for growth inhibition were 21.8 mM in mesothelioma cells, 9.1 mM in DND-1A cells and 6.4 mM in HeLa cells, suggesting that the antiproliferative activity of verapamil was partly Ca^{++} independent. These data may be of interest to elucidate the mechanisms of the two-way interactions of tumors with the hemostatic system and may help to identify new pharmacologic strategies for their control.
I.F. = 1,508
N. citazioni = 6

41. Moroni M, **Porta C**, Gualtieri G, Nastasi G, Tinelli C. Inhaled sodium cromoglycate to treat cough in advanced lung cancer patients. *Br J Cancer* 1996;74:309-11.

SUMMARY - C-fibres probably represent the common final pathway in both ACE inhibition and neoplastic cough. A recent report demonstrated that inhaled sodium cromoglycate is an effective treatment for ACE inhibitors' cough; this effect might be due to the suppression of afferent unmyelinated C-fibres. We tested the hypothesis that inhaled sodium cromoglycate might also be effective in lung cancer patients who presented with irritative neoplastic cough. Twenty non-small-cell lung cancer (NSCLC) patients complaining of cough resistant to conventional treatment were randomized to receive, in a double-blind trial, either inhaled sodium cromoglycate or placebo. Patients recorded cough severity daily, before and during treatment, on a 0 to 4 scale. The efficacy of treatment was tested with the Mann-Whitney U-test for non-parametric measures, comparing the intergroup differences in the measures of summary of symptom scores calculated in each patient before and after treatment. We report that inhaled sodium cromoglycate can reduce cough, also in NSCLC patients and that such reduction, observed in all patients treated, is statistically significant ($p<0.001$). Inhaled sodium cromoglycate appears to be a cost-effective and safe treatment for lung cancer-related cough.
I.F. = 3,666
N. citazioni = 36

42. **Porta C**, Centurioni R, Vianelli N, Bobbio-Pallavicini E, Gugliotta L, Billio A and the Italian Cooperative Group for TTP. Thrombotic thrombocytopenic purpura (TTP) and relapses. Why do case series differ? *Am J Hematol* 1996;52:215-6.

ABSTRACT - We examined the retrospective case series of the Italian Cooperative Group to determine the incidence of relapses in TTP patients. Of 60 patients who have crossed the 10-year threshold from the first episode, only 9 (15%) relapsed during that period, a figure far better than that reported recently. Such difference is hardly explainable on the basis of our current knowledge of the biological behaviour of TTP. Furthermore, we unsuccessfully analyzed the treatment performed in each of our relapsed patients, in search of some element that could retrospectively predict the subsequent relapse.
I.F. = 1,802
N. citazioni = 5

43. **Porta C**, Moroni M, Guallini P, Torri C, Marzatico F. Antioxidant enzymatic system and free radicals pathway in two different human cancer cell lines. *Anticancer Res* 1996;16:2741-8.

ABSTRACT - Resistance to oxidative damage is an important feature of cancer cells. Cellular anti-radical enzymes, lipid peroxidation, gluthathione pathway, capability to produce ROS, and cells' susceptibility to H_2O_2 and menadione toxicity, were analyzed in DND-1A and HeLa cancer cell lines. SOD and GSHPx activities were higher in DND-1A than in HeLa cells. Lipid peroxidation was the same in both cell lines, while menadione stimulation of ROS production was tenfold higher in HeLa cells. Total and reduced, but not oxidized, gluthathione levels were tenfold smaller in HeLa cells. H_2O_2 proved fatal to HeLa cells after 12 hours' incubation, while it was ineffective on DND-1A; DND-1A cells were more sensitive to menadione toxicity than HeLa cells. The two lines behaved differently in response to the above treatments. These observations might be important in designing more specific cancer treatments.
I.F. = 1,049
N. citazioni = 11

44. Mazzone A, **Porta C**, Fossati G, Gritti D, Mazzucchelli I, Ricevuti G. Granulocyte dysplasia and dysfunction, and CD11/CD18 defects in myelodysplastic syndromes. *Leukemia and Lymphoma* 1996;23:267-75 [Review].

ABSTRACT - In myelodysplastic syndromes (MDS), dysplastic changes in neutrophils are a common feature reflecting the total degree of bone marrow dysplasia. Furthermore, granulocyte function is abnormal, so that a high risk of life-threatening infections has been documented. In this review we shall focus on the defects of both granulocytes and their CD11b/CD18 glycoprotein complex, which regulate granulocyte adherence, locomotion, diapedesis and migration into inflammatory sites, in patients suffering from primary MDS. The defective surface membrane glycoprotein expression of myelodysplastic phagocytes is not only a useful diagnostic tool, but also a powerful prognostic one, since MDS patients with such defects present both an increased susceptibility to infections and a decreased survival. Moreover, the administration of colony-stimulating factors is known to be able to elicit long-lasting improvement in neutrophil count, CD11b/CD18 expression and function, marrow myeloid maturation, and possibly to decrease bacterial infections in MDS patients.
I.F. = 1,134
N. citazioni = 21

45. Nastasi G, **Porta C**, Moroni M, Alessiani M, Fossati G. Intrahepatic fluorodeoxyuridine to treat unresectable hepatocellular carcinoma patients. *Oncol Rep* 1997;4:511-4.

ABSTRACT - Of 16 HCC patients who received intrahepatic FdUrd at a dose of 0.3 mg/Kg/day for 14 consecutive days by continuous infusion, every 28 days, no one achieved a CR, while 3 patients achieved PRs (18.75%), lasting 6, 9 and 18 months, respectively. Seven patients (43.75%) exhibited SD and their mean time to progression was 4.28 months; in the extant 6 patients (37.5%) the disease progressed. Major biliary toxicity was observed. On the basis of these data, intra-arterial chemotherapy should not yet be considered the golden standard for the treatment of unresectable HCCs.
I.F. = 0,407

46. Bognoni V, Quartuccio A, Nastasi G, Riso S, Moroni M, **Porta C**. Endodermal sinus tumor of the ovary in pregnancy: a case report and review of the literature. *Oncol Rep* 1997;4:599-601.

ABSTRACT - The ultrasonographic evidence of an irregular mixed mass, cystic and solid, in retrouterine area and the high levels of α1-FP values in a young pregnant woman, indicated the possibility of an ovarian germ cell neoplasia. Respecting the patient's will, pregnancy was protracted until the36th week. A cesarian section allowed the releasing of a vital fetus and the removal of a neoplastic mass which proved to be an endodermal sinus tumor (EST) at stage Ia. Then the patient, the 12th case of EST in pregnancy reported in the literature so far, underwent 5 PVB chemotherapy cycles and, 3 years after the intervention, appears disease-free.
I.F. = 0,407
N. citazioni = 1

47. Bobbio-Pallavicini E, Gugliotta L, Centurioni R, **Porta C**, Vianelli N, Billio A, Tacconi F, Ascari E for the Italian Cooperative Group for TTP. Antiplatelet agents in Thrombotic Thrombocytopenic Purpura (TTP). Results of a randomized multicenter trial by the Italian Cooperative Group for TTP. *Haematologica* 1997;82:429-35.

ABSTRACT - Background and objective: Antiplatelet agents are often included in plasma exchange-based regimens for thrombotic thrombocytopenic purpura (TTP) patients; however, the opportuneness of their use in TTP is still controversial. The Italian Cooperative Group for TTP carried out a randomized trial to investigate their actual effectiveness, both in acute TTP and as maintenance treatment. Methods: Seventy-two TTP patients were randomized to receive plasma exchange and steroids with (group B) or without (group A) aspirin and dipyridamole. Treatment efficacy was evaluated after 15 days and salvage treatments were also considered for non-responders. Upon disease remission, the patients already treated with antiplatelet agents received ticlopidine for one year. Results: Regarding the treatment of acute phase TTP, similar overall response rates were observed in the two groups (91.4% in group B vs. 75.6% in group A), but lower mortality rates were observed at 15 days in the patients treated with antiplatelet agents; as a matter of fact, 5 patients from arm A died in the first 15 days (13.5%) versus only one in arm B (2.8%). These figures, while not statistically significant, seem to suggest that antiplatelet agents might be useful in preventing deaths in acute TTP; moreover, bleeding did not worsen in antiplatelet agent-treated patients. As for the role of maintenance treatment, our results support the efficacy and safety of one-year ticlopidine therapy since the current relapse rate is significantly higher in non-treated patients; as a matter of fact, 6 patients (21.4%) in the non-ticlopidine group and only 2 (6.25%) in the ticlopidine group relapsed (p = .0182 in favor of maintenance treatment). Interpretation and conclusions: Our results suggest the usefulness of antiplatelet agents in the treatment of acute phase TTP patients. Moreover, one-year ticlopidine maintenance therapy appears to be beneficial in preventing TTP relapses; however, only the completion of an adequate follow-up for all patients will definitely confirm this observation.
I.F. = 2,560
N. citazioni = 90

48. **Porta C**, Buggia I, Bonomi I, Caporali R, Scatola C, Montecucco C. Nitrite and nitrate plasma levels, as markers of nitric oxide synthesis, in antiphospholipid antibodies-related conditions and in thrombotic thrombocytopenic purpura. *Thromb Haemost* 1997;78:965-7 [Letter].

ABSTRACT - Thrombotic thrombocytopenic purpura (TTP) shares a lot of clinical features with antiphospholipid antibodies (aPL)-related conditions; furthermore, an altered endothelial function has been postulated as a key pathogenetic event in both TTP and aPL-related conditions. Using a sensitive and specific HPLC assay, we determined NO stable end-products nitrites and nitrates in the plasma of both aPL-positive and negative systemic lupus

erythematosus (SLE) patients and in the plasma of PAPS patients; subsequently, we compared them with those of a previously described population of acute-phase, aPL-negative, TTP patients, and with those of 25 control volunteers. Median NO_3 titer in aPL-positive patients was 35.605 mM/L (mean: 38.271± 24.912 SD, range: 18.34-127.44), while it was 33.24 (mean: 29.12 ± 12.053, range: 11.6-41.92) in aPL-negative patients, 20.86 (mean: 25.868 ± 15.628, range: 7.66-67.68) in TTP patients, and 26.65 (mean: 29.434 ± 17.811, range: 8-90.15) in controls; no patient within the 4 groups showed titrable levels of NO_2. The differences in NO_3 titers between the four groups considered were analyzed using the one-way variance analysis, which yielded no statistically significant differences (f = 1.633, p = 0.188). In conclusion, we could not demonstrate an altered NO synthesis in aPL-related conditions, as already observed in TTP. These data made the involvement of NO pathway within a more complex endothelial cells dysfunction, unlikely; the exact mechanism responsible for thromboses in these conditions remains therefore to be clarified by further studies.

I.F. = 4,582

N. citazioni = 7

49. **Porta C**, Moroni M, Bobbio-Pallavicini E, Tinelli C, Regazzi-Bonora M. Nitrate plasma levels, as marker of nitric oxide production, after subcutaneous interleukin-2 immunotherapy. *J Natl Cancer Inst* 1997;89:1545 [Letter].

ABSTRACT - IL-2 schedules were initially developed using chemotherapy guidelines in which the maximum tolerable dose was given by intravenous bolus or continuous infusion over a few days; however, relevant cardiovascular effects were common. Evidence has increased that nitric oxide (NO) may contribute to cause it through its vasodilator properties. Using a sensitive HPLC method, we studied NO stable end product nitrate (NO_3), the ultimate metabolite of NO in blood, in the plasma of 11 advanced renal cell carcinoma patients receiving subcutaneous low dose IL-2 (Atzpodien's protocol), and of 7 renal cell carcinoma patients enrolled in a national multicentric adjuvant study of very low-dose subcutaneous IL-2 (Buzio's protocol). In the patients treated with Atzpodien's schedule, the mean NO_3 titers were 32.027 mM/L (±7.857 SD) before treatment and 79.011 (± 13.381 SD) after treatment; the differences between pre- and post-treatment NO_3 titers were statistically significant (p=.003). In patients treated with Buzio's schedule, the mean NO_3 titers were 36.126 mM/L (±7.901 SD) before treatment and 46.019 (± 6.561 SD) after treatment (p=n.s.). Our data demonstrate 163.1% (± 89.0 SD) and 10.7% (± 12.0 SD) increase in NO_3 titers after the first IL-2 cycle according to Atzpodien's and Buzio's protocols, respectively. Both these figures are much lower than the 669.7% and 935.0% increase reported by Ochoa et al. for two different schedules of high-dose intravenous IL-2. The low rate or even the total absence of cardiovascular toxicity reported by Atzpodien and Buzio, respectively, were confirmed in our patients. This safe toxicologic profile, compared to the severe systemic manifestations described in high-dose trials, is consistent with a poorer stimulation of NO production.

I.F. = 11,403

N. citazioni = 6

50. Moroni M, **Porta C**, Finotti N, Borasio E, Greco R, Bertorelli L, Regazzi-Bonora M, Marzatico F. Amifostine (WR-2721, Ethyol™) can protect human endothelial but not tumor cells from cisplatin-induced cytotoxicity. An *in vitro* study. *Oncol Rep* 1997;4:729-32.

ABSTRACT - Amifostine (WR-2721, Ethyol™) is a chemo- and radioprotective agent which is increasingly used in clinical practice to minimize antitumor therapy-induced toxicities. The key of this property of amifostine is certainly its selective action in terms of differential protection of normal tissue and not of tumor cells. Using HUVEC cells and three different cancer cell lines (A549 non-small cell lung cancer, DND-1A melanoma and HeLa cervical carcinoma) we provide evidence that amifostine could protect normal, and not cancer cells, from cisplatin (CDDP)-induced cytotoxicity in vitro. Furthermore, low doses of amifostine, easily attainable in vivo, can protect 50% of normal cells in vitro from CDDP-induced cytotoxicity.

I.F. = 0,407

N. citazioni = 4

51. Bobbio-Pallavicini E, **Porta C**, Moroni M, Bertulezzi G, Civelli L, Pugliese P, Nastasi G. Epirubicin and etoposide combination chemotherapy to treat hepatocellular carcinoma patients. A phase II study. *Eur J Cancer* 1997;33:1784-8.

ABSTRACT - Approximately half the patients affected with hepatocellular carcinoma (HCC) present with unresectable disease, so that efficacious systemic chemotherapy protocols are badly needed. We report the results of a phase-II study aimed at testing the efficacy and toxicity of a combination of epirubicin and VP-16. 36 patients (30 men and 6 women) received epirubicin (40 mg/m^2, on day 1) and VP-16 (120 mg/m^2, on days 1, 3 and 5) every 28th day. Chemotherapy was stopped in case of disease progression, while the patients who achieved an objective response or who had stable disease continued treatment for a maximum of 10 cycles. One patient (3%) achieved a complete response, while 13 patients (36%) achieved partial response, i.e. 14 objective responses in all (39%, 95% CI: 23-55%). 11 patients (31%) exhibited stable disease, while in the other 11 patients (31%) the disease progressed. Median overall survival time was 10 months and 13.5 months in the subgroup of patients responding to treatment. Significant, especially hematological, toxicity was documented, but in no case was it so severe as to require discontinuation of treatment or reduction of the dosage. In conclusion, this combination appears to be an active and tolerable therapeutic option for HCC patients who are not candidates for surgical or locoregional procedures, and in our opinion it deserves further exploration within a randomized controlled trial versus best supportive care.

I.F. = 2,407

N. citazioni = 62

52. Zanirato S, **Porta C**, Moroni M, Nastasi N. Jaw bone metastasis from hepatocellular carcinoma. A case-report. *It J Gastroenterol Hepatol* 1997;29:478-9 [Letter].

ABSTRACT - Bone metastases are found in 1-20% of the HCC patients submitted to autopsy, but symptomatic lesions are a very uncommon event. Jaw bone involvement from HCC appears to be even rarer, with only 15 cases reported in the literature to date. We report on a new HCC patient presenting with jaw bone metastasis in whom the secondary lesion was diagnosed before the primary carcinoma. Following locoregional radiation-therapy and systemic treatment, the patient, despite never showing an objective response, experienced a fairly prolonged survival.

I.F. = 0,383

N. citazioni = 1

53. Moroni M, **Porta C**, Gritti D, De Amici M, Giacobbe O, Bobbio-Pallavicini E, Notario A. Cationic protein-rich supernatants of cultured eosinophils from IL-2-treated patients have no cytotoxic activity on human renal cell carcinoma and melanoma cells. A preliminary report. *Ann NY Acad Sci* 1997;832:295-303.

ABSTRACT - Hypereosinophilia is a common finding in IL-2-treated cancer patients. The exact role of eosinophils and of their major products, the cationic proteins ECP and EPX, is controversial. Since these proteins are involved in tissue damage in several inflammatory and allergic conditions, a possible cytotoxic role on tumor cells has been postulated. We isolated eosino-

phils from peripheral blood of three IL-2-treated cancer patients and from three age- and sex-matched healthy controls; purified eosinophils were cultured and supernatants collected after 8 days. Different concentrations of cationic protein-rich supernatant were added to ACHN (renal cell carcinoma) and A375 (melanoma) cells, previously seeded in a 24-well plate and grown in appropriate media. Cell growth was assessed after 4 days' incubation with different concentrations of cationic protein-rich supernatant at 37°C in CO_2 and compared with the growth of control (untreated) cells; cell growth and viability were assessed using both Trypan blue exclusion and the MTT assay. No signs of growth inhibition or of cytotoxicity were found after incubation with cationic protein-rich supernatants in either cell line; moreover, the number of cells grown with cationic proteins was higher than the control one, even though the difference did not reach statistical significance. To conclude, on the basis of these preliminary data on a small sample, IL-2-stimulated eosinophils appear unlikely to exert any anticancer activity through their cationic proteins ECP and EPX.

I.F. = 0,903

N. citazioni = 7

54. Moroni M, **Porta C**. Possible efficacy of allopurinil vaginal washings in the treatment of chemotherapy-induced vaginitis. *Cancer Chemother Pharmacol* 1998;41:171-2 [Letter].

ABSTRACT - Mucositis is an extremely common side-effect of antimetabolites-containing chemotherapy regimens, and the genital tract, especially in women, may be frequently involved by mucositis. Treatment for chemotherapy-induced mucositis mostly relies on the management of mucositis-induced symptoms. We previously demonstrated allopurinol mouthwashes efficacy in reducing chemotherapy-induced stomatitis, probably thanks to the well-known free radicals-scavenging properties of this drug. We briefly report on the case of a patient who developed severe vaginitis due to concomitant 5-FU and MTX administration, and who was effectively and rapidly cured by means of the administration of allopurinol vaginal washings. However, only an adequate prospective, placebo-controlled, randomized clinical trial would definitely confirm allopurinol efficacy to treat chemotherapy-induced vaginitis.

I.F. = 1,74

N. citazioni = 2

55. Alessiani M, Vai L, Jemos V, Dionigi P, Spada M, **Porta C**, Moroni M, Nastasi G, Fossati GS, Zonta A. Catheter seeding of hepatocellular carcinoma following placement of a total implantable access port system. *Hepatogastroenterology* 1998;45:206-8.

SUMMARY - A 61-year-old cirrhotic patient underwent hepatic resection for hepatocellular carcinoma and placement of a total implantable access port system in the hepatic artery for chemotherapy infusion. A year later, he developed a parietal metastasis at the port site as a consequence of tumor seeding along the arterial catheter. The metastasis was excised but the patient died because of disseminated disease two years after the first operation. Tumor seeding along the catheter should be included in the group of potential complications after placement of total implantable access port systems for intrahepatic chemotherapy The possible causes of this rare but life-threatening complication are discussed.

I.F. = 0,925

N. citazioni = 2

56. **Porta C**, Moroni M, De Amici M. Eosinophils and serum eosinophilic cationic proteins in interleukin-2-based immunotherapy for cancer. *Br J Haematol* 1998;100:607-9 [Letter].

SUMMARY - Several studies suggest that eosinophils may play a major role, in vivo, in the vast and complex anticancer activity of the immune system activated by IL-2 administration. Particularly, eosinophils may effect direct or antibody-dependent cancer lysis, or else they may interact with $CD4^+$ lymphocytes serving as antigen-presenting cells, since HLA-DR expression seems to be inducible on eosinophils. If these are nearly given facts, the potential mechanisms by which eosinophils are reported to effect direct cytolysis remain debated. Thus, even though such products of eosinophil oxidative metabolism as superoxide anions, hydroxyl radicals and singlet oxygen can damage several cell types, and eosinophilic free radicals are therefore likely to participate in the supposed anticancer cytotoxicity of eosinophils, great attention has also been paid to eosinophilic cationic proteins, which can damage surrounding tissues. Using a sensitive radioimmunologic assay, our Group has recently found that eosinophilc cationic protein (ECP) and EPX increase significantly during IL-2 immunotherapy according to Buzio's schedule relative to pretreatment values in 12 renal carcinoma patients. Our data are in disagreement with recently reported Swedish results because baseline ECP and EPX values in renal carcinoma patients do not differ from those of age- and sex-matched healthy controls. A possible explanation is that the Swedish patients present a metastatic disease the immune system (and therefore eosinophils) activated against, while our patients were operated on and the primary lesion resected and their immune system is less active. Moreover, immunotherapy caused a marked increase in both eosinophilic proteins in our patients, different from Trulson's. The role of eosinophilic cationic proteins in IL-2-induced anticancer activity suggested by Trulson partially clashes with other in vitro observations from our Group. Such contradictions will be solved only by accurate statistical analyses of the influence of eosinophils and eosinophilic cationic proteins on the survival of large cohorts of IL-2-treated cancer patients.

I.F. = 3,209

N. citazioni = 10

57. Rizzo V, Montalbetti L, Rozza AL, Bolzani W, **Porta C**, Balduzzi G, Scoglio E, Moratti R. NO_2/NO_3 balance during photoinduced cerebral ischemia in the rat by HPLC with UV and electrochemical detection. *J Chromatography A* 1998;798:103-8.

ABSTRACT - A specific and simple method for the direct simultaneous detection of extracellular nitrite (NO_2) and nitrate (NO_3) has been developed, using HPLC separation with UV and electrochemical detection in series. These stable end-products of nitric oxide (NO) were determined in dialysis perfusate obtained through in vivo brain microdialysis during and after photoinduced cerebral ischemia in rats. The chromatographic conditions were optimized with a reversed-phase column (250 x 46 mm) using 10 mM n-Octylamine pH 6.0 as a mobile phase. Absorbance was measured at 220 nm for NO_3 detection; electrochemical detection was performed at +0.7 V for NO_2 evaluation. This assay holds the advantages of in vivo consecutive measurements, high precision, good reproducibility, technical semplicity, fast response (about 7 minutes), and wide availability.

I.F. = 2,321

N. citazioni = 22

58. Diani G, Poma G, Novazzi F, Zanirato S, **Porta C**, Moroni M, Melzi d'Eril GV, Moratti R. Elevated serum lipase with associated normoamylasemia in cancer patients. *Clin Chem* 1998;44:1043-5.

ABSTRACT -We report on four patients with increased serum lipase activity but without associated hyperamylasemia or signs and symptoms of pancreatic injury. Lipase activity increase anticipated the progression or relapse of a previously known malignancy in three cases, while increased lipase titers preceded the development of a hepatocellular carcinoma in the latter patient. Lipase activity increase preceded, by an average of 2.6 months, the

elevation of specific tumor markers, such as CA 19.9 and α1-FP. Even though we did not investigate the possible mechanisms of such an increase, we consider extremely interesting the hypothesis of a tumor marker role for lipase. However, only prospective studies will definitely confirm or dismiss this hypothesis.
I.F. = 3,423
N. citazioni = 6

59. **Porta C**, Moroni M, Ferrari S, Nastasi G. Endothelin-1 and 5-fluorouracil-induced cardiotoxicity. *Neoplasma* 1998;45:81-2.

ABSTRACT - Cardiotoxicity is an uncommon side-effect of 5-FU-based chemotherapy. Coronary artery vasospasms have been postulated to be involved in the pathogenesis of this rare but serious problem. We found high plasma levels of ET-1, a potent natural vasoconstrictor, in two patients who experienced two of the commonest clinical manifestations of 5-FU-induced cardiac toxicity - i.e., angina pectoris and chronic heart failure. We therefore propose ET-1 as the ultimate mediator of this toxicity, even though the mechanism of ET-1 increase in peripheral venous blood is still unknown. Finally, another important question still remains unresolved: is the release of ET-1 from normal coronary endothelial cells the prime cause or simply the consequence of 5-FU-related cardiotoxicity?
I.F. = 0,657
N. citazioni = 45

60. Moroni M, **Porta C**, Tua A, Magnone S, Grignani G. Platelet agonists induce Ca^{2+} transients in tumor cells by opening distinct receptor-operated channels: an effect unrelated to the presence of classical multi-drug resistance phenotype. *Cancer J* 1998;11:141-6.

ABSTRACT - Background: Modulation of the cytoplasmic calcium concentration is a mechanism of signal transduction regulating several biological phenomena and may also play a role in the stimulation of cell proliferation. In the present study we have investigated the effect of different platelet agonists on cytoplasmic Ca^{2+} levels in tumor cells with or without the multi-drug resistance (MDR) phenotype and the effects of verapamil on agonist induced Ca^{2+} transients and on in vivo cell growth. Methods: LoVo cells and doxorubicin-resistant LoVoDx cells, derived from a human colon adenocarcinoma, were cultured in vitro using standard methods. Cytoplasmic Ca^{2+} levels in aequorin-loaded tumor cells were determined in a Platelet Inoized Calcium Aggregometer. Results: ADP, GRGDS, PAF, collagen and thrombin were able to induce Ca^{2+} transients in both cell lines, while U46619, a throboxane A2 mimetic agent, PGDF and carbachol were not. Tumor cells of both cell lines became refractory to thrombin after the first addition, but remained sensitive to the other inducers. Furthermore, the calcium channel blocker verapamil significantly inhibited thrombin-induced Ca^{2+} fluxes in both LoVo and LoVoDx cells and had no significant effect on Ca^{2+} movements induced by the other agonists. Finally, the drug inhibited the in vitro growth of both cell lines in a dose-dependent manner, with an effect more evident in resistant cells. Conclusions: These data may help to explain the ability of verapamil to reverse the MDR phenotype and may contribute to identifying new mechanisms for the two-way interaction of tumors with the hemostatic system.
I.F. = 0,902
N. citazioni = 1

61. **Porta C**, Moroni M, Grignani G. Platelet agonists and calcium homeostasis in endothelial cells: possible role in the interaction of endothelium with hemostatic system. *Haematologica* 1998;83:610-5.

SUMMARY - Background and objective: The endothelium is a complex tissue which modulates a vast array of biological functions and Ca^{++} transients are critically important to these endothelium-dependant functions. We addressed the hypothesis that some platelet agonists and products of activation of the hemostatic system could determine Ca^{++} transients in a bovine pulmonary artery endothelial cell line (CPA-47). Methods: The effect of thrombin, collagen, ADP, PAF, PDGF, GRGDS, and the TxA2 mimetic U46619 on CPA-47-cytoplasmic Ca^{++} transients was evaluated using a Platelet Ionized Calcium Aggregometer, after cells were loaded with the photoprotein aequorin. Results: ADP, GRGDS, PAF, U46619 and collagen were able to induce rapid Ca^{++} transients in CPA-47 endothelial cells and the response was stable after repeated additions, while thrombin acted slightly differently, as cells became refractory to this agonist after the first response, but they remained sensitive to the other inducers. Only PDGF was completely ineffective. Furthermore, calcium-channel blockers verapamil and flunarizine (but not nifedipine) caused a reduction only of thrombin-induced cytoplasmic Ca^{++} transients, while the addition of depolarizing concentration of KCl suggests the presence also of voltage-operated channels on endothelial cell membrane. Finally, EGTA caused the complete suppression of Ca^{++} transients induced by all the tested agonists but collagen. Interpretation and conclusions: Our study demonstrated that the different agents tested are able to induce Ca^{++} transients on bovine endothelial cultured cells, similarly to what observed in platelets and other non excitable cells, including tumor ones, and that calcium channel blockers had only limited inhibitory effect on these changes; these results may help more thoroughfully understand the biochemical basis of the interaction between endothelium and the hemostatic system.
I.F. = 1,876
N. citazioni = 2

62. Amedeo A, Bertulezzi G, Civelli L, **Porta C**, Moroni M. Plasma and urinary endothelin-1 titers and plasma Von Willebrand activity in Pseudoxanthoma Elasticum. *Haematologica* 1998;83:952-3 [Letter].

SUMMARY - We found high endothelin-1 and Von Willebrand factor plasma titers not only in two individuals (daughter and father) affected with Pseudoxanthoma Elasticum but also in a young unaffected relative. These findings raise the possibility that these molecules could be the first biochemical fingerprints of this, still not clinically evident, rare inherited disorder of the elastic tissue.
I.F. = 1,876

63. Bertulezzi G, Paris R, Moroni M, **Porta C**, Nastasi G, Amadeo A. Atrial septal aneurysm in a patient with pseudoxanthoma elasticum. *Acta Cardiol* 1998;53:223-5.

SUMMARY - Pseudoxanthoma elasticum (PXE) is a rare heritable disorder of the connective tissue characterized by marked clinical heterogeneity. Common cardiovascular complications of PXE include renovascular hypertension, premature coronary artery disease and calcification of peripheral arteries frequently leading to claudicatio intermittens; fibrous thickening of the endocardium and atrioventricular valves, leading to a restrictive cardiomyopathy and/or mitral valve prolapse have been also described. We herein report on a PXE patient who developed an atrial septal aneurysm as a previously undescribed cardiologic manifestation of her disease.
I.F. = 0,308
N. citazioni = 6

64. Ghigna C, Moroni M, **Porta C**, Riva S, Biamonti G. Altered expression of heterogeneous nuclear ribonucleoproteins and SR factors in human colon adenocarcinomas. *Cancer Res* 1998;58:5818-24.

SUMMARY - Alternative splicing is part of the expression program of a wide number of genes implicated in cell growth and differentiation. Although the occurrence of inappropriate alternative splicing in tumors has started to emerge, the underlying molecular mechanisms have been, thus far, largely unexplored. We have investigated the alternative splicing pattern of the CD44 gene in specimens of nonfamilial colon adenocarcinomas at different stages of tumor progression. In the same patients, we have assessed by Northern blotting analysis the mRNA levels of different heterogeneous nuclear ribonucleoproteins and SR factors, all involved in pre-mRNA splicing and, more in general, in mRNA maturation. The results of this analysis highlight a general rule for the mode of splicing of the CD44 pre-mRNA. Moreover, we found that the mRNA levels of different SR proteins in tumor specimens are different from, and usually lower than, those detected in samples of nonpathological tissue adjacent to the tumor. Quantitative analysis demonstrates that, in tumors, the mRNA levels of ASF, SRp40, SRp55, and SRp75, when normalized to those of heterogeneous nuclear ribonucleoprotein A1, are lower than those of SRp20 and SRp30. Interestingly, this reduction is more drastic in patients showing a more altered CD44 splicing pattern and seems to be related to the propensity to develop metastases.
I.F. = 8,37
N. citazioni = 70

65. Moroni M, **Porta C**, Invernizzi R, Inzoli A, Bobbio-Pallavicini F, Bobbio-Pallavicini E. 'TUNEL' evidence of reduced bone marrow cells apoptosis in a refractory anaemia patient treated with Amifostine. *Br J Haematol* 1999;104: 423-4 [Letter].

ABSTRACT - Recently, it has been demonstrated that treatment with the thiol derivative Amifostine can promote multilineage hematopoiesis in patients with myelodysplastic syndromes (MDS). The putative role of Amifostine in MDS patients relies on its ability to scavenge oxygen-reactive species which are assumed to be mediators of apoptosis. Indeed, it has been reported that bone marrow hematopoietic cells of MDS patients have increased apoptosis compared to normal bone marrow cells. A 62-year-old caucasian male affected with long-lasting refractory anemia (RA) was treated with amifostine, given at 200 mg/m^2 i.v., three days a week, for three consecutive weeks. A clinical response was observed at the end of the three weeks' treatment period, with a marked decrease of red blood cell transfusion requirement and a steady increase of both white blood cells and platelets. Furthermore, apoptosis was measured on bone marrow smears using a terminal-deoxynucleotidyl-transferase-mediated deoxyuridine triphosphate nick end labelling (TUNEL) technique. A marked reduction of the apoptotic index (AI) within the bone marrow was evidenced after treatment; after an 11-weeks amifostine treatment withdrawal, leukopenia reappeared and patient's transfusional requirement returned to baseline levels; only platelets, despite a constant decrease, remained higher than before treatment. The TUNEL examination of patient's bone aspirate again showed an increased AI of 4%. This is the first time a reduction of bone marrow cell apoptosis after amifostine treatment was morphologically demonstrated in a MDS patient.
I.F. = 3,204
N. citazioni = 10

66. **Porta C**, Caporali R, Montecucco C. Thrombotic thrombocytopenic purpura and autoimmunity: a tale of shadows and suspects. *Haematologica* 1999;84:260-9.

ABSTRACT - Background and objective: The key pathogenic feature of TTP is the formation of platelet aggregates within the microcirculation; however, the etiology of such aggregates has been elusive for years. A large amount of evidence points to an abnormal interaction between damaged vascular endothelium and platelets, altough the cause of the primary microvascular endothelial cell injury is seldom clear. The autoimmune hypothesis often recurs, and this is based on a number of observations: the claimed superiority of plasma-exchange over plasma infusion, the anecdotal report of the presence of immunocomplexes and autoantibodies in TTP patients, the efficacy of the administration of corticosteroids and other immunosuppressant agents, and the concomitant occurrence of TTP in association with autoimmune diseases, especially systemic lupus erythematosus (SLE). This review will focus on the complex relationships between TTP and humoral autoimmunity; in particular, similarities and differences between TTP, SLE and antiphospholipid (aPL) antibodies syndrome, as well as the putative role of several other antibodies directed towards endothelial cells and/or platelets, including the recently discovered anti-CD36 antibodies and antivWF-cleaving metalloprotease, will be discussed. Design and methods: The Authors have been involved in the study and treatment of TTP and autoimmune diseases for years; furthermore, the PubMed data base of the National Library of Congress has been extensively searched using the Internet. Conclusions: Although over the years evidence has increased in favor of the autoimmune hypothesis for TTP etiopathogenesis, TTP should not yet be considered an autoimmune disease. Autoantibodies should be regarded as only one of the many different insults which can trigger microvascular thrombosis even though the autoimmune theory of the pathogenesis of TTP is gaining more and more strenght. As far as concerns the relationship between TTP, SLE and aPL antibodies-related disorders, these diseases should be distinguished on the basis of both different clinical presentations and accurate antibody screening, altough this approach should definitely not delay the prompt start of treatment.
I.F. = 2,074
N. citazioni = 53

67. **Porta C**, Danova M, Riccardi A, Bobbio-Pallavicini E, Ascari E. Cancer chemotherapy-related thrombotic thrombocytopenic purpura: biological evidence of increased nitric oxide production. *Mayo Clin Proc* 1999;74:570-4.

ABSTRACT - The occurrence of thrombotic thrombocytopenic purpura (TTP) in cancer patients receiving chemotherapy has been well established; although this entity is rare, its clinical importance seems to be growing. We describe 3 cases of TTP developing in cancer patients receiving different chemotherapeutic regimens. Using a sensitive high-performance liquid chromatographic method, we evaluated the stable nitric oxide end-products, nitrite and nitrate, in the plasma of these patients. Nitric oxide is one of the key components involved in mantaining the normal nonthrombogenicity of the vascular endothelium. In our 3 patients, we found increased nitrate titers that were substantially higher than those observed in patients with de novo TTP. The observed increased release of nitrate could be interpreted as the consequence of massive disruption of endothelial integrity, with consequent passive nitric oxide release in vivo, or an adaptative mechanism of the endothelium to compensate for diffuse microvascular occlusion. The 2 mechanisms may both be involved, but the normal titers of nitrci oxide end-products in de novo TTP suggest that the former mechanism is more important, at least in cancer chemotherapy-related TTP.
I.F.= 2,024
N. citazioni = 22

68. Ferrari S, Danova M, **Porta C**, Comolli G, Brugnatelli S, Pugliese P, Riccardi A, Ascari A. Circulating progenitor cell release and functional characterization after Topotecan plus G-CSF and erythropoietin in small cell lung cancer patients. *Int J Oncol* 1999;15:811-5.

SUMMARY - Topotecan is a new antineoplastic agent active in ovarian cancer, with promising activity in small cell lung cancer and predictable toxicity. As a part of our ongoing attempt to optimize the use of disease-specific drugs as circulating progenitor cell (CPC) priming in solid tumors, we have evaluated the effects on CPC release of single-agent Topotecan followed by gra-

nulocyte colony-stimulating factor (G-CSF) + human recombinant erythropoietin (rhEPO), together with the cell cycle status of the collected CD34+ cells. Ten pretreated patients with small cell lung cancer received Topotecan (1 mg/m², i.v. for 5 consecutive days) followed by G-CSF (5 μg/kg/day, s.c.) + rhEPO (10,000 I.U. daily, s.c.), starting 24 hours after Topotecan. The combination was well tolerated and no relevant side-effects were recorded. On day +10 (range +9 to +11) after the last dose of Topotecan, the median WBC count and the CD34+ cell peak were 8.2 x 10³/μL (range 4.9-13.9) and 55/μL (range 28-75), respectively. Using flow cytometry, a detailed cell cycle analysis was performed on these CD34+ cells. The cell cycle distribution was determined by DNA content coupled with bromodeoxyuridine incorporation analysis. Apoptosis was evaluated by quantitating DNA strand breaks. The percentage of CD34+ cells in active S-phase was 10.2 ± 5%, while early apoptotic CD34+ cells were detected in a low percentage (5.5 ± 3%). Topotecan followed by G-CSF and rhEPO mobilizes CPCs effectively. This sequence exerts a stimulation on CD34+ cell cycle with a protective effect from chemotherapy-induced apoptosis. Taken together, these data could be of value for the incorporation of Topotecan, as well as of the combination of G-CSF and rhEPO, into high-dose chemotherapy programs with CPC support.

I.F.=1,381

N. citazioni = 8

69. Palmeri S, Leonardi V, Danova M, **Porta C**, Ferrari S, Fincato GL, Citarella P. Prospective randomized trial of sequential interleukin-3 and granulocyte- or granulocyte-macrophage colony-stimulating factor after standard-dose chemotherapy in cancer patients. *Haematologica* 1999;84:1016-23.

ABSTRACT - Background and Objectives: Several in vitro and animal studies have shown that IL-3 primes hematopoietic stem cells to become more sensitive to later acting growth factors. We wanted to compare the toxicity and the synergistic stimulatory effects of interleukin-3 (IL-3) followed by granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) on white blood cell (WBC) and platelet counts, after standard-dose chemotherapy (CT) in patients with solid tumors. Design and Methods: Fifty consecutive cancer patients with thrombocytopenia and/or leukopenia registered during a previous course of CT were randomized to receive, after the following course, IL-3 (10 μg/Kg/day, s.c., day 1-5) followed by G- or GM-CSF (5 μg/Kg/day, day 6-8). Results: The nadir of WBC in the cycles supported with the combination of IL-3 and G-CSF was significantly higher than that observed in the CT cycles not supported by growth factors (p < 0.005). Furthermore, severe leukopenia was abrogated in all the cycles supported with IL-3 + G-CSF, while in the cycles without cytokines, this event was registered in 62.5% of the cases (p < 0.0005). Finally, the recovery of WBC was achieved a mean of 4 days earlier in the cycles supported with IL-3 + G-CSF. As for thrombocytoprotection, no significant differences were evidenced, but severe thrombocytopenia was abrogated in all the cycles supported by IL-3 + G-CSF (p < 0.05). Furthermore, platelet recovery after CT was achieved on average 3.5 days earlier in the IL-3 + G-CSF group than in the previous cycles. The nadir of WBC count in the cycles supported by the combination of IL-3 and GM-CSF was significantly higher than that observed in the CT cycles not supported by growth factors (p < 0.005). Furthermore, severe leukopenia was abrogated in 40% of the cycles supported by IL-3 + GM-CSF, while in the cycles without cytokines, this event was registered in 80% of the cases (p < 0.005). Finally, the recovery of WBC was achieved a mean of 3.5 days earlier in the cycles supported by IL-3 + GM-CSF. As far as thrombocytoprotection is concerned, there were no significant differences in the nadir between the cycles supported by the association IL-3 + GM-CSF and the cycles not supported by cytokines. However, severe thrombocytopenia was registered in 20% of the cycles not supported by growth factors but in only 10% of the cycles supported by IL-3 + GM-CSF (p < 0.05). Furthermore, platelet recovery after CT was achieved on average 3 days earlier in the IL-3 + GM-CSF group. The combination of IL-3 and G-CSF would appear to be more active than the combination of IL-3 and GM-CSF in the control of both severe thrombocytopenia and leukopenia. Indeed, severe leukopenia was abrogated in all the cycles in arm A, but only in 40% of the cycles in arm B (p < 0.0005). Furthermore, considering a platelet count below 49 x10⁹/L, such a toxicity was avoided in 90% of the cycles in arm B, but in 100% of the cycles in arm A (p < 0.05). Interpretation and Conclusions: The sequential administration of IL-3 and myeloid growth factors can be given safely after standard-dose CT programs. The combination of IL-3 + G-CSF seems to be more effective than the association IL-3 + GM-CSF in the control of CT-induced myelosuppression, even though further studies are needed to confirm these results.

I.F. = 2,074

N. citazioni = 14

70. Marzatico F, **Porta C**, Moroni M, Bertorelli L, Borasio E, Finotti N, Pansarasa O, Castagna L. *In vitro* antioxidant properties of amifostine (WR-27121, Ethyol™). *Cancer Chemother Pharmacol* 2000;45:172-6.

SUMMARY - Purpose: Amifostine (WR-2721), a phosphorylated aminothiol pro-drug which is an analogue of cysteamine, is a selective cytoprotective agent for normal tissues from the toxicities associated with chemotherapy and irradiation. Despite a growing number of reports strongly supporting Amifostine's clinical efficacy, few Authors have focused on the biochemic basis of Amifostine's antioxidant activity. Methods: We report on Amifostine's free-radical scavenging activity against superoxide (O_2^-), hydroxyl (OH^-) and lipoperoxyl radicals in an in vitro model, using pure chemical systems. Amifostine was dephosphorylated to its active metabolite, WR-1065, by adding 10% non-heat.inactivated serum; different Amifostine concentrations (1, 10, 50, 100 μM and 200 μM) and pH conditions (pH 5, 7.4 and 9) were tested. Results: Independent of the concentration, Amifostine exhibited no major activity against O_2^- ions, neither did any pH variations in the experimental model provide any scavenger effects of the drug against O_2^- radicals. On the other hand, the protective effects of Amifostine against OH^- was confirmed, yielding an EC_{50} of 255 μM at pH 7.4 and 230 μM at pH 5. Finally, Amifostine exhibited scavenging activity against spontaneous lipoperoxidation, but no apparent antioxidant effect on iron ascorbate-induced lipoperoxidation. Conclusions: With this in vitro study, we are able to confirm the scavenging activity of the chemo- and radioprotector Amifostine, whose activity seems to be particularly important from a biological point of view, since it is exerted mainly against highly reactive OH^-.

I.F.= 2,081

N. citazioni = 72

71. Moroni M, **Porta C**, De Amici M, Quaglini S, Cattabiani MA, Buzio C. Eosinophils and C4 predict clinical failure of combination immunotherapy with very low dose subcutaneous interleukin-2 and interferon in renal cell carcinoma patients. *Haematologica* 2000;85:298-303.

SUMMARY - Background and objective: The clinical and immunologic activities of interleukin-2 (IL-2) in cancer patients have been extensively studied and described; however, in most of these studies, IL-2 was administered by intravenous bolus or continuous infusion, while the immunologic effects of IL-2 given by the subcutaneous (s.c.) route have not yet been well studied. Design and methods: The present study was aimed at evaluating the effects of IL-2, given at very low doses s.c. in patients with advanced renal cell carcinoma (RCC), on a number of immunologic parameters: number of total lymphocytes, number of CD4-, CD8-, CD25-positive cells, number of natural killer (NK) cells, titers of IL-2 soluble receptors (sIL-2R) and of C4, eosinophils, eosinophilic cationic protein (ECP) and eosinophilic protein X (EPX). Finally, a logistic regression model was performed to identify early immunologic parameters that correlate with a favorableor unfavorable treatment outcome. Results: Independently from the mere report of the changes induced by immunotherapy, the analysis showed that, within the pre-treatment model,

a large eosinophil number predicts the failure of IL-2 treatment; in contrast, within the post-treatment model, high C4 serum titers and, again, a large number of circulating eosinophils predict immunotherapy failure. Interpretation and conclusions: As far as concerns C4, its negative predictive value could be related to the fact that it is an indirect index of macrophage activation; thus, even though macrophages release substances with antitumor activity, they can also stimulate the release of sIL-2R, which may compete for exogenous IL-2. Some authors have postulated that macrophages may even stimulate tumor cell growth, or impair NK activity. Despite a great amount of uncertainty concerning the role of eosinophils, in our study, blood eosinophilia predicts a poor response to immunotherapy in patients with advanced RCC, thus supporting previous observations from our own group.
I.F. = 2,538
N. citazioni = 18

72. Rock G, **Porta C**, Bobbio-Pallavicini E. Thrombotic thrombocytopenic purpura treatment in year 2000. *Haematologica* 2000;85:410-9.

ABSTRACT - Background and objectives: For several decades clinicians worlwide considered TTP a severe and frustrating therapeutic problem. Fortunately, however, the prognosis of TTP patients has greatly benefited from the use of plasma manipulation techniques, particularly plasma-exchange (PE), so that the overall rate of complete responses currently ranges between 70 and 85%, and may even exceed these figures. Despite this dramatic improvement, a number of questions remain concerning the best treatment for TTP patients. Analyzing acquired data and discussing future perspectives, this review will address the following key issues: 1) is PE really the treatment of choice for TTP and what is the role of PE with cryosupernatant? 2) what is the role of all the drugs which are commonly combined with PE, antiplatelet drugs and steroids in particular? 3) what, if any, is the role of cytotoxic agents, especially vincristine? 4) is there a treatment for PE-resistant patients? 5) does secondary TTP need different treatments? Design and methods: The Authors have been involved in the study and treatment of TTP for years; furthermore, they extensively searched the PubMed database of the National Library of Congress through the Internet. Interpretation and conclusions: PE remains the treatment of choice for TTP. A large randomized trial now in progress will assess whether exchange with cryosupernatant plasma can improve treatment efficacy. The administration of antiplatelet drugs in combination with PE was fiercely debated over the past years but seems indicated both in acute TTP and as a prophylactic treatment to prevent relapses. It appears that steroids cannot be avoided, especially in light of the latest findings on TTP pathogenesis, but only specific trials will assess the optimal cortisone type and dose. Presently, different treatments can be suggested only to patients failing to respond to PE, while no specific therapy can be indicated for secondary TTP, which usually has a very poor prognosis. Finally, we would like to stress that only international cooperative (multicenter) trials on large series of patients will be able to shed light on a still obscure, if fascinating, disease. Our hope and wish is that the new century will see TTP among the diseases defeated by man's clever mind and heart.
I.F. = 2,538
N. citazioni = 53

73. Danova M, **Porta C**, Ferrari S, Brugnatelli S, Comolli G, Riccardi A, Ascari E. Cell cycle status and apoptosis of hematopoietic progenitor cells released into the peripheral blood after taxanes and granulocyte colony-stimulating factor in breast cancer patients. *Oncol Rep* 2000;7:585-9.

SUMMARY - Paclitaxel and its analogue docetaxel show a significant antitumor activity, particularly evident in breast cancer. Paclitaxel has also been proved to be effective as a peripheral blood progenitor cell (CPC) mobilizing agent. To optimize the use of active, disease-specific drugs as CPC priming, we have evaluated the effects of either paclitaxel or docetaxel both at standard dosages and followed by granulocyte colony-stimulating factor (G-CSF) on circulating CPC release and function in 18 patients with advanced breast cancer who had failed previous anthracycline-based regimens. The reported differences in biological behaviour between bone marrow and blood-derived hematopoietic progenitor cells and the ability of both paclitaxel and docetaxel to induce apoptosis, prompted us to simultaneously evaluate the cell cycle perturbations induced on $CD34^+$ cells. Median $CD34^+$ peaks were 24 μL (range: 10-58) in the paclitaxel-treated patients and 39 μL (range: 17-91), respectively, in the patients who received docetaxel. After paclitaxel, the percentage of $CD34^+$ cells in S-phase was low (bromodeoxyuridine, BrdU, labelling index = 3.4 ± 2%) with a concomitant presence of early apoptotic cells (8.1 ± 3%). On the contrary, after docetaxel, the percentage of $CD34^+$ cells in S-phase was higher (BrdU labelling index = 14.5 ± 4%, $p < 0.05$ vs. paclitaxel), while early apoptotic cells were detected at a similar rate (8.6 ± 3%, p = n.s. vs. paclitaxel). In conclusion, when used at standard dosages, with respect to paclitaxel + G-CSF, docetaxel + G-CSF is a more satisfactory tool to mobilize CPC and to induce them into the cell cycle. These data should be taken into account when combinations of docetaxel with other agents are explored as CPC mobilizing regimens for autografting.
I.F. = 1,29
N. citazioni = 5

74. Balloni L, Pugliese P, Ferrari S, Danova M, **Porta C**. Colon cancer in pregnancy: report of a case and review of the Literature. *Tumori* 2000;86:95-7.

SUMMARY - Most colon cancers occur in patients over 50 years of age, although about 3% of colorectal cancer patients are younger than 40. During pregnancy the incidence of this neoplasm is estimated to be 0.002%. To date, only 32 cases of colonic cancer arising above the peritoneal reflection-during pregnancy have been described in the Literature. We report another such case, stressing the need for constant alertness on the part of physicians in the presence of abdominal pain and/or distension, a palpable abdominal mass, rectal bleeding and/or weight loss during pregnancy. In fact, the reportedly poorer prognosis of this cancer in pregnant patients is mainly due to the fact that the initial symptoms of the malignancy are usually attributed by the patient, but also by physicians, to normal pregnancy.
I.F. = 0,485
N. citazioni = 15

75. Balloni L, **Porta C**, Rossi S, Gola A, Pugliese P, Ferrari S, Bovio A, Danova M, Riccardi A. Left ventricular function in colon cancer patients receiving adjuvant fluoro-folate chemotherapy: an echocardiographic study. *Oncol Rep* 2000;7:887-90.

ABSTRACT - Cardiotoxicity has been reported with increasing frequency after 5-FU administration. Since 5-FU-based regimens are increasingly used as adjuvant treatment for resected colon cancer patients, this carries a potential increased risk of cardiotoxicity. In the present study, we evaluated if fluoro-folate chemotherapy has any effect on left ventricular (LV) diastolic function in resected colon cancer. Twenty-five resected colon cancer patients receiving adjuvant fluoro-folate chemotherapy, were prospectively studied. Both digitized M-mode and Doppler echocardiography were performed, in order to investigate different aspects of LV diastolic function. None of the studied parameters was influenced by chemotherapy administration. Indeed values recorded at the end of the 6-month treatment and 6 months later were not statistically different from baseline values. This study suggests that the use of fluoro-folate chemotherapy in otherwise normal subjects carries a very low risk of severe cardiotoxicity.
I.F. = 1,29
N. citazioni = 13

76. **Porta C**, Danova M, Orengo AM, Ferrini S, Moroni M, Gaggero A, Libener A, Betta PG, Ferrari S, Procopio A,

Strizzi L, Mutti L. Interleukin-2 induced cell cycle perturbations leading to cell growth inhibition and death in malignant mesothelioma cells *in vitro*. *J Cell Physiol* 2000;185:126-34.

ABSTRACT - Previous reports indicated that Interleukin-2 (IL-2) is able to inhibit the growth of IL-2-receptor-positive cancer cell lines without any involvement of the immune system, through IL-2-induced alterations of the cell cycle kinetics. In this study we provide evidence that IL.2 exerts anti-proliferative effects on three human malignant mesothelioma (MMe) cells in vitro, while no effects were observed on normal human mesothelial cell (HMC) primary cultures. The growth inhibitory effect of IL-2 on neoplastic cells appeared to depend on the baseline proliferative status of these cells. Indeed, in highly proliferaying MMe cells, we observed a reduction of malignant cells in the S-phase of the cell cycle, with an accumulation in G0/G1, followed by apoptosis for longer incubations or exposure to higher doses. On the contrary, in MMe cells proliferating at lower rate, IL-2 induces only a late cytotoxic effect, leading to apoptosis, without significantly affecting the cell cycle. IL-2Rβ mRNA was detectable by RT-PCR in all MMe cells, IL-2Rα mRNA in one only out of the three assayed and IL-2Rγ in none. In addition, mRNA specific for the IL-2Rβ-associated Jak-1 tyrosine kinase was expressed in all MMe cell lines, further suggesting that IL-2Rβ may play a role in the observed effects. Very low, albeit detectable, levels of IL-2Rβ chain appeared to be expressed at the cell surface of MMe cells by indirect immunofluorescence and FACS analyses. Finally, Ca^{++} fluxes were rapidly induced when MMe cells were exposed to exogenous IL-2.
I.F. = 3,474
N. citazioni = 17

77. **Porta C**, Maiolo A, Tua A, Grignani G. Amifostine, a reactive oxigen species scavenger with radiation- and chemoprotective properties, inhibits in vitro platelet activation induced by ADP, collagen and PAF. *Haematologica* 2000;85:820-5.

ABSTRACT - Background and objectives: Reactive oxygen species (ROS) generation has been suggested to represent an important regulatory mechanism of platelet reactivity in both physiologic and pathologic conditions; consistent with this hypothesis is the observation that free-radical scavengers may inhibit platelet activation, thus contributing to the regulation of their reactivity. The purpose of the present study is to study the in vitro effects of amifostine (WR-2721, ethyol), a selective cytoprotective agent for normal tissues against the toxicities of chemotherapy and radiation, on platelet activation induced by the physiologic agonists ADP, collagen and PAF. Design and method: The effect of amifostine, added to the experimental system at final concentrations ranging from 10^{-7} M to 10^{-5} M, was studied on platelet aggregation induced by the following physiologic agonists at the given concentrations: ADP (1 μM), collagen (2 μg/mL), and PAF (0.1 μg/mL). Platelet aggregation was investigated using a platelet ionized calcium aggregometer and was expressed as the percentage change in light transmission. Furthermore, thromboxane B_2 (TxB_2 levels and nitric oxide (NO) production were determined by radioimmunoassay and by evaluating the total nitrite/nitrate concentration using a commercially available colorimetric kit, respectively, both in the control system and after the addition of amifostine. Results: Amifostine inhibited both platelet aggregation and TxB_2 production induced by ADP, collagen and PAF, in a dose-dependent manner. Amifostine proved to be an effective inhibitor of platelet function and the effect was more pronounced if platelets were stimulated with ADP, intermediate when collagen was the chosen agonist, and less evident, though present, when PAF was used. Platelets stimulated with ADP, collagen or PAF produced significant amounts of NO over the baseline. When amifostine was added at a final concentration of 5 μM, it significantly increased ADP, collagen and PAF-induced NO production, which suggests that NO release by activated platelets was involved in the inhibitory effect of amifostine. Interpretation and conclusions: Amifostine proved to be an effective inhibitor of platelet activation induced in vitro by physiologic inducers. This previously unrecognized effect was more evident with the weak agonist ADP and was related to reduced NO consumption by free radicals generated during platelet activation. Amifostine proved to be not only a powerful cytoprotectant, but, more generally, a therapeutic agent endowed with several relevant, though largely unknown, biological effects. Finally, our data once again support the concept that oxidative balance is of crucial importance in regulating platelet reactivity in both health and disease.
I.F. = 2,538
N. citazioni = 13

78. Siragusa S, **Porta C**, Falaschi F, Pirrelli S, Bressan MA. Rebuttal to: The usefulness of compression ultrasonography of the lower limbs in patients with a clinical suspicion of pulmonary embolism. *Thromb Haemost* 2001;86:724-5.

ABSTRACT - Data from the literature provide discordant results regarding the importance of positive compression ultrasonography (CUS) results in patients with proven pulmonary embolism (PE). In a recent publication, Mac Gillavry questioned about the usefulness of bilateral CUS of the lower limbs in a mixed population of in- and out-patients with the clinical suspicion of PE. In this study, either two-points or extensive examinations of the deep venous system were used. We prospectively investigated 96 out-patients admitted to our Emergency Room (ER) for the clinical suspicion of PE; evaluation of standardized clinical probability, CUS and D-dimer test were applied as triage test and patients managed according to test results. Among the patients with proven PE, we found a rate of CUS-detected venous thrombosis higher (66%) than that reported by Mac Gillavry et al. (on the average 10% of the entire population). A possible explanation for this discrepancy lies in the approach for CUS performance, which in our case was the extensive scanning of the entire deep and superficial venous system. As demonstrated in previous studies, a negative CUS does not allow the exclusion of an ongoing PE. Our data, however, shows that a positive CUS provides a high likelihood ratio of a positive test and allows us the diagnosis of almost 70% of patients with proven PE. In conclusion, in our opinion an extensive CUS (performed along the deep and superficial veins), used as a triage test at ER, is a potentially useful tool for the management of patients with a suspected PE.
I.F. = 4,91

79. Danova M, **Porta C**, Ferrari S, Riccardi A. Strategies of medical treatment for metastatic breast cancer. Review. *Int J Oncol* 2001;19:733-9.

ABSTRACT - Resently, metastatic breast cancer cannot be cured and therefore good palliation of symptoms and longer overall survival make the most important targets, always considering quality of life. In addition to the established hormonal therapies or chemotherapy regimens, several recent advances have accelerated progress in metastatic breast cancer treatment. As demonstrated in recent studies, the third-generation aromatase inhibitors are playing a significant role in the improvement of the therapeutic approach. The development of new drugs with novel mechanisms of action, such as taxanes, used alone in innovative schedules or in association with other drugs (mainly the anthracyclines), vinorelbine and gemcitabine, or capecitabine, which is administered orally, has broadened the scope of metastatic breast cancer chemotherapy. A new investigation field is represented by high-dose chemotherapy with stem cell support, which has provided controversial preliminary results but is also acknowledged to deserve larger and randomized trials. Finally, the emergence of biological therapies such as the anti-HER2 monoclonal antibody Trastuzumab opens new and exciting prospects for the treatment of this disease. Moreover, the present trend is to try to rationalize the therapeutic approach on the basis of biological parameters which are prognostic and predictive of treatment response.
I.F. = 2,33
N. citazioni = 9

80. **Porta C**, Barone M, Bressan MA. The irreplaceable

image: superficial thrombosis of a varicose vein of the abdominal wall as the first sign of an otherwise occult locally advanced ovarian cancer. *Haematologica* 2001;86:1120.

ABSTRACT - We report and comment on case of a young woman who was admitted to the Emergency Department due to the onset of a superficial thrombosis of a varicose vein of the abdominal wall; the thrombotic complication proved to be caused by an otherwise occult locally advanced ovarian cancer.

I.F. = 3,216

N. citazioni = 1

81. Cacciotti P, Libener R, Betta P, Martini F, **Porta C**, Procopio A, Strizzi L. Penengo L, Tognon M, Mutti L, Gaudino G. SV40 replication in human mesothelial cells induces HGF/Met receptor activation: a model for viral-related carcinogenesis of human malignant mesothelioma. *Proc Natl Acad Sci USA* 2001;98:12032-7.

ABSTRACT - Recent studies suggested that simian virus 40 (SV40) may cause malignant mesothelioma, although the pathogenic mechanism is unclear. We found that in SV40-positive malignant mesothelioma cells, the hepatocyte growth factor (HGF) receptor (Met) was activated. In human mesothelial cells (HMC) transfected with full-length SV40 DNA (SV40-HMC), Met receptor activation was associated with S-phase entry, acquisition of a fibroblastoid morphology, and the assembly of viral particles. Coculture experiments revealed the ability of SV40-HMC to infect permissive monkey cells (CV-1), HMC, and murine BNL CL cells. Cocultured human and murine SV40-positive cells expressed HGF, showed Met tyrosine phosphorylation and S-phase entry, and acquired a spindle-shaped morphology (spBNL), whereas CV-1 cells were lysed. Cocultured HMC inherited from SV40-HMC the infectivity, as they induced lysis in cocultured CV-1 cells. Treatment with suramin or HGF-blocking antibodies inhibited Met tyrosine phosphorylation in all large T antigen (Tag)-positive cells and reverted the spindle-shaped morphology of spBNL. This finding indicated that Met activation and subsequent biological effects were mediated by an autocrine HGF circuit. This, in turn, was causally related to Tag expression, being induced by transfection with the SV40 early region alone. Our findings suggest that when SV40 infects HMC it causes Met activation via an autocrine loop. Furthermore, SV40 replicates in HMC and infects the adjacent HMC, inducing an HGF-dependent Met activation and cell-cycle progression into S phase. This may explain how a limited number of SV40-positive cells may be sufficient to direct noninfected HMC toward malignant transformation.

I.F. = 10,896

N. citazioni = 123

82. Siragusa S, Terulla V, Pirrelli S, **Porta C**, Falaschi F, Anastasio R, Guarnone R, Scarabelli M, Odero A, Bressan MA. A rapid D-dimer assay in patients presenting at the emergency room with suspected acute venous thrombosis: accuracy and relation to clinical variables. *Haematologica* 2001;86:856-61.

SUMMARY - Background and objectives: The measurement of D-dimer is claimed to have potential value in excluding deep vein thrombosis (DVT). New rapid methods have been proposed, but few clinical trials have assessed their performance in an emergency context. The different accuracies found between the D-dimer assays have been related to the test used (latex or ELISA), but other variables (such as population investigated, thrombus extension, duration of symptoms or concomitant heparin treatment) may be important, even if not sufficiently investigated. Design and methods: We evaluated the accuracy of a rapid semi-quantitative D-dimer test (Dimertest, Dade Behring), with reference to: a) its use at an emergency unit; b) concomitant heparin administration; c) location of venous thrombosis (VT) (in the deep or superficial venous system limited to the great saphenous vein) and d) symptoms older than 14 days. Results: Two hundred and ninety-eight patients suspected of having DVT and 116 suspected of thrombosis of the great saphenous vein (GSV) were investigated. In the DVT patients, the sensitivity, specificity, positive and negative predictive values were 77.4% (95% CI 68.9-85.9), 81.4% (95% CI 76.1-86.7), 65.4% (95% CI 56.5-74.3) and 88.8% (95% CI 84.2-93.4), respectively. Excluding patients receiving heparin and those with symptoms older than 15 days, the sensitivity and negative predictive value increased to 86.3% (95% CI 78.4-94.2) and 92.8% (95% CI 88.4-97.2), respectively. In patients with GSV thrombosis, the sensitivity, specificity, positive and negative predictive values were 48% (95% CI 34.5-61.5), 90.6% (95% CI 83.2-97.9), 80.6% (95% CI 66.6-94.6) and 68.2% (95% CI 57.8-78.6), respectively. Excluding patients receiving heparin and those with symptoms older than 15 days, did not change the sensitivity or negative predictive value significantly. Interpretation and conclusions: Our results show that previous or concomitant heparin administration, non-acute symptoms and thrombosis localized to superficial veins reduce the clinical usefulness of the D-dimer test as the rate of false negative results is increased.

I.F. = 3,216

N. citazioni = 32

83. **Porta C**, Danova M, Accurso S, Tinelli C, Girino M, Riccardi A, Palmeri S. Sequential intrahepatic and systemic fluoropyrimidine-based chemotherapy for metastatic colorectal cancer confined to the liver. A phase II study. *Cancer Chemother Pharmacol* 2001;47:423-8.

ABSTRACT - Purpose: Several trials have suggested that intrahepatic chemotherapy increases the likelihood of response in advanced colon cancer patients, but has no significant impact on survival due to the development of extrahepatic metastases. We report our experience of combined hepatic intraarterial and systemic chemotherapy in advanced colorectal cancer patients. Methods: A group of 35 patients received intrahepatic FUDR (0.3 mg/kg per day for 14 days by continuous infusion), followed, after 1 week's rest, by systemic 5-FU and L-leucovorin (370 and 100 mg/m^2 per day, respectively, both for 5 consecutive days). After another week off therapy, the combined intrahepatic and systemic regimen was repeated and cycles continued until disease progression. Results: Of 32 assessable patients, 17 (53.1%) had an objective response, while 8 (25%) had disease stabilization. Median time to progression (TTP) was 32 weeks (range 8-104 weeks), while the median overall survival was only 39 weeks (range 9-109 weeks). Incomplete liver perfusion was the only variable that showed a significant correlation with a poorer survival (P = 0.046, log-rank test). Conclusions: Our results are in agreement with previous data suggesting a relative efficacy of such a treatment approach for advanced colon cancer patients. More thorough investigations are warranted, especially as an adjuvant treatment for selected high-risk patients.

I.F. = 2,17

N. citazioni = 16

84. Bobbio-Pallavicini E, Tacconi F, **Porta C**, Brambilla G, Mainardi E, Bianchessi C, Moroni M. Cisplatin, mitomycin-C, 5-fluorouracil and leucovorin (l-FCM) in locally advanced unresectable or metastatic gastric carcinoma: a phase II study. *Oncol Rep* 2001;8:167-71.

ABSTRACT - Despite relevant progress, the impact of chemotherapy on advanced gastric cancer patients' survival is still unsatisfactory. Thus, the key objective of our efforts should be palliation of the symptoms and the maintenance of an adequate quality of life. In this phase-II study, we evaluated toxicity and efficacy of the combination of cisplatin, fluorofolates and mitomycin C. Thirty-one advanced gastric cancer patients received cisplatin (15 mg/m^2)

and 5-fluorouracil (350 mg/m^2), both for 5 consecutive days every 4 weeks; 5-fluorouracil infusion was preceded by a rapid i.v. injection of 100 mg/m^2 leucovorin, while mitomycin-C (10 mg/m^2) was administered on day 1 of odd cycles. Cycles were repeated every 4 weeks until disease progression. We recorded 16 objective responses (51.6%, 95% confidence interval: 42.63-60.57); furthermore, such a response rate was coupled with a moderate degree of toxicity and an extremely good tolerance. In particular, alopecia, a frequent and distressing side-effect in patients, especially women, in our series occurred only in two patients. This treatment appears to be an active and tolerable therapeutic option for patients with advanced gastric carcinoma.
I.F. = 1,224

85. Cacciotti P, Strizzi L, Vianale G, Iaccheri L, Libener R, **Porta C**, Tognon M, Gaudino G, Mutti L. The presence of Simian-Virus 40 sequences in mesothelioma and mesothelial cells is associated with high levels of vascular endothelial growth factors. *Am J Respir Cell Mol Biol* 2002;26:189-93.

SUMMARY - The aim of this study was to evaluate whether the presence of simian virus-40 (SV40) is associated with increased release of vascular endothelial growth factor (VEGF) in human malignant mesothelioma (MM) cells. We studied nine cell lines derived from pleural effusion (PE) of patients with MM, and three different cultures of normal human mesothelial cells (NHMC) derived from pleural fluid of patients with congestive heart failure. NHMC were transfected with full lenght SV40 (NHMC-FL) or large T antigen (NHMC Tag) DNAs. High levels of VEGF were detected in conditioned media of each of two MM cells that tested positive for SV40 by PCR amplification and Southern blot hybridization and for Tag transcript by reverse transcription-polymerase chain reaction (RT-PCR) and immunoprecipitation. We also found that NHMC-FL released high amounts of VEGF. Conditioned media from SV40-positive MM cells and from FL-NHMC increased proliferation of human umbilical vein cells (HUVEC) and this effect was partially abrogated by adding specific blocking antibodies against VEGF. These results offer the first evidence that SV40 can cause VEGF release in SV40-positive MM cells and that the entire viral genome is required for this effect.
I.F. = 4,17
N. citazioni = 59

86. Rizzo V, **Porta C**, Moroni M, Scoglio E, Moratti R. Determination of free and total (free plus protein-bound) melatonin in plasma and cerebrospinal fluid by high-performance liquid chromatography with fluorescent detection. *J Chromatogr B* 2002;774:17-24.

ABSTRACT - A simple, sensitive and accurate method for the estimation of free and total (free plus protein-bound) melatonin (MLT) in human plasma and cerebrospinal fluid (CSF) is described. Via Chem-Elut cartridges, free and total MLT (the latter obtained after a deproteinization step) were quantified in dichloromethane-extracted samples and analyzed in one chromatographic run by high-performance liquid chromatography (HPLC) with fluorimetric detection. The column used was an Extrasil ODS-2 (3 μm, 150 x 4.6 mm I.D.), while the mobile phase consisted of 75 mM sodium acetate-acetonitrile (72:28, v/v) (pH 5.0). Repeatability and reproducibility of the method were 3.24 and 9.4%, respectively. The recovery of melatonin from plasma and CSF was 99.9 ± 4.0% for non-deproteinized samples and 93.2 ± 4.8% for deproteinized samples. The detection limit of the assay was 0.5 pg/mL. In human plasma, the mean ± SD concentrations in the darkness period were 23.18 ± 7.44 pg/mL for free melatonin and 82.5 ± 36.48 pg/mL for total melatonin, while the lowest concentrations detected during daytime were 2.33 ± 2.22 and 7.40 ± 5.68 pg/mL, respectively. Detection of MLT in CSF was 5.01 ± 2.31 and 28.55 ± 6.95 pg/mL for the free and total fraction, respectively.
I.F. = 1,913
N. citazioni = 53

87. Ferrari S, Danova M, **Porta C**, Brugnatelli S, Pugliese P, Bertolini A, Riccardi A. Recombinant human interleukin-11 (Neumega, rhIL-11) reduces thrombocytopenia in breast cancer patients receiving tandem autologous circulating progenitor cell transplantation. *Ann Hematol* 2002;81:354-6 [Letter].

SUMMARY - Although thrombocytopenia associated with conventional doses of CT rarely requires treatment, it is still a major cause of morbidity and mortality in cancer patients undergoing high-dose (HD) CT. Interleukin-11 (IL-11) acts synergistically with IL-3, thrombopoietin, or stem cell factor to stimulate various stages of human megakaryocytopoiesis. Starting in October 2000, five patients with early breast cancer at high risk of relapse due to axillary node involvement, received a CPC mobilizing course of HD cyclophosphamide, followed by G-CSF. Patients then underwent a tandem CPC transplant, the former after mitoxantrone plus thiotepa, and the second, 1 month later, after mitoxantrone and etoposide. On day +1 after each CPC reinfusion, patients started G-CSF until bone marrow engraftment. Neumega (50 μg/Kg per day) was started when the PLT count dropped under 35 x 10^3/μL and was continued until PLT values ≥ 50 x 10^3/μL were reached. Each patient received a median of five daily administration of Neumega (range: 2-10). Platelet nadir (median value: 23.1 x 10^3/μL, range: 16-33) occured on day +6 (range: +4 - +8), while complete platelet recovery occurred on day +11 (range: +8 - +13). No significant differences between the first and the second autograft have been observed. Only one patient required a platelet transfusion after the second CPC transplant. Treatment with Neumega was generally well tolerated, leading to modest and reversible side-effects, i.e., erythematous skin flushing and edema of the extremities. In conclusion, IL-11 is well tolerated and shows the potential to significantly reduce treatment-related thrombocytopenia.
I.F. = 1,416
N. citazioni = 4

88. Zimatore M, Danova M, Vassallo E, **Porta C**, Macaluso MC, Schittone L, Riccardi A, Palmeri S. Weekly taxanes in metastatic breast cancer (Review). *Oncol Rep* 2002;9:1047-52.

ABSTRACT - Metastatic breast cancer is still considered an incurable and difficult to treat disease, even if several classes of antineoplastic agents have shown various levels of activity in these patients. Taxanes are the most effective drugs in breast cancer, together with the anthracyclines, but they have several important side-effects with standard administration schedules. The weekly administration of both paclitaxel and docetaxel, respectively at 80-100 mg/m^2/week and 35-40 mg/m^2/week, is feasible and it has an efficacy level at least comparable with the standard 21-day administration. These schedules can also be administered at an increased dose-intensity with a better toxicity profile. Even if most of the data available today come from small phase I and/or II trials, the weekly schedules of taxane administration are an attractive therapeutic chance, especially (but not only) in the elderly patients. Moreover, the minimal side-effects make this approach very interesting for combination therapy with other drugs as well as with new biological agents such as anti-HER-2 and anti-EGF molecules. Ongoing phase III trials will clarify the efficacy of the weekly administration schedules and will define their role in the treatment of metastatic breast cancer.
I.F. = 1,171
N. citazioni = 19

89. Ferrari S, Rovati B, Cucca L, Scarabelli C, Presti M, Beccaria C, Collovà E, **Porta C**, Danova M. Impact of Topotecan-based chemotherapy on the immune system of advanced ovarian cancer patients: an immunophenotypic

study. *Oncol Rep* 2002;9:1107-13.

ABSTRACT - The effects of topotecan-based chemotherapy (CT) on peripheral blood lymphocyte (PBL) subsets were evaluated in ovarian cancer patients. Fourteen patients with epithelial ovarian cancer, at the diagnosis or relapsed after platinum-based CT, were treated with: a) topotecan in association with carboplatin and and taxanes as first line CT; b) topotecan alone or c) topotecan in association with carboplatin, both as second line of treatment after platinum. The phenotype of PBL was determined before starting treatment and immediately before each CT course by flow cytometric analysis. Before starting CT, the absolute number of lymphocytes and the $CD2^+$, $CD3^+$, $CD4^+$ subsets were significantly lower in pre-treated patients and not significantly altered in CT-naive patients with respect to a cohort of 20 healthy donors utilized as control. Lymphocytes co-expressing $CD4^+/CD8^+$ were significantly higher in both subgroups of patients than in normal donors. $CD4^+/CD45RA^+$ and $CD4^+/CD45RO^+$ subsets were significantly decreased in pre-treated patients and normal in CT-naive patients. $CD3^+/HLA\text{-}DR^+$ T cell population significantly increased in CT-naive patients at baseline. During CT and after its discontinuation, no relevant changes were recorded for both subgroups of patients with respect to the baseline in lymphocyte absolute count, $CD2^+$, $CD3^+$, $CD4^+$, $CD4^+/CD45RO^+$ subsets, while $CD4^+/CD45RA^+$ subpopulation was significantly decreased in CT-naive patients. $CD8^+$, $CD19^+$, $CD20^+$, $CD16^+$, $CD56^+$, $CD2^+/CD25^+$ subsets did not differ statistically comparing to normal donors both at baseline and during CT. The treatment was well tolerated and no patient developed non-neutropenic infection. Topotecan-based therapy does not have a negative impact on PBL, in either CT-naive or in pretreated ovarian cancer patients. This information should be considered when utilizing topotecan with other anticancer drugs in the adjuvant setting as well as when dose-intensification of topotecan with stem cell support is planned.
I.F. = 1,171
N. citazioni = 7

90. **Porta C**, Rizzo V, Zimatore M, Sartore-Bianchi A, Danova M, Mutti L. Intrapleural interleukin-2 induces nitric oxide production in pleural effusions from malignant mesothelioma: a possible mechanism of interleukin-2-mediated cytotoxicity? *Lung Cancer* 2002;38:159-62.

ABSTRACT - Due to the frequent use of intrapleural interleukin-2 (IL-2) to treat pleural effusions from malignant mesothelioma (MMe), we measured nitric oxide (NO) end product nitrite (NO_2^-) in pleural effusions of 12 MMe patients with chronic or chronic-relapsing pleurisy. Through high performance liquid chromatography analysis, NO_2^- was found in the initial pleural fluid sample of all patients (156.25 pmol mL^{-1}), and increased significantly following IL-2 intrapleural instillation, both at 24 (589.91 pmol mL^{-1}, $p \leq 0.0005$) and 48 h (756 pmol mL^{-1}, $p \leq 0.0005$). Even though it is difficult to argue if the large amounts of NO end product NO_2^- we observed is produced by IL-2 stimulated and recruited immune cells, by MMe cells themselves, or by both, it is possible that NO could contribute to the complex antitumor activity of IL-2..
I.F. = 2,451
N. citazioni = 7

91. Riccardi A, Mora O, Tinelli C, **Porta C**, Danova M, Brugnatelli S, Grasso D, Tolcà B, Spanedda R, De Paoli A, Barbarano L, Cavanna L, Giordano M, Delfini C, Nicoletti G, Bergonzi C, Rinaldi E, Piccinini L, Ascari E for the Cooperative Group of study and treatment of Multiple Myeloma. Response to first-line chemotherapy and long-term survival in patients with multiple myeloma: results of the MM87 prospective randomised protocol. *Eur J Cancer* 2003;39:31-7.

ABSTRACT - In this study we evaluated whether a good response to conventional chemotherapy, i.e., a significant tumor reduction, is a prerequisite for improved survival in multiple myeloma (MM). Between January 1987 to March 1990, 341 consecutive previously untreated patients with MM received chemotherapy within the prospective, multicentre, randomised protocol MM87. Of these, 258 patients were evaluable for both response and long-term survival and 244 (94.6%) have died. The median survival of all patients was 40 months (6-162 months). The median survival did not differ between patients who had complete response (CR) (50 months, 9-162 months), partial response (PR) (46 months, 8-147 months) or stable disease (SD) (41 months, 7-135 months). The median survival was shorter (13.6 months, 6-135 months) ($p < 0.0001$) in patients whose disease progressed while they were receiving first induction chemotherapy. causes of death were more frequently ($p = 0.04$) related to MM in patients who had progressive disease (PD) than in patients who had a CR or a PR or SD. The main clinical and laboratory characteristics were similar in the four groups. These data indicate that patients who maintain SD during first-line chemotherapy have a prognosis similar to that of patients who attain a response. Only patients whose disease progresses have a distinctly worse outcome.
I.F. = 3,694
N. citazioni = 15

92. Valle MT, **Porta C**, Megiovanni AM, Libener R, Mele L, Gaudino G, Strizzi L, Guida R, Toma S, Mutti L. Transforming growth factor-β released by PPD-presenting malignant mesothelioma cells inhibits interferon-γ synthesis by an anti-PPD $CD4^+$ T-cell clone. *Int J Mol Med* 2003;11:161-7.

ABSTRACT - Besides acting complexely on both normal and tumor cells, transforming growth factor-b (TGF-β) can determine the nature of the response to the antigen, strongly inhibiting the differentiation of naive $CD4^+$ T-cells toward a T helper-1 (Th-1) phenotype; in a number of experimental models, TGF-β also appeared to be a potent immunosuppressant factor. TGF-β was shown to be released by some human malignant mesothelioma (MMe) cells, which affects the immune response to this tumor. Thus, for a better understanding of the role of TGF-β in the immune response to MMe cells, we evaluated the production of a Th-1 cytokine (IFN-γ) and of a Th-2 cytokine (IL-4), following purified protein derivative (PPD) recall antigen presentation by human MMe cells to a class-II major histocompatibility complex (MHC-II)-matched PPD clone (PPD clone). Our data confirm that human MMe cells possess the unusual capability of presenting a common recall antigen to $CD4^+$ lymphocytes but also show that these tumor cells can abrogate Th-1 immune response, as evidenced by a shift in favor of the production of IL-4 over that of IFN-γ, through a TGF-β-mediated pathway; only the simultaneous block of TGF-β1 and β2 effects can significantly restore a typical Th-1 pattern of cytokine production by PPD clone in response to PPD presentation by MMe. Even though the role of TFG-β in the promotion of MMe growth should be further and better defined, this effect should be considered when designing new therapeutical approaches aimed at improving the immune response to MMe.
I.F. = 1,94
N. citazioni = 4

93. Ferrari S, Rovati B, **Porta C**, Alessandrino PE, Bertolini A, Collovà E, Riccardi A, Danova M. Lack of dendritic cell mobilization into the peripheral blood of cancer patients following standard- or high-dose chemotherapy plus granulocyte-colony stimulating factor. *Cancer Immunol Immunother* 2003;52:359-66.

ABSTRACT - Background: Dendritic cells (DC), the most specialized antigen-presenting cells, can be detected in the peripheral blood (PB) and divided into two subsets of populations, DC1 and DC2, endowed with different functions. The aim of this study was to evaluate the effect on DC release and

on their subsets of three regimens utilized to mobilize CD34+ cells into the PB in cancer patients and in normal CD34+ cell donors. Patients and methods: The mobilizing sequences were: standard-dose epirubicin + taxol + granulocyte-colony-stimulating factor (G-CSF; 15 patients with advanced breast cancer), high-dose cyclophosphamide (CTX) + G-CSF (10 patients with breast cancer patients and 7 with non-Hodgkin's lymphoma, NHL), and G-CSF alone (5 normal donors of CD34+ cells for allogeneic transplantation). Comparative data were obtained from the steady-state PB of 20 healthy volunteers. For flow cytometric analysis, DC were gated as negative for specific lineage markers (CD3, CD11b, CD14, CD16, CD56, CD19, CD20, CD34) and positive for HLA-DR. The DC1 and DC2 subsets were defined as CD11c and CDw123 positive, respectively. Results: The percentages of DC at baseline and the time of CD34+ cell peak were: 0.48 and 0.51 for standard-dose chemotherapy (CT); 0.55 and 0.63 for breast cancer after high-dose CTX+G-CSF; 0.53 and 0.71 for NHL after high-dose CTX + G-CSF; and 0.51 and 0.54 for normal donors of CD34+ cells after G-CSF alone (all p=n.s.). Mean DC1/DC2 ratios in each study group at the time of CD34+ cell peak were 0.10, 0.12, and 0.18, respectively. Finally, in the group of healthy volunteers, the percentage of circulating DC was 0.95 and the mean DC1/DC2 ratio was 1.28. Conclusion: To our knowledge, this is the first report that demonstrates that both standard-dose or high-dose CT, when utilized together with G-CSF, do not induce DC mobilization into the PB, whereas a reversed DC1/DC2 ratio is observed. Furthermore, a lack of significant DC mobilization after G-CSF alone was also seen, in contrast to what was previously observed by others. These data should be taken in account when evaluating clinical correlations between DC number and CPC engraftment in both the transplantation setting, when monitoring the effects on the immune system of combinations of new drugs and/or cytokines, and when high numbers of DC are required for both experimental and clinical applications.
I.F. = 3,13
N. citazioni = 29

94. **Porta C**, Caporali R, Epis O, Ramaioli I, Invernizzi R, Rovati B, Comolli G, Danova M, Montecucco C. Impaired bone marrow hematopoietic progenitor cell function in rheumatoid arthritis patients candidated to autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2004;33:721-8.

SUMMARY - We have evaluated bone marrow morphology, percentage of bone marrow CD34+ cells, proliferative activity of bone marrow precursors, clonogenic assay (BFU-E and CFU-GM) in short-term bone marrow cultures, and bone marrow cell apoptosis, together with serum TNF-α and IL-6, in 16 chronic, refractory RA patients, as well as in five healthy controls. Of 16 RA patients (68.7%), 11 showed a reduced bone marrow cellularity, while it was normal in all the controls. In RA patients, the median percentage of CD34+ bone marrow cells, the median percentage of proliferating bone marrow myeloid precursors, and the median number of both BFU-E and CFU-GM colonies were significantly lower than observed in the controls. As far as TNF-α and IL-6 titers is concerned, the latter did not significantly differ fron controls' values, while TNF-α titers were significantly lower in healthy controls. Finally, the median apoptotic index of early bone marrow myeloid cells of RA patients was significanetly higher compared with controls. These observations may identify biological risk factors for impaired mobilization and/or engraftment when RA patients are candidates for autologous hematopoietic stem cell grafting.
I.F. = 2,101
N. citazioni = 23

95. Airoldi M, Cattel L, Cortesina G, Giordano C, Pedani F, Recalenda V, Danova M, Gabriele AM, Tagini V, **Porta C**, Bumma C. Docetaxel, Carboplatin and concomitant radiotherapy for unresectable squamous cell carcinoma of the head and neck. Pharmacokinetic and clinical data of a phase I-II study. *Am J Clin Oncol (CCT)* 2004;27:155-63.

ABSTRACT - Concomitant chemoradiotherapy is the most effective treatment of unresectable head and neck cancer. Docetaxel and carboplatin are two active drugs that potentiate radiotherapy. Thirty patients (median age = 56 years; median Eastern Cooperative Oncology Group performance status = 1) received radiotherapy (70 Gy, 2 Gy/d, 5 d/wk) concurrent with carboplatin AUC 0.3 to 0.5 on day 1-5, weeks 1,3,5,7, and docetaxel 15 to 25 mg/m^2 on day 4 of weeks 2,4, and 6. Site of unresectable squamous cell carcinoma was as follows: oropharynx, 41%; hypopharynx, 27%; oral cavity, 16%; and larynx, 16%. Stage was III in 13% and IV in 87%. In 11 patients, pharmacokinetic parameters were evaluated. Acute G4 toxicity was as follows: neutropenia, 20%; mucositis, 33%. We had the following acute G3 toxicities: mucositis, 40%, neutropenia, 37%; dermatitis, 23%; and anemia, 13%. The maximum tolerated dosage was area under the curve 0.5 for carboplatin and 20 mg/m^2 for docetaxel. Median radiotherapy dose was 69 Gy, and 175 out of 210 courses (83%) were administered. At the end of the treatment, we had 20 complete responses (CR) (67%), 9 partial responses (30%), and 1 no change (3%). After radical neck dissection, 2 patients achieved a CR (overall CR = 73%). After a median follow-up of 2.5 years, we had a 3-year local progression-free survival of 85%, failure-free survival of 69%, and overall survival of 60%. A significant increase of C_{max} of carboplatin concentration was noted at the beginning of weeks 3,5, and 7. Total plasma platinum raises during each course of 5 days of carboplatin without reaching a steady state. Carboplatin, docetaxel, and concomitant conventional radiotherapy is a feasible and effective treatment of unresectable head and neck cancer. The concurrent administration of two drugs does not alter pharmacokinetic drug behavior compared with single-agent data.
I.F. = 1,703
N. citazioni = 17

96. **Porta C**, Zimatore M, Imarisio I, Natalizi A, Sartore-Bianchi A, Danova M, Riccardi A. Gemcitabine and Oxaliplatin in the treatment of patients with immunotherapy-resistant advanced renal cell carcinoma: final results of a single-institution phase II study. *Cancer* 2004;100:2132-8.

ABSTRACT - Background: At present there is no standard treatment for advanced renal cell carcinoma (RCC) who do not respond to first-line immunotherapy regimens. Within this phase II study we explored the antitumor activity of a combination of Gemcitabine and Oxaliplatin (L-OHP) in this setting of patients. Methods: Forty-two RCC patients who progressed under immunotherapy received Gemcitabine (1,000 mg/m^2, i.v., days 1 and 8, q21) and L-OHP (90 mg/m^2, i.v., day 1, every 21) for a minimum of 2 cycles before response evaluation. Response to treatment and toxicity were recorded according to RECIST and NCI-CTC version 3.0 criteria, respectively. Results: No complete responses were recorded, but 6 patients obtained a partial reponse (14.28%, 95% confidence interval: 5.43 to 28.5%); 11 patients (26.19%) had, as their best response, only a temporary SD, while the remaining 25 patients (59.52%) progressed despite treatment. Median time to progression (TTP) was 2.5 months (average: 3.86, range: 1.5-11), while median overall survival was 9.5 months (average: 10.46, range: 4-22.5). As far as toxicity, treatment was generally well tolerated with only a case of grade IV toxicity, and predictable grade III toxicity that included myelosuppression and neuropathy. Conclusions: Our results suggest a certain activity, with an acceptable toxicity profile, of the combination of Gemcitabine and L-OHP in immunotherapy-unresponsive advanced RCC patients.
I.F. = 4,434
N. citazioni = 23

97. Sartore-Bianchi A, Soriani A, Mattioni R, Vaglio A, Buzio C, **Porta C**. Low doses of subcutaneous interleukin-2 plus interferon-α do not induce thyroid function alterations in advanced renal cell carcinoma patients. *Oncol Rep* 2004;12:855-9.

SUMMARY - The incidence of thyroid function changes among renal cell carcinoma (RCC) patients treated with high-dose IL-2 plus IFN-alpha ranges from 9 to 59%, independently of the administration route (i.v. or s.c.) of IL-2. Although several studies demonstrated a correlation between high-dose IL-2/IFN-alpha regimens and autoimmune thyroid disease, only very limited data are available when low doses of IL-2 plus IFN-alpha are used. We prospectively studied thyroid function in 52 patients with metastatic RCC undergoing immunotherapy with low-dose IL-2 + IFN-alpha. All patients received treatment cycles consisting of both s.c. IL-2 and i.m. IFN-alpha for 4 consecutive weeks; cycles were repeated at 4-month intervals in all patients, irrespectively of their response. Thyroid stimulating hormone (TSH), 3,3',5-triiodo-L-thyronine (T3), thyroxine (T4), human anti-thyroglobulin antibodies (hTg-Ab) and human anti-thyroid peroxidase antibodies (hTPO-Ab) were assayed in all patients before and after each of the first 3 cycles. None of the patients showed clinical signs of dysthyroidism, nor required replacement or suppressive treatment on thyroid function; specifically, no statistically significant differences were found when the median pre- and post-treatment TSH, T3, T4, hTg-Ab and hTPO-Ab levels of each cycle were compared. The median TSH values after the 3 cycles were, respectively, 1.06 [Inter Quartile Range (IQR) 0.58-1.51], 1.21 (IQR 0.58-1.51) and 1.05 μU/ml (IQR 0.67-1.73). As for thyroid hormones, median values after each of the 3 cycles were: 1.38 (IQR 1.19-1.50), 1.46 (IQR 1.17-1.66) and 1.36 (IQR 1.16-1.46) ng/ml for T3, and 8.74 (IQR 7.26-9.45), 8.67 (IQR 7.12-9.18) and 8.40 (IQR 7.12-9.33) μg/dl for T4. These data show that a regimen of low-dose IL-2 plus IFN-alpha does not seem to affect thyroid function, neither inducing signs or symptoms of dysthyroidism, nor by causing major biochemical changes in TSH and thyroid hormone levels, or an increase in thyroid-specific auto-antibodies.
I.F. = 1,356
N. citazioni = 2

98. Siragusa S, Anastasio R, **Porta C**, Falaschi F, Pirrelli S, Palmieri P, Gamba G, Granzow K, Malato A, Minardi V, Tatoni P, Bressan MA, Mariani G. Deferment of objective assessment of deep vein thrombosis and pulmonary embolism without increased risk of thrombosis: a practical approach based on the pretest clinical model, D-dimer testing, and the use of low-molecular-weight heparins. *Arch Intern Med* 2004;164:2477-82.

ABSTRACT - Background: Treatment of patients with suspected deep vein thrombosis (DVT) or pulmonary embolism (PE) is problematic if diagnostic imaging is not immediately available. Pretest clinical probability (PCP) and D-dimer assessment can be used to identify patients for whom empirical protective anticoagulation is indicated. To evaluate whether PCP and D-dimer assessment, together with the use of low-molecular-weight heparins (LMWHs), allow objective appraisal of DVT and PE to be deferred for up to 72 hours, patients with suspected DVT and PE were prospectively examined. Methods: Patients identified with a high PCP or a moderate PCP with positive D-dimer test results received a protective full-dose treatment of LMWH; the remaining patients were discharged without anticoagulant administration. However, all patients were scheduled to undergo objective tests for DVT or PE within 72 hours. Standard antithrombotic therapy was administered when deferred diagnostic tests confirmed venous thromboembolism. Results: In total, 409 consecutive patients with suspected DVT and 124 with suspected PE were included in this study. A total of 23.8% (95% confidence interval [CI], 20.3%-27.3%) of patients had confirmed venous thromboembolism. At the short-term follow-up (72 hours), only a single thromboembolic event (0.2%; upper 95% CI, 0.6%) had occurred, whereas at the 3-month follow-up, 5 events (1.2%; 95% CI, 0.2%-2.1%) had occurred in patients in whom diagnosis of DVT or PE had previously been ruled out. None of the patients had major bleeding events. Ninety percent of patients were treated as outpatients. Conclusion: Our study demonstrates that this approach allows the safe deferral of diagnostic procedures for DVT and PE for up to 72 hours.
I.F. = 7,508
N. citazioni = 22

99. **Porta C**, Imarisio I, De Amici M, Bonomi L, Paglino C, Biscaldi E, Zimatore M, Sartore-Bianchi A, Danova M, Riccardi A. Pro-neoangiogenic cytokines (VEGF and bFGF) and anemia in solid tumor patients. *Oncol Rep* 2005;13:689-95.

ABSTRACT - Using a commercial ELISA assay, we evaluated circulating VEGF and bFGF levels in 203 consecutive patients with solid tumors, and sought a correlation between them and with the grade of anemia. Serum VEGF values were within the normal range in 128 patients (63.05%), with a mean value of 675.04 pg/ml (median, 571.00; range, 0-2796.54). The analysis of VEGF values per tumor group did not provide any statistically significant difference. Regarding bFGF, 143 patients (70.44%) had measurable, and thus abnormal, bFGF values. Overall, mean bFGF serum value was 57.14 pg/ml (median, 8.30; range, 0-4334.71), with the highest bFGF levels found in breast carcinoma patients. As expected, a large number of our patients was fairly anemic, mean hemoglobin level being 11.47 g/dl (median, 11.30; range, 7.1-19.20), the lowest titers being observed in prostate carcinoma patients. No statistically significant correlation was found between serum VEGF and hemoglobin values ($r=0.004$) but a significant negative correlation was seen between serum bFGF and hemoglobin ($r=-0.22$, $p<0.05$). Considering the different tumor groups, a statistically significant negative correlation between bFGF and hemoglobin becomes even more apparent in the subgroup of renal carcinoma patients ($r=-0.55$, $p<0.05$). In conclusion, our results demonstrate that there is a statistically significant correlation between systemic hypoxia (evaluated in terms of hemoglobin levels) and circulating bFGF values, but not VEGF; this correlation may lead to therapeutic interventions.
I.F. = 1,572
N. citazioni = 7

100. **Porta C**, Zimatore M, Bonomi L, Imarisio I, Paglino C, Sartore-Bianchi A, Mutti L. Raltitrexed-Oxaliplatin combination chemotherapy is inactive as second-line treatment for malignant pleural mesothelioma patients. *Lung Cancer* 2005;48:429-34.

ABSTRACT - Within a single-institution phase II trial, we investigated the antitumor activity of the Raltitrexed-Oxaliplatin combination as second-line therapy for malignant pleural mesothelioma (MPM). Fourteen patients were enrolled and all were assessable for response. The trial was then closed because chemotherapy, though well tolerated, yielded no objective responses. The best response observed was disease stabilization in 4 patients only (28.57%), while the other 10 patients (71.42%) progressed despite treatment. Median time to progression (TTP) was 8 weeks (average: 9.85, range: 7-20), while median overall survival was just 14 weeks (average: 21.69, range: 9-66+).
I.F. = 3,172
N. citazioni = 50

101. Ramos-Nino ME, Vianale G, Sabo-Atwood T, Mutti L, **Porta C**, Heintz N, Mossman BT. Human mesothelioma cells exhibit tumor cell-specific differences in posphatidylinositol 3-kinase/AKT activity that predict the efficacy of Onconase. *Mol Cancer Ther* 2005;4:835-42.

ABSTRACT - Malignant mesothelioma is an aggressive cancer with no

known cure, which has become a therapeutic challenge. Onconase is one of few chemotherapeutic agents that have been studied in patients with malignant mesothelioma that has the advantage of low toxicity and limited side effects. Here, we evaluate the effect of Onconase on killing of malignant mesothelioma cells and how the phosphatidylinositol 3-kinase/AKT (PI3-K/AKT) survival pathway influences this effect. Our results show that Onconase induces apoptosis in malignant mesothelioma cell lines and that this effect is tumor cell specific. Malignant mesothelioma cell lines with the highest AKT activation, which correlated with the presence of the SV40 large and small T antigen (SV40+), were the most resistant to the drug. Finally, a cooperative effect was observed between small molecule inhibitors of PI3-K and Onconase in the killing of malignant mesothelioma cells. Our results suggest that kinase screening of individual malignant mesotheliomas for endogenous levels of activated PI3-K/AKT may be predictive of the efficacy of Onconase and possibly other chemotherapeutic agents.
I.F. = 5,171
N. citazioni = 46

102. Ferrari S, Malugani F, Rovati B, **Porta C**, Riccardi A, Danova M. Flow cytometric analysis of circulating dendritic cell subsets and intracellular cytokine production in advanced breast cancer patients. *Oncol Rep* 2005;14:113-20.

ABSTRACT - Patients with advanced cancer are known to have dysfunctions of the immune system. Dendritic cells (DCs) are potent antigen-presenting cells that play a crucial role in antitumor immune response. At least two peripheral blood DC subsets have been described: myeloid-derived $CD11c^+CD123^-$. DCs (DC1) and lymphoid-derived $CD11c^-CD123^+$. DCs (DC2). Upon interaction with T cells, DC2 seemed to support the generation of a Th2 response, while DC1 predominantly prime a Th1 response. Our study was aimed at investigating the number of circulating DCs, and their subsets and functions in 32 patients with advanced breast cancer that achieved an objective response after a standard-dose sequential chemotherapy (CT), compared to 40 healthy controls. Circulating DC subsets and intracellular cytokine production in $CD4^+$ and $CD8^+$ subsets were analyzed using a tri-color flow cytometry assay. DC subsets were identified in peripheral blood, calculating their percentage gated as lin^- $HLA\text{-}DR^+$ and using BDCA-1, BDCA-2 and BDCA-3 specific markers, as DC1 and DC2 according to expression of CD11c and CD123, respectively. Intracellular cytokines were evaluated in CD4+ (Th1 and Th2) and $CD8^+$ (Tc1 and Tc2) T lymphocytes. The mean percentage of BDCA-1 + BDCA-2 + BDCA-3 was similar to that of DC1 + DC2 (p=ns). The mean percentage of DCs and DC1/DC2 ratio were slightly decreased before CT in cancer patients compared with healthy controls (p=ns). After CT, the percent-age of DC1 further decreased (p=0.02). The production of IFN-γ (Th1 and Tc1) significantly decreased ($p<0.03$) while that of IL-4 (Th2 and Tc2) increased (p=0.04), thus confirming a shift toward a Th2 CD4 and Tc2 CD8 phenotype and the predominance of type 2 DCs. Our results could help clarify the mechanisms of the immune response or immune status of patients with advanced breast cancer that undergo cytotoxic CT and contribute to improve the selection of potential candidates for active immunotherapy trials.
I.F. = 1,572
N. citazioni = 21

103. Cacciotti P, Barbone D, **Porta C**, Altomare DA, Testa JR, Mutti L, Gaudino G. SV40-dependent AKT activity drives mesothelial cell transformation after asbestos exposure. *Cancer Res* 2005;65:5256-62.

ABSTRACT - Human malignant mesothelioma is an aggressive cancer generally associated with exposure to asbestos, although SV40 virus has been involved as a possible cofactor by a number of studies. Asbestos fibers induce cytotoxicity in human mesothelial cells (HMC), although cell survival activated by key signaling pathways may promote transformation. We and others previously reported that SV40 large T antigen induces autocrine loops in HMC and malignant mesothelioma cells, leading to activation of growth factor receptors. Now we show that SV40 induces cell survival via Akt activation in malignant mesothelioma and HMC cells exposed to asbestos. Consequently, prolonged exposure to asbestos fibers progressively induces transformation of SV40-positive HMC. As a model of SV40/asbestos cocarcinogenesis, we propose that malignant mesothelioma originates from a subpopulation of transformed stem cells and that Akt signaling is a novel therapeutic target to overcome malignant mesothelioma resistance to conventional therapies.
I.F. = 7,616
N. citazioni = 72

104. Vogelzang NJ, **Porta C**, Mutti L. New agents in the management of advanced mesothelioma. *Semin Oncol* 2005;32:336-50.

ABSTRACT - Malignant pleural mesothelioma (MPM) is a seemingly uncommon tumor whose incidence has in fact increased steadily and progressively over the last 30 years. Indeed, an actual "epidemic" is expected in Europe over the next 20 years. Despite unquestionable improvement in the diagnostic methods at our disposal and the availability of new treatment strategies, the prognosis of MPM patients remains dramatically poor (12 to 18 months' median survival from diagnosis), although exceptional cases of long-survivors are reported in all literature series. The current review will cover the dramatic improvements in the treatment of this rare disease that have been recently achieved, as well as the promise that new, molecular-targeted therapies, such as bortezomib, mTOR (mammalian target of rapamycin) inhibitors, and Met inhibitors, seem to offer for the next few years. With pemetrexed we now have a drug that is able to impact patient survival. Together with the newer drugs, rapidly emerging from the laboratory to be applied in the clinic, we have the hope of making further advances in the struggle against this disease.
I.F. = 3,634
N. citazioni = 39

105. Hofheinz RD, **Porta C**, Hartung G, Santoro A, Hanauske A, Kutz K, Stern A, Barbieri P, Verdi E, Hehlmann R, Hochaus A. BBR 3438, a novel 9-aza-anthrapyrazole, in patients with advanced gastric cancer: a phase II study group trial of the Central European Society of Anticancer-Drug Research (CESAR). *Invest New Drug* 2005;23:363-8.

ABSTRACT - BR 3438, a member of the 9-aza-anthrapyrazole family designed to decrease anthracycline dependent cardiotoxicity and to improve efficacy provided high in vivo activity in gastric carcinoma xenograft models. The present study was carried out to assess the efficacy and safety of BBR 3438 applied at a dose of 50 mg/m^2 four-weekly as an 1-hour infusion to pretreated patients with gastric cancer. Twenty-seven patients received at least one administration of BBR 3438. Lymph nodes and liver were the most common sites of metastases. A total of 94 cycles were administered (median 2, range 1-6). The main toxicity consisted of (worst per patient [%]; NCIC CTC grades 1/2/3/4) neutropenia 7/7/19/52 (one case of febrile neutropenia), stomatitis 15/19/4/-, nausea 22/26/7/-, vomiting 19/7/7/-, alopecia 15/33/-/-. Neutrophil nadir (520/mul) was reached after a median 15 days. The median time to recovery to </=grade 1 neutropenia was 13.5 days. The median average cumulative dose of BBR 3438 was 166.8 mg, and the median dose intensity was 48.8 mg/m^2. Left ventricular ejection function (LVEF) was monitored with multiple-gated angiography (MUGA). Median LVEF values at baseline and at the end of cycle 2 were 67.5% and 65%, respectively, and no patient showed a relevant decrease of LVEF. In 25 patients evaluable for response no remission was observed. Four patients (16%) had stable disease. Median time to progression was 51 days, median overall survival was 64 days. In all, the feasibility and tolerability of BBR 3438 applied 4-weekly at a dose of 50 mg/m^2 was confirmed and neither relevant LVEF decreases nor hints of cardiac toxicity were observed. In terms of antitumor activity, BBR 3438 was found to be

ineffective in the treatment of gastric cancer.
I.F. = 2,417
N. citazioni = 9

106. **Porta C**, Caporali R, Montecucco C. Autoimmunity in thrombotic thrombocytopenic purpura. *Semin Thromb Haemost* 2005;31:633-40.

ABSTRACT - In the last few years, an autoimmune hypothesis for the pathogenesis of thrombotic thrombocytopenic purpura (TTP) has been proposed often, with variable success because of inconsistent supporting data. We are now aware that at least one subgroup of TTP patients does present with pathogenic autoantibodies (i.e., anti-ADAMTS13); this group consequently is a putative candidate for a curative treatment including plasma exchange (still the cornerstone of TTP treatment), together with corticosteroids or other immunosuppressants. Furthermore, for patients not responding to or relapsing following plasma exchange, the use of stronger immunosuppression (e.g., with the use of the anti-CD20 monoclonal antibody Rituximab) should be considered as appropriate. Conversely, few data are actually available regarding the complex relationship between TTP and the antiphospholipid (aPL) syndrome, as well as other autoimmune diseases. Indeed, a correct differential diagnosis should be done on the basis of both different clinical presentations and autoantibody profile. At present, the presence of aPL antibodies should give evidence against a diagnosis of TTP, even though we cannot exclude that aPL antibodies may, in a minority of patients, be associated with a primary endothelial damage ultimately resulting in overt TTP.
I.F. = 2.077
N. citazioni = 8

107. **Porta C**, Ardizzoni A, Gaudino G, Maio M, Mutti L, Pinto C, Porru S, Puntoni R, Tassi GF, Tognon M. Malignant mesothelioma in 2004: how advanced technology and new drugs are changing the perspectives of mesothelioma patients. Highlights from the VIIth Meeting of the International Mesothelioma Interest Group. *Med Lav* 2005;96:360-9.

ABSTRACT - Malignant mesothelioma (MMe) is a seemingly uncommon tumor whose incidence has in fact increased steadily and progressively over the last 30 years. Indeed, an actual "epidemic" is expected in the next 20 years, with over 1300 new cases a year till 2020 at least. Despite unquestionable improvement in the diagnostic methods at our disposal and the availability of new treatment strategies, the prognosis of MMe patients remains dramatically poor. For all the above reasons, translational research is key for success; indeed, an increasing knowledge of the molecular mechanisms underlying MMe pathogenesis could lead (and is actually leading) to new, hopefully more active, treatment options. To foster discussion among investigators working in this field, and to exchange different viewpoints concerning the newest advances in MMe pathogenesis and treatment, the VII International Mesothelioma Interest Group (IMIG) meeting has been held in Brescia (Italy) between the 24th and 26th of June 2004 in cooperation with the Italian Group for the Study and Therapy of MMe (GIMe). The aim of this report is to summarize the most significant advances in the different disciplines applied to MMe presented and discussed during the IMIG meeting and how these advances will be changing the perspective of the patients with MMe.
I.F. = n.r.
N. citazioni = 5

108. **Porta C**. Adding raltitrexed to cisplatin improves overall survival in people with malignant pleural mesothelioma. *Cancer Treat Rev* 2006;32:229-33 [Commentary].

ABSTRACT - Rarely suitable for radical surgical resection, usually resistant to irradiation and to most chemotherapeutic agents, malignant mesothelioma (MMe) carries a very poor prognosis. Until recently, no regimen has emerged as the standard of care for non surgical patients. Only in 2003, following the publication of a large, randomised, phase III study of the multi-target antifolate Pemetrexed in combination with Cisplatin versus Cisplatin alone, was the combination approved by the FDA. Recently, an EORTC-NCI Canada randomised phase III study of Cisplatin with or without Raltitrexed was published (Van Meerbeeck JP et al. Randomized phase III study of Cisplatin with or without Raltitrexed in patients with malignant pleural mesothelioma: an Intergroup of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005;23:6881-9) demonstrating the superiority of the combination, with results very similar to those reported for the Pemetrexed/Cisplatin combination. The trial could have yielded even more striking results if accrual had been extended, as recommended by an Independent Data Monitoring Committee after two interim analyses, but lack of funding precented it. This study provides an important confirmation of the role of antifolates in MMe but, on other hand, opens new key questions: are these two schedules (i.e., Pemetrexed/Cisplatin and Raltitrexed/Cisplatin) mutually exclusive or could they be used sequentially? Does Raltitrexed really have a future in this tumor, i.e., is Astra Zeneca really willing to further develop Raltitrexed is such a relatively rare tumor as MMe? Are there any new antifolates that could advance the struggle against this cancer, at least theoretically?
In conclusion, we now know that there are at least two combinations of an antifolate with Cisplatin (or a platinum derivative) that could impact on MMe patients' survival and should thus be added to our limited armamentarium of chemotherapy agents active against this disease. But can this good news actually make a difference in clinical practice? Probably not so much. Thus, we can only wait for the results of ongoing trials of new agents under development and transfer molecular research findings into new drugs to test in this still lethal cancer.
I.F. = 4,549
N. citazioni = 5

109. **Porta C**. Maintenance biotherapy with Interleukin-2 and Interferon for metastatic renal cell cancer. *Expert Rev Anticancer Ther* 2006;6:141-52.

ABSTRACT - The term maintenance immunotherapy comprises at least two different therapeutic approaches: the continuation of immunotherapy beyond disease progression and the use of chronic immunotherapy after the achievement of an initial response (or disease stabilization) with more intensive treatment modalities, such as chemotherapy. The former therapeutic approach was proposed in renal cell carcinoma patients some years ago relying on several immunological considerations. Some years later, we have learned that it is feasible and endowed with a favorable therapeutic index; furthermore, its immunologic effects are well described and reproducible, and it has antitumor activity. However, due to the lack of adequate randomized phase III studies, the actual impact of this treatment strategy on patient survival has not yet been proved. The rationale of this treatment, its immunological and clinical results, as well as its pitfalls and perspectives, will be presented and discussed in this review.
I.F. = 1,988
N. citazioni = 3

110. Invernizzi R, Bencardino K, **Porta C**, Vercelli A, Viglio A, Manzoni M, Sagrada P, Danova M. Sigmoid colon metastasis from sarcomatoid renal cell carcinoma. *Tumori* 2006;92:246-8.

ABSTRACT - The sarcomatoid histological type of renal cell carcinoma is a clinically aggressive variant of parenchymal tumor, typically resistant to systemic treatment. We report the case of a 65-year-old female patient who had undergone a left radical nephrectomy for a sarcomatoid renal cell carcinoma together with enucleation of a mass of the right kidney and a contrala-

teral nodule diagnosed as clear cell carcinoma. One year later lung, adrenal and sigmoid colon metastases from sarcomatoid renal cell carcinoma were detected and the patients was started on systemic immunotherapy with Interleukin-2 and Interferon-α. Computed tomography showed marked disease progression and the patient died 3 weeks later. Sigmoid colon metastases from a primary sarcomatoid renal cell carcinoma has never been described in the literature.

I.F. = 0,739

N. citazioni = 9

111. Palmeri S, Lorusso V, Palmeri L, Vaglica M, **Porta C**, Nortilli R, Ferraù F, Comella G, Massidda B, Danova M for the Carcinomas of Unknown Primary Italian Study Group. Cisplatin and Gemcitabine with either Vinorelbine or Paclitaxel in the treatment of carcinomas of unknown primary site. Results of an italian multicenter, randomized, phase II study. *Cancer* 2006;107:2898-905.

ABSTRACT - Background: To date, the standard treatment for patients who have carcinoma of unknown primary site has not been established. Methods: In this randomized phase II study, 66 previously untreated patients (33 patients per arm) with carcinomas of unknown primary site received Cisplatin (35 mg/m^2) and Gemcitabine (1000 mg/m^2) with either Paclitaxel (70 mg/m^2) or Vinorelbine (25 mg/m^2), and all drugs were administered intravenously on days 1 and 8 of a 21-day cycle. Twenty-nine patients (44%) presented with ≥ 2 involved sites. The pathologic diagnosis was mainly adenocarcinoma (48 patients; 72.7%) and squamous carcinoma (7 patients; 10.6%). Results: In the first arm, 16 patients (48.5%) experienced an objective response, and 9 patients (27.2%) had disease stabilization. In the Vinorelbine-containing arm, 14 patients (42.3%) experienced an objective response, and 8 patients (24.2%) had disease stabilization. The median response duration and the median time to progression were similar in both treatment arms; the median overall survival was 9.6 months (95% confidence interval, 7.11 - 12.09 months) for patients who received the Cisplatin/Gemcitabine/Paclitaxel regimen and 13.6 months (95% confidence interval, 6.61 - 20.59 months) for patients who received the Vinorelbine combination. Grade 3 and 4 toxicities were more frequent in the Paclitaxel-containing arm. Conclusions: Both combinations satisfied the 2-step design, demonstrating antitumor activity without relevant differences in response rates or response duration; however, the Vinorelbine-containing regimen yielded superior results both in terms of overall survival (13.6 months vs. 9.6 months) and in terms of treatment tolerability. Therefore, according to a pick the winner attitude, the combination of Cisplatin/Gemcitabine/Vinorelbine may be considered in the designof future randomized, phase III trials for patients with carcinomas of unknown primary site.

I.F. = 4,800

N. citazioni = 33

112. **Porta C**, Mutti L, Tassi GF. Negative results of an Italian Group for Mesothelioma (G.I.Me.) pilot study of single-agent Imatinib mesylate in malignant pleural mesothelioma. *Cancer Chemother Pharmacol* 2007;59:149-50.

ABSTRACT - Platelet-derived growth factor receptor (PDGFR) and C-kit are two tyrosine kinase receptors that have been implicated in several malignancies, including malignant mesothelioma (MME). We performed a pilot study of single-agent Imatinib mesylate, a tyrosine kinase inhibitor that targets both PDGFR and C-kit in naive as well as pre-treated MMe patients. Among the 11 patients enrolled, no objective responses were observed, the best result being disease stabilization in 4 patients only (36.6%); the remaining 7 patients (63.6%) progressed, despite treatment. Median time to progression was 8 weeks (average: 10.9 ± 4.39, range: 7-19), while median overall survival was 20 weeks (average: 22.09 ± 11.16, range: 9-42), fairly better for those who obtained a disease stabilization (average: 29.5 vs. 14 weeks). Treatment was well tolerated, with few cases of grade 3/4 toxicities (nausea 2/11, i.e., 18.1%; neutropenia, fatigue, edema and rash 1/11, i.e., 9% each). In accordance with two previous experiences, we demosntrated no acticity of single-agent Imatinib in MMe patients. However, recent data from our laboratory suggest that Imatinib could synergize with some chemotherapeutic agents, at least in vitro. Thus, despite the above results, the inhibition of the PDGFR and C-kit pathways deserves further studies in MMe.

I.F. = 2,568

N. citazioni = 57

113. Fagnani D, Franchi R, **Porta C**, Pugliese P, Borgonovo K, Bertolini A, Duro M, Ardizzoia A, Filipazzi V, Isa L, Vergani C, Milani M, Cimminello C on behalf of PoloNord Group. Thrombosis-related complications and mortality in cancer patients with central venous devices: an observational study on the effect of antithrombotic prophylaxis. *Ann Oncol* 2007;18:551-5.

ABSTRACT - Background: Recent guidelines do not recommend antithrombotic prophylaxis (AP) to prevent catheter-related thrombosis in cancer patients with a central line. Patients and methods: This study assessed the management of central lines in cancer patients, current attitude towards AP, catheter-related and systemic venous thromboses, and survival. Results: Of 1410 patients enrolled, 1390 were seen at least once in the 6-month median follow-up. Continuous AP, mainly low-dose warfarin, was given to 451 (32.4%); they were older, with a more frequent history of venous thromboembolism (VTE), and more advanced cancer. There was no difference in catheter-related thrombosis in patients given AP or not (2.8% and 2.2%, odds ratio 1.29, 95% confidence interval 0.64–2.6). The median time to first catheter-related complication was 120 days. Systemic VTE including deep and superficial thromboses and pulmonary embolism, were less frequent with AP (4% versus 8.2%, P = 0.005). Mortality was also lower (25% versus 44%, P = 0.0001). Multiple logistic regression analysis found only advanced cancer and no AP significantly associated with mortality. No major bleeding was recorded with AP. Conclusions: Current AP schedules do not appear to prevent catheter-related thrombosis. Systemic VTE and mortality, however, appeared lower after prophylaxis.

I.F. = 4,875

N. citazioni = 19

114. Bertino P, **Porta C**, Barbone D, Germano S, Busacca S, Pinato S, Tassi GF, Favoni R, Gaudino G, Mutti L. Preliminary data suggestive of a novel translational approach to mesothelioma therapy: Imatinib mesylate with Gemcitabine or Pemetrexed. *Thorax* 2007;62:690-5.

ABSTRACT - Malignant mesothelioma is a cancer refractory to current therapies. Imatinib mesylate (STI571, Glivec™) is a selective inhibitor of tyrosine kinases as bcr-abl, c-Kit, C-Fms and Platelet Derived Growth Factor Receptor β (PDGFRβ). PDGFRβ is often overexpressed in mesothelioma cells and is a therapeutic target for Imatinib in some solid tumors. The aim of this study is to assess whether Imatinib alone or in combination with a chemotherapeutic agent. We show here that Imatinib induces cytotoxicity and apoptosis selectively on PDGFRβ-positive mesothelioma cells, via blockade of receptor phosphorylation and interference with the Akt pathway. Among chemotherapeutics tested in combination, Imatinib synergizes with Gemcitabine and Pemetrexed. We provide a rationale for a novel translational approach to mesothelioma therapy, relying on enhancement of tumor chemosensitivity, via inhibition of Akt.

I.F. = 6,226

N. citazioni = 46

115. **Porta C**, Bonomi L, Lillaz B, Paglino C, Rovati B,

Imarisio I, Morbini P, Villa C, Danova M, Mensi M, Rovereto B. Renal cell carcinoma-induced immunosuppression: an immunophenotypic study of lymphocyte subpopulations and circulating dendritic cells. *Anticancer Res* 2007;27:165-73.

ABSTRACT - Background: we investigated renal cell carcinoma (RCC)-induced immune dysfunction in patients at first diagnosis. Patients and methods: the main circulating lympocyte subsets, the total number of circulating and intratumor dendritic cells and the titers of circulating VEGF were quantified in 47 RCC patients, using flow cytometric, immunohistochemical and ELISA assays. Results: despite a significant activation of CD3/HLA-DR$^+$ lymphocytes and of the CD56$^+$ NK subset, RCC patients presented a marked immunosuppression of CD4/CD45RA naive T-cells, CD4/CD45RO memory T-cells, CD16$^+$ NK-cells, and total circulating dendritic cells, as well as a significant increase of lymphocytes co-expressing the CD4 and CD8 antigens. Finally, CD16$^+$/CD56$^+$ NK and DCs were poorly represented in tumor specimens. Conclusion: the complex immunological dysfunctions demonstrated involve different levels of immunocompetence and indicate a pattern of major disturbance of the immune system.
I.F. = 1,414
N. citazioni = 24

116. Bertino P, Marconi A, Palumbo L, Bruni B, Barbone D, Germano S, Dogan AU, Tassi GF, **Porta C**, Mutti L, Gaudino G. Erionite and asbestos differently cause transformation of human mesothelial cells. *Int J Cancer* 2007;121:12-20.

ABSTRACT - Malignant mesothelioma (MM) is an aggressive tumor associated with environmental or occupational exposure to asbestos fibers. Erionite is a fibrous zeolite, morphologically similar to asbestos and it is assumed to be even more carcinogenic. Onset and progression of MM has been suggested as the result of the cooperation between asbestos and other cofactors, such as SV40 virus infection. Nevertheless, several cases of MM were associated with environmental exposure to erionite in Turkey, where SV40 was never isolated in MM specimens. We show here that erionite is poorly cytotoxic, induces proliferating signals and high growth rate in human mesothelial cells (HMC). Long term exposure to erionite, but not to asbestos fibers, transforms HMC in vitro, regardless the presence of SV40 sequences, leading to foci formation in cultured monolayers. Cells derived from foci display constitutive activation of Akt, NF-κB and Erk1/2, show prolonged survival and a deregulated cell cycle, involving cyclin D1 and D overexpression. Our results reveal that erionite is able per se to turn HMC into transformed highly proliferating cells and disclose the carcinogenic properties of erionite, prompting for a careful evaluation of environmental exposure to these fibers. The genetic predisposition to the effect of erionite is a separate subject for investigation.
I.F. = 4,555
N. citazioni = 40

117. **Porta C**, Paglino C, Imarisio I, Bonomi L. Cytokine-based immunotherapy for advanced kidney cancer: past results and future perspectives in the era of molecularly targeted agents. *TheScientificWorldJournal* 2007;7:837-49.

ABSTRACT - Until recently, immunotherapy has been the only therapeutic option available for patients with advanced kidney cancer, even though different choices were often made on the two sides of the Atlantic Ocean. The absence of alternatives made different immunotheapeutic approaches common practice, even with few adequate randomized studies that addressed key questions, such as the best treatment and schedule, and so on. The recent registration of the first two, molecularly targeted, agents Sorafenib and Sunitinib could (and will) render many therapeutic approaches, e.g., single-agent Interferon, obsolete. In this review, we shall cover the past achievements obtained so far with cytokine-based immunotherapy and discuss the present role of immunotherapy in the era of molecularly targeted agents. In particular, specific indications for immunotherapy are emerging (e.g., the use of Interleukin-2 in patients with high CAIX expression), while new trials are ongoing to test immunotherapy in combination with molecularly targeted agents, such as Sorafenib, Sunitinib, or Bevacizumab.
I.F. = 2.52
N. citazioni = 25

118. Gish R, **Porta C**, Lazar L, Ruff P, Feld R, Croitoru A, Feun L, Jeziorski K, Leighton J, Gallo J, Kennealey GT. A phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with Nolatrexed or Doxorubicin. *J Clin Oncol* 2007;25:3069-75.

ABSTRACT - Purpose - The study objective was to compare the overall survival (OS) of patients with unresectable or metastatic hepatocellular carcinoma (HCC) treated with nolatrexed (NOL) or doxorubicin (DOX). Patients and Methods - Patients from North America, Europe, and South Africa (N = 445) with HCC were randomly assigned to receive NOL or DOX. Eligible patients had Karnofsky performance status (KPS) ≥ 60%, Cancer of the Liver Italian Program (CLIP) score ≤ 3, and adequate organ function. Primary end point was OS. Secondary end points included progression-free survival (PFS), objective response rates, and safety. The treatment groups were well-balanced with regards to age, sex, ethnic origin, and underlying liver disease. Randomization was stratified according to KPS and CLIP score. Results - At the time of the final analysis, 377 patients had died. Median OS was 22.3 weeks for NOL and 32.3 weeks for DOX (p = .0068). The hazard ratio was 0.753 in favor of DOX. Objective response rate (complete response [CR] plus partial response [PR]) was 1.4% for NOL and 4.0% for DOX. Median PFS was 12 weeks for NOL and 10 weeks for DOX (p = .7091). Median time to treatment failure was 8.4 weeks for NOL and 9.1 weeks for DOX (p = .0969). Grade 3 and 4 stomatitis, vomiting, diarrhea, and thrombocytopenia were more common in the NOL arm. Alopecia was more common in the DOX arm. More patients were withdrawn from study for toxicity in the NOL arm than in the DOX arm. Conclusions - NOL showed minimal activity in this phase III trial. Further exploration at this dose and schedule in HCC is not warranted.
I.F. = 15,484
N. citazioni = 200

119. Sartore-Bianchi A, Gasparri F, Galvani A, Nici L, Darnowski JW, Barbone D, Fennell DA, Gaudino G, **Porta C**, Mutti L. Bortezomib inhibits Nuclear Factor-κB-dependent survival and has potent *in vivo* activity in mesothelioma. *Clin Cancer Res* 2007;13:5942-51.

ABSTRACT - Purpose: Purpose of this study has been the assessment of nuclear factor-κB (NF-κB) as a survival factor in human mesothelial cells (HMC), transformed HMC and malignant mesothelioma (MMe) cells. We aimed at verifying whether the proteasome inhibitor Bortezomib could abrogate NF-κB activity in MMe cells, leading to tumor cell death and may be established as a novel treatment for this aggressive neoplasm. Experimental Design: In HMC and MMe cells, NF-κB nuclear translocation and DNA binding were studied by electrophoretic mobility shift assay, following treatment with tumor necrosis factor-α (TNF-α). The IKK inhibitor Bay11-7082 was also tested to evaluate its effects on HMC, transformed HMC, and MMe cell viability upon exposure to asbestos fibers. Following Bortezomib treatment, cytotoxicity of MMe cells was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, whereas apoptosis and cell-cycle blockade were investigated by high-content analysis. Bortezomib was also given to mice bearing i.p. xenografts of MMe cells, and its effects on tumor growth

were evaluated. Results: Here, we show that NF-κB activity is a constitutive survival factor in transformed HMC, MMe cells, and acts as a survival factor in HMC exposed to asbestos fibers. Bortezomib inhibits NF-κB activity in MMe cells and induces cell cycle blockade and apoptosis in vitro as well as tumor growth inhibition in vivo. Conclusions: Inhibition of NF-κB constitutive activation in MMe cells by Bortezomib resulted in in vitro cytotoxicity along with apoptosis and in vivo tumor regression. Our results support the use of Bortezomib in the treatment of MMe and has led to a phase II clinical trial currently enrolling in Europe.

I.F. = 6,25

N. citazioni = 81

120. **Porta C**, Paglino C, Imarisio I, Bonomi L. Uncovering Pandora's vase: the growing problem of new toxicities from novel anticancer agents. The case of Sorafenib and Sunitinib. *Clin Exp Med* 2007;7:127-34.

ABSTRACT - As newer, molecularly targeted, anticancer drugs are entering clinical practice, a wide array of previously unrecognised and ill defined side effects of these drugs are increasingly observed. Sorafenib and sunitinib are two of these novel agents, acting on tumour angiogenesis as well as on other key proliferative pathways; recently approved for the treatment of advanced kidney cancer, they may cause peculiar cutaneous, vascular and mucosal toxicities, including hand-foot skin reaction, skin rash, hypertension and GERD-like oesophagitis/gastritis. In this review, we shall deal with these poorly recognised, but sometimes extremely distressing, toxicities; pathophysiologic mechanisms will be discussed and suggestions for treatment of each toxicity will be proposed, based on the few pieces of evidence available and, especially, on our empirical experience.

I.F. = 1,531

N. citazioni = 127

121. **Porta C**, De Amici M, Quaglini S, Paglino C, Tagliani F, Boncimino A, Moratti R, Corazza GR. Circulating Interleukin-6 as a tumor marker for hepatocellular carcinoma. *Ann Oncol* 2008;19:353-8.

ABSTRACT - Background: A large amount of evidence suggests a possible role of interleukin-6 (IL-6) in the pathogenesis of hepatocellular carcinoma (HCC). Patients and methods: We studied both IL-6 and alpha1-fetoprotein (A1FP) in patients with HCC, non-neoplastic liver disease or in healthy controls. Results: IL-6 titers were four-fold higher in cancer than in cirrhotic patients and 25-fold higher than in healthy controls. As for A1FP titers, the highest levels were observed in cancer patients. Receiver operating characteristic (ROC) curves analysis demonstratedthat IL-6 is significantly more discriminant than A1FP, with 'optimal' cut-off values of 7.9 pg/ml (sensitivity = 0.83, specificity = 0.83, efficiency = 0.83). The ROC curves used to distinguish HCC from cirrhotic patients only, showed higher discriminant power of IL-6 versus A1FP titers, with a new cut-off value of 12 pg/ml (sensitivity = 0.73, specificity = 0.87, efficiency = 0.8). Discriminant analysis on HCC and non-HCC subjects yielded sensitivity, specificity and efficiency rates of 77%, 93% and 88%, respectively. The overall efficiency of the two tests combined was 82%. Conclusions: IL-6 could be considered a promising tumor marker for HCC. In particular, the diagnostic value of the test is significantly increased when combined with A1FP.

I.F. = 4,935

N. citazioni = 120

122. **Porta C**, Imarisio I, Paglino C. Re: Damien Pouessel, Stéphane Culine. High Frequency of Intracerebral Hemorrhage in Metastatic Renal Carcinoma Patients with Brain Metastases Treated with Tyrosine Kinase Inhibitors Targeting the Vascular Endothelial Growth Factor Receptor. *Eur Urol* 2008;53:1092-3.

ABSTRACT - We read with both interest and surprise the recent paper by Puessel and Culine who reported a 7% incidence of intracerebral hemorrhage in 67 patients with metastatic renal cell carcinoma (RCC) treated with either sorafenib or sunitinib within the respective compassionate use programs. Of the five patients who experienced such an event, four had known brain metastases. The report by the French group raises concerns about both the safety of the use of tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor receptor (VEGFR) pathway in patients with brain metastases, as well as on the real incidence of such a life-threatening side effect; indeed, patients with known brain metastases are usually excluded from enrollment into clinical trials. However, the particularly high incidence of intracerebral hemorrhage reported by Pouessel and Culine hardly finds confirmation by lager series. For example, in our center, in the past few years, we have treated 144 patients with either sorafenib or sunitinib outside clinical trials; 14 (9.72%) of these patients had known brain metastases. Among this large case series, no patient experienced central nervous system (CNS) bleeding while receiving treatment. Furthermore, among the 1155 patients so far analyzed in terms of safety within sorafenib's European compassionate access program, only 3 cases of intracranial hemorrhage (ie, 0.3%) were reported; of the whole patient population considered, 28 patients had brain metastases (2.42%). Furthermore, within the 2502 patients recently reported from the US compassionate use program, no CNS-related bleeding events occurred, despite the presence of 50 patients (1.99%) with brain metastases. A similar safety profile has been reported in the 2341 patients treated with sunitinib within the global compassionate use program of this TKI. Despite the inclusion of 182 patients with CNS involvement (7.77%), CNS-related bleeding events occurred in <1% of the cases. Why such a striking difference? In the French series, all but one of the patients who experienced CNS bleeding had uncontrolled hypertension at diagnosis, whereas our patients had more controlled pressure values at the time of starting treatment. Such a baseline uncontrolled hypertension could probably justify, not only the particularly high rate of such a complication, but also the short time interval between starting TKI treatment and the onset of cerebral hemorrhage, that is, 6.2 days on the average. Thus, is the risk of CNS bleeding really a major concern in patients with RCC treated with TKIs or do the potential benefits warrant the risk of such a dramatic complication (in the French series, average survival after hemorrhage was a dismal 2 days)? The available evidence supports the safe use of TKI also in patients with CNS metastases and a potential activity (at least of sorafenib) in delaying the onset of CNS metastases. Certainly, adequate control of underlying hypertension in candidates for TKI administration remains mandatory, especially in those with brain metastases. Only well-designed, prospective trials will ultimately address the relevant question of the acitivity and safety of such drugs in this peculiar setting.

I.F. = 6,512

N. citazioni = 8

123. Bertino P, Piccardi F, **Porta C**, Favoni R, Cilli M, Mutti L, Gaudino G. Imatinib mesylate enhances therapeutic effects of Gemcitabine in human malignant mesothelioma xenografts. *Clin Cancer Res* 2008;14:541-8.

ABSTRACT - Purpose: Platelet-derived growth factor receptor beta (PDGFRbeta), frequently activated in malignant mesothelioma, is a promising cancer therapeutic target. Imatinib mesylate (STI571; Glivec) is a selective inhibitor of tyrosine kinases as bcr-abl, c-kit, c-fms, and PDGFRbeta and enhances tumor drug uptake by reducing the interstitial fluid pressure. We previously showed that imatinib mesylate synergizes with gemcitabine and pemetrexed in PDGFRbeta-positive mesothelioma cells. Here, we aimed at investigating these combined treatments in a novel mesothelioma model. Experimental design: REN mesothelioma cells, infected with a lentiviral vector carrying the luciferase gene, were injected in the peritoneum of severe combined immunodeficient mice. This model allowed imaging of live animals treated with pemetrexed or gemcitabine chemotherapeutics, or with imatinib

mesylate alone, as well as with a combination of gemcitabine and imatinib mesylate. Results: We show here that, consistent with our previous in vitro studies, gemcitabine inhibited tumor growth, whereas pemetrexed was ineffective, even at the highest dosage tested. Compared with monotreatment, the combination of gemcitabine with imatinib mesylate led to a further tumor growth inhibition and improved mice survival, by a decrease rate of tumor cell proliferation and an increase in number of apoptotic tumor cells. Conclusions: Imatinib mesylate enhances the therapeutic response to gemcitabine, in accordance with our previous in vitro data. These in vivo results validate imatinib mesylate and gemcitabine as a combination treatment of malignant mesothelioma, also in view of its known positive effects on tumor drug uptake. These evidences provide the rationale for the currently ongoing clinical trials.
I.F. = 6,488
N. citazioni = 60

124. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, Cosme de Oliveira A, Santoro A, Raoul JL, Forner A, Schwartz M, **Porta C**, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Haussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J, for the SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378-90.

ABSTRACT - Background: No effective systemic therapy exists for patients with advanced hepatocellular carcinoma. A preliminary study suggested that sorafenib, an oral multikinase inhibitor of the vascular endothelial growth factor receptor, the platelet-derived growth factor receptor, and Raf may be effective in hepatocellular carcinoma. Methods: In this multicenter, phase 3, double-blind, placebo-controlled trial, we randomly assigned 602 patients with advanced hepatocellular carcinoma who had not received previous systemic treatment to receive either sorafenib (at a dose of 400 mg twice daily) or placebo. Primary outcomes were overall survival and the time to symptomatic progression. Secondary outcomes included the time to radiologic progression and safety. Results: At the second planned interim analysis, 321 deaths had occurred, and the study was stopped. Median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group (hazard ratio in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87; P<0.001). There was no significant difference between the two groups in the median time to symptomatic progression (4.1 months vs. 4.9 months, respectively, P=0.77). The median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group (P<0.001). Seven patients in the sorafenib group (2%) and two patients in the placebo group (1%) had a partial response; no patients had a complete response. Diarrhea, weight loss, hand-foot skin reaction, and hypophosphatemia were more frequent in the sorafenib group. Conclusions: In patients with advanced hepatocellular carcinoma, median survival and the time to radiologic progression were nearly 3 months longer for patients treated with sorafenib than for those given placebo. (ClinicalTrials.gov number, NCT00105443.).
I.F. = 50,017
N. citazioni = 8299

125. Motzer RJ, Escudier B, Oudard S, Hutson TE, **Porta C**, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A, for the RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008;372:449-56.

ABSTRACT - Background: Everolimus (RAD001) is an orally administered inhibitor of the mammalian target of rapamycin (mTOR), a therapeutic target for metastatic renal cell carcinoma. We did a phase III, randomised, double-blind, placebo-controlled trial of everolimus in patients with metastatic renal cell carcinoma whose disease had progressed on vascular endothelial growth factor-targeted therapy. Methods: Patients with metastatic renal cell carcinoma which had progressed on sunitinib, sorafenib, or both, were randomly assigned in a two to one ratio to receive everolimus 10 mg once daily (n=272) or placebo (n=138), in conjunction with best supportive care. Randomisation was done centrally via an interactive voice response system using a validated computer system, and was stratified by Memorial Sloan-Kettering Cancer Center prognostic score and previous anticancer therapy, with a permuted block size of six. The primary endpoint was progression-free survival, assessed via a blinded, independent central review. The study was designed to be terminated after 290 events of progression. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00410124. Findings: All randomised patients were included in efficacy analyses. The results of the second interim analysis indicated a significant difference in efficacy between arms and the trial was thus halted early after 191 progression events had been observed (101 [37%] events in the everolimus group, 90 [65%] in the placebo group; hazard ratio 0.30, 95% CI 0.22-0.40, p<0.0001; median progression-free survival 4.0 [95% CI 3.7-5.5] vs 1.9 [1.8-1.9] months). Stomatitis (107 [40%] patients in the everolimus group vs 11 [8%] in the placebo group), rash (66 [25%] vs six [4%]), and fatigue (53 [20%] vs 22 [16%]) were the most commonly reported adverse events, but were mostly mild or moderate in severity. Pneumonitis (any grade) was detected in 22 (8%) patients in the everolimus group, of whom eight had pneumonitis of grade 3 severity. Interpretation: Treatment with everolimus prolongs progression-free survival relative to placebo in patients with metastatic renal cell carcinoma that had progressed on other targeted therapies
I.F. = 28,409
N. citazioni = 2555

126. **Porta C**, Imarisio I, Paglino C, Ferraris E, Mensi M, Rovereto B. Prognostic factors in advanced renal cell cancer. *Eur J Cancer* 2008;6(Suppl.):35-7.

ABSTRACT - The identification of reliable and reproducible prognostic factors (defined as those factors that define the risk of death, or of recurrence, independently of therapy) in advanced renal cell carcinoma patients has became a priority in this field. To date, the Memorial Sloan Kettering Cancer Center – or Motzer's – criteria are those more commonly used, especially within clinical trials, but their role in the era of molecularly-targeted therapies is challenged. Molecular and genetic factors are currently being studied – with still conflicting results –, trying to incorporate them into presently available score systems and algorithms. The next generation of prognostic tools will probably include both genomic and proteomic techniques.
I.F. = 3,406
N. citazioni = 1

127. **Porta C**, Bonomi L, Lillaz B, Klersy C, Imarisio I, Paglino C, Rovati B, Danova M, Ferraris E, Mensi M, Rovereto B. Immunological stress in kidney cancer patients undergoing either open nephrectomy or nephron-sparing surgery: an immunophenotypic study of lymphocyte subpopulations and circulating dendritic cells. *Oncol Rep* 2008;20:1511-9.

ABSTRACT - Immunosuppression is a characteristic hallmark of renal cell carcinoma (RCC), with several complex immune defects, almost solely at the level of cell-mediated immune function, well evident even in patients at first diagnosis. The main circulating lymphocyte subsets and the total number of circulating dendritic cells were quantified in 47 RCC patients at diagnosis (T0), 12 h (T1), 24 h (T2) and 8 days following either radical nephrectomy or nephron-sparing surgery using flow cytometry. RCC patients presented, at

baseline, (T0) a profound state of immunosuppression involving naïve T-cells, memory T-cells, CD16+ NK and total circulating dendritic cells, that worsened after 12 (T1) and 24 h (T2) from surgery, involving the majority of the analysed subsets; after 8 days (T3) from surgical removal of tumor, however, there was a return of all the analyzed parameters to the basal state. In conclusion, surgery causes transient but relevant immune suppression in RCC patients; even though, by day +8, this tends to return to baseline, immunostimulatory therapies could be considered in the peri-operative setting with the aim of reducing immunosuppression and, hopefully, also disease recurrence.

I.F. = 1,524

N. citazioni = 2

128. **Porta C**, Paglino C, Mutti L. Ranpirnase and its potential for the treatment of unresectable malignant mesothelioma. *Biologics: Targets and Therapy* 2008;2:601-9.

ABSTRACT - Ribonucleases are a superfamily of enzymes which operate at the crossroads of transcription and translation, catalyzing the degradation of RNA; they can be cytotoxic because the cleavage of RNA renders indecipherable its information. Ranpirnase is a novel ribonuclease which preferentially degrades tRNA, thus leading to inhibition of protein synthesis and, ultimately, to cytostasis and cytotoxicity. Ranpirnase has demonstrated antitumor activity both in vitro and in vivo in several tumor models. The maximum tolerated dose emerging from phase I studies was 960 g/m^2, with renal toxicity as the main dose-limiting toxicity. A large phase II trial showed that ranpirnase has disease-modifying activity against malignant mesothelioma. Ranpirnase proved to be superior to doxorubicin in a phase III trial, while preliminary results of another large, phase III trial, suggest that the combination of ranpirnase and doxorubicin could be more effective than doxorubicin alone. In all the above studies, ranpirnase seems to act mainly as a cytostatic rather than a cytotoxic drug, stabilizing progressive disease and potentially prolonging patients' survival. Ranpirnase may thus find its niche in combination with doxorubicin for mesothelioma as a second-line therapy, where no standard of care presently exists.

I.F. = n.r.

N. citazioni = 40

129. **Porta C**, Szczylik C. Tolerability of first-line therapy for metastatic renal cell cancer. *Cancer Treat Rev* 2009;35:297-307.

ABSTRACT - The treatment options for metastatic renal cell carcinoma have expanded rapidly over the past 3 years, with four new agents available and others in late-stage development. This has resulted in a change of the standard of first-line care, with sunitinib or bevacizumab plus interferon the treatments of choice for patients with good or intermediate-risk renal cell carcinoma and temsirolimus treatment of choice for poor-risk disease. Sunitinib and bevacizumab plus interferon have similar efficacy, meaning that treatment choice is influenced by other factors: disease-related factors such as clear cell versus non-clear cell histology; patient factors such as co-morbidities, Memorial Sloan-Kettering Cancer Center risk and patient preference; and drug-related factors such as tolerability profile. The aim of this review is to describe the tolerability of the first-line treatment options for clear cell renal cell carcinoma, giving consideration to how tolerability profiles relate to drug mechanism of action. Thus, the incidence and aetiology of side effects related to vascular endothelial growth factor and vascular endothelial growth factor receptor inhibition using sunitinib and bevacizumab, as well as those of the non-specific side effects observed with sunitinib, are described. In addition, the potential patient impact and management of these side effects, as well as those of interferon and temsirolimus, are considered. Finally, the implications of the tolerability profiles of these agents for combination therapy and use in broader populations than those enrolled in trials are assessed.

I.F. = 4,729

N. citazioni = 38

130. **Porta C**, Paglino C, Imarisio I, Ferraris E. Sorafenib tosylate in advanced kidney cancer: past, present and future. *Anticancer Drugs* 2009;20:409-15.

ABSTRACT - The objective of this study was to review the development of sorafenib tosylate in kidney cancer. The MedLine database, the Proceedings of the Annual American Society of Clinical Oncology meeting, as well as those of other key international meetings were extensively searched to identify relevant publications. Furthermore, the authors' direct experience with the drug was taken into account when commenting on the results retrieved. Sorafenib is a multikinase inhibitor that targets VEGF and PDGF receptors, other kinases, as well as the serine-threonine kinase Raf. Following early signs of activity from phase I and II studies, it has been shown to improve survival of pretreated advanced kidney cancer patients within a placebo-controlled, randomized, phase III trial, leading to its approval both in the United States and in Europe. Its activity has been subsequently confirmed in a real-world population by two expanded access programs performed globally, but not in a first-line setting; it also proved to be non-cross-resistant with two other molecularly targeted agents. Finally, its toxicity profile, which is acceptable and highly predictable, makes sorafenib appealing for combination treatments, especially with other molecularly targeted agents. Despite having been already demonstrated to be active in kidney cancer, the exact role of sorafenib in the first-line setting, in patients who have failed other molecularly targeted agents, and especially in combination with other agents, deserves further, prospective, studies.

I.F. = 2,358

N. citazioni = 18

131. Ferraris E, Di Cesare P, Lasagna A, Paglino C, Imarisio I, **Porta C**. Use of Sorafenib in two metastatic renal cell cancer patients with end-stage renal impairment undergoing replacement hemodialysis. *Tumori* 2009;95:542-4.

ABSTRACT - Patients with renal cell carcinoma (RCC) may exhibit renal impairment as a more or less direct consequence of their primary disease. Renal impairment may become a severe complication and alter the normal pharmacokinetic and pharmacodynamic behavior of treatment drugs, thus increasing the risk of side-effects. We will discuss the cases of two advanced RCC patients with end-stage renal impairment submitted to dialysis who were treated with Sorafenib tosylate in our Center. Our experience confirms the little literature data available so far that indicate that Sorafenib can be used in patients undergoing dialysis. Dialysis cannot be considered per se a contraindication to Sorafenib therapy, which can be effective. However, patients must be carefully selected and monitored, since Sorafenib administration unquestionably increases the risk of side-effects in patients affected with several conditions.

I.F. = 0,791

N. citazioni = 14

132. Aceto N, Bertino P, Barbone D, Tassi GF, Manzo L, **Porta C**, Mutti L. Gaudino G. Taurolidine and oxidative stress: a rationale for local treatmet of mesothelioma. *Eur Resp J* 2009;34:1399-407.

ABSTRACT - Malignant mesothelioma is an asbestos-related, aggressive tumor, resistant to most anti-cancer therapies. Akt is a key mediator of mesothelioma cell survival and chemoresistance. Question of the study: the mechanism by which Taurolidine, a known synthetic compound with antimicrobial and antineoplastic properties, leads to mesothelioma cell death. Material and Methods: Apoptosis was studied by Annexin V binding, cell cycle analysis, caspase 8 activation, PARP cleavage and TUNEL. Oxidative stress was measured by nitrites production and DNA oxidative damage.

Protein expression and phosphorylation were evaluated by immunoprecipitation and immunoblotting. Results: Taurolidine induces cell death of mesothelioma cells, but not of non-neoplastic human mesothelial cells. After Taurolidine treatment of mesothelioma cells, Akt but not Erk 1/2 activity is inhibited in time- and dose-dependent manner. PP1α and PP2A are activated several hours after drug addition. Apoptosis induced by Taurolidine is driven by oxidative stress and cell exposure to sulphydryl donors, as Glutathione-monoethyl-ester (GSH) and L-N-acetylcysteine (L-NAC), significantly reduced pro-apoptotic effects and Akt inhibition. Conversely, expression of constitutively activated Akt did not affect cytoxicity elicited by Taurolidine, which retained its ability to inhibit the kinase. Answer to the question: Taurolidine induces mesothelioma cell death via oxidative stress, accompanied by inhibition of Akt signalling. This provides a promising molecular rationale for Taurolidine as local treatment of malignant mesothelioma
I.F. = 5,545
N. citazioni = 21

133. Gore ME, Szczylik C, **Porta C**, Bracarda S, Bjarnason GA, Oudard S, Hariharan S, Lee SH, Haanen J, Castellano D, Vrdoljak E, Schöffski P, Mainwaring P, Nieto A, Yuan J, Bukowski R. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol* 2009;10:757-63.

ABSTRACT - Background: Results from clinical trials have established sunitinib as a standard of care for first-line treatment of advanced or metastatic renal-cell carcinoma (RCC); however, many patients, particularly those with a poorer prognosis, do not meet inclusion criteria and little is known about the activity of sunitinib in these subgroups. The primary objective of this trial was to provide sunitinib on a compassionate-use basis to trial-ineligible patients with RCC from countries where regulatory approval had not been granted. Methods: Previously treated and treatment-naive patients at least 18 years of age with metastatic RCC were eligible. All patients received open-label sunitinib 50 mg orally once daily on schedule 4-2 (4 weeks on treatment, 2 weeks off). Safety was assessed regularly, tumour measurements done per local practice, and survival data collected where possible. Analyses were done in the modified intention-to-treat (ITT) population, which consisted of all patients who received at least one dose of sunitinib. This study is registered with ClinicalTrials.gov, NCT00130897. Findings: As of December, 2007, 4564 patients were enrolled in 52 countries. 4371 patients were included in the modified ITT population. This population included 321 (7%) patients with brain metastases, 582 (13%) with Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, 588 (13%) non-clear-cell RCC, and 1418 (32%) aged 65 years or more. Patients received a median of five treatment cycles (range 1-25). Reasons for discontinuation included lack of efficacy (n=1168 [27%]) and adverse events (n=362 [8%]). The most common treatment-related adverse events were diarrhoea (n=1936 [44%]) and fatigue (n=1606 [37%]). The most common grade 3-4 adverse events were fatigue (n=344 [8%]) and thrombocytopenia (n=338 [8%]) with incidences of grade 3-4 adverse events similar across subgroups. In 3464 evaluable patients, the objective response rate (ORR) was 17% (n=603), with subgroup ORR as follows: brain metastases (26 of 213 [12%]), ECOG performance status 2 or higher (29 of 319 [9%]), non-clear-cell RCC (48 of 437 [11%]) and age 65 years or more (176 of 1056 [17%]). Median progression-free survival was 10.9 months (95% CI 10.3-11.2) and overall survival was 18.4 months (17.4-19.2). Interpretation: In a broad population of patients with metastatic RCC, the safety profile of sunitinib 50 mg once-daily (initial dose) on schedule 4-2 was manageable and efficacy results were encouraging, particularly in subgroups associated with poor prognosis who are not usually entered into clinical trials.
I.F. = 13,283
N. citazioni = 501

134. Bertino G, Occhini A, Falco CE, **Porta C**, Corbella F, Colombo S, Balcet V, Morbini P, Zappoli F, Azzaretti A, Rodolico G, Tinelli C, Benazzo M. Concurrent intra-arterial carboplatin administration and radiation therapy for the treatment of advanced head and neck squamous cell carcinoma: short term results. *BMC Cancer* 2009;9:313.

ABSTRACT - Background: The aim of the present study was to evaluate the survival, efficacy and safety of a modified RADPLAT-like protocol using carboplatin instead of cisplatin. Methods: Fifty-six patients with primary head and neck squamous cell carcinoma received 4 cycles of intra-arterial carboplatin (350 mg/m^2 per cycle every 2 weeks), with concurrent three-dimensional conformal radiation therapy. Results: Two major and 4 minor complications were observed. Forty-five of the 56 patients (80%) completed the protocol, while 11 (20%) patients had to discontinue the intra-arterial infusions due to the occurrence of severe haematological toxicity, but were able to complete radiotherapy. Forty-four (98%) of the 45 patients who completed the protocol and 10 (91%) of the 11 who did not, were free of disease at the end of the treatment, for a comprehensive 96% of CR overall. After a median 23.55 months (range: 2 to 58 months) of follow-up, 40 patients (71%) are alive and disease-free, 1 (2%) is alive but affected by disease and 15 (27%) have died of the disease or other causes. Conclusions: Intra-arterial carboplatin administration with concurrent three-dimensional conformal radiation therapy seems to be a promising alternative to RADPLAT in the treatment of advanced head and neck tumours. Haematological and non-haematological toxicities are virtually similar, but carboplatin has the advantage in that it is not nephrotoxic and can be used at very high doses without any significant increase in the extent of side effects.
I.F. = 3,087
N. citazioni = 7

135. **Porta C**, Figlin RA. Phosphatidyl-inositol-3-kinase (PI3K)/Akt signalling pathway in kidney cancer and the therapeutical potential of PI3K/Akt inhibitors. *J Urol* 2009;182:2569-77.

ABSTRACT - Purpose:The phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway is activated by many cellular stimuli and regulates fundamental cellular functions, including transcription, translation, proliferation, growth and survival; it closely interacts with many other key pathways, such as mTOR, thus being linked with angiogenesis. A disturbed activation of the PI3K/Akt pathway has been associated with the development of many human malignancies. The aim of this paper is to review the available Literature on PI3K/Akt and PI3K/Akt-targeting drugs in renal cell carcinoma (RCC). Materials and methods: MedLine and the Proceedings of the main Oncological Meetings were extensively searched to identify the available Literature concerning the role of this pathway in the pathogensis of RCC, as well as the pre-clinical and clinical activity of compounds specifically targeting this pathway. Clinical data and perspectives for several compounds in different stages of development are also reviewed. Results: Evidence has accumulated which links PI3K/Akt alterations with RCC, which thus represent an ideal setting to test compounds specifically targeting this pathway. Several PI3K/Akt inhibitors are presently under preclinical and early clinical development as anticancer agents, but only Perifosine appears to be in a more advanced stage, having being tested, with promising results, alone or in combination with other molecularly-targeted agents. Conclusions: The PI3K/Akt pathways plays a pivotal role in RCC pathogenesis and thus represents an ideal target for therapeutical interventions. Among the several compounds which are in early phases of development, only Perifosine has already proved to be clinically active and thus should be regarded as an extremely interesting drug to be used either alone or in combination.
I.F. = 3,952
N. citazioni = 72

136. Negrier S, Jäger E, **Porta C**, McDermott D, Moore M,

Bellmunt J, Anderson S, Cihon F, Lewis J, Escudier B, Bukowski R. Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET. *Med Oncol* 2010;27:899-906.

ABSTRACT - Before the development of targeted therapies, administration of cytokines (e.g., interleukin-2, interferon-alpha) was the primary systemic treatment option for advanced renal cell carcinoma. Sorafenib, an oral targeted, multikinase inhibitor, significantly prolonged progression-free survival and overall survival in the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), a large (N = 903) phase III, double-blind, randomised, placebo-controlled study of patients with advanced renal cell carcinoma resistant to standard therapy. This analysis of a patient subgroup from TARGET evaluated the safety and efficacy of sorafenib in patients who had received prior cytokine therapy (sorafenib: n = 374; placebo: n = 368) and in patients who were cytokine-naïve (sorafenib: n = 77; placebo: n = 84). Progression-free survival was significantly prolonged with sorafenib therapy compared with placebo among patients with and without prior cytokine therapy (respectively 5.5 vs. 2.7 months; hazard ratio, 0.54; 95% confidence interval, 0.45-0.64 and 5.8 vs. 2.8 months; hazard ratio, 0.48; 95% confidence interval, 0.32-0.73). Clinical benefit rates for sorafenib-treated patients compared with placebo patients were also higher (cytokine-treated: 83 vs. 54.3%; cytokine-naïve: 85.7 vs. 56.0%). Sorafenib was well tolerated in both subgroups (grade 3/4: 20 and 22%, respectively). Sorafenib demonstrated a consistent, significant clinical benefit against advanced renal cell carcinoma, with a twofold improvement in progression-free survival and disease control rate, with similar toxicities in patients with or without prior cytokine treatment.
I.F. = 2,21
N. citazioni = 26

137. de Pangher Manzini V, Recchia L, Cafferata M, **Porta C**, Siena S, Giannetta L, Morelli F, Oniga F, Bearz A, Torri V, Cinquini M. Malignant peritoneal mesothelioma: a multicenter study on 81 cases. *Ann Oncol* 2010;21:348-53.

ABSTRACT - Background: Malignant peritoneal mesothelioma (MPM) is a rare disease characterized by a difficult diagnosis, different types of presentation, variable course and poor prognosis. Materials and methods: Eighty-one patients with MPM observed in 14 Italian oncology institutions from 1982 to 2007 have been examined with the aim of delineating the history of MPM. Results: Presentation symptoms were ascites, abdominal pain, asthenia, weight loss, anorexia, abdominal mass, fever, diarrhea and vomiting in various associations. Computed tomography scan and echotomography signs were ascites, abdominal mass and peritoneal thickening. Peritoneal fluid cytology (61 cases) was positive for mesothelioma in 31 and for malignancy, not mesothelioma, in 13. Laparoscopy was carried out in 40 cases and laparotomy in 36. Thrombocytosis was present in 59 cases. Associated tumors diagnosed during the lifetime were colorectal cancer in two cases and cheek carcinoma, thyroid carcinoma, tongue carcinoma, bladder carcinoma and testicular seminoma. Thirty patients were treated with surgery and 45 with chemotherapy. The median survival time from diagnosis is 13 months. Ascites, fever and vomiting were significative variables at presentation; only vomiting holds significance in a multivariate analysis. Conclusions: MPM is a disease with various types of presentation, frequently associated with thrombocytosis, sometimes with other tumors. Survival and diagnosis time can differ in various types of MPM. Prognosis is poor.
I.F. = 6,452
N. citazioni = 81

138. Passalacqua R, Buzio C, Buti S, **Porta C**, Labianca R, Pezzuolo D, Camisa R, Sabbatini R, Benecchi L, Messina C, Cengarle R, Vaglio A, Dalla Chiesa M, Tomasello G, Caminiti C. Phase III, randomised, multicentre trial of maintenance immunotherapy with low-dose interleukin-2 and interferon-alpha for metastatic renal cell cancer. *Cancer Immunol Immunother* 2010;59:553-61.

ABSTRACT - This is the first phase III randomised trial to evaluate maintenance immunotherapy in metastatic renal cell cancer (mRCC). Patients were randomised to receive treatment with a 4-week cycle of subcutaneous low doses IL-2 + IFN in months 1, 3 and 5, and then every 3 months until the first documented disease progression (arm A, suspension), or the same regimen, with chronic maintenance of immunotherapy, regardless of tumour response, until death or intolerable toxicity (arm B, maintenance). The primary endpoint was overall survival (OS); secondary endpoints were time from first progression to death (TFPTD) and tolerability. One hundred and eighty-three patients were enrolled between January 1998 and November 2003. After a median follow-up of 53.9 months, response rate, median OS and median TFPTD were 14.7% (6.3% CR) versus 11.3% (5.5% CR), 14 versus 14 months, 6 versus 5 months, in arms A and B, respectively with no significant differences between the groups. Cox regression analysis showed that the use of chemotherapy after first progression (HR 0.54; 95% CI 0.35-0.86; p = 0.008), PS = 0 (HR 0.53; 95% CI 0.35-0.81; p = 0.001) and female gender (HR 0.63; 95% CI 0.41-0.98; p = 0.038) were significantly associated with a longer TFPTD; treatment arm was not significant (HR 0.88; 95% CI 0.60-1.31; p = 0.54). Toxicity was mainly limited to WHO grades 1 or 2. Chronic maintenance immunotherapy after disease progression is feasible, but does not significantly increase OS or the TFPTD.
I.F. = 4,293
N. citazioni = 20

139. **Porta C**, Bellmunt J, Eisen T, Szczylik C, Mulders P. Treating the individual: the need for a patient-focused approach to the management of renal cell carcinoma. *Cancer Treat Rev* 2010;36:16-23.

ABSTRACT - Five targeted agents have shown efficacy in advanced renal cell carcinoma. These agents were evaluated in pivotal phase III clinical trials using different treatment settings and different patient populations. As patients encountered in 'real life' clinical practice are frequently under-represented in phase III trials, making treatment decisions based on phase III data alone may have limitations. In order to support treatment decisions for patients who do not fit within the inclusion criteria of many phase III trials, physicians must consider additional data sources such as expanded access programmes, sub- and retrospective analyses, and also clinical experience. The suitability of a specific targeted agent for a given patient group, e.g. elderly, will depend on a number of factors, including disease-, patient- and treatment-related characteristics. Here, we identify the need for an individualised patient-focused approach to the management of advanced renal cell carcinoma in clinical practice. In order to optimise therapy for individual patients, we present a schema providing guidance on the wide range of parameters that should be considered when making treatment decisions. We recommend the integration of this approach into everyday clinical practice.
I.F. = 6,811
N. citazioni = 36

140. **Porta C**, Paglino C, De Amici M, Quaglini S, Sacchi L, Imarisio I, Canipari C. Predictive value of baseline serum vascular endothelial growth factor and neutrophil gelatinase-associated lipocalin in advanced kidney cancer patients receiving Sunitinib. *Kidney Int* 2010;77:809-15.

ABSTRACT - To identify factors that might predict response to sunitinib in patients with renal cell carcinoma we measured serum vascular endothelial growth factor (VEGF) and neutrophil gelatinase-associated lipocalin (NGAL) levels. Eighty-five patients were selected and, using the Motzer classification, 46 were assigned to the good- and 38 to the intermediate-risk groups. With

univariate Cox analysis, baseline serum VEGF and NGAL titers, determined by ELISA, both significantly predicted progression-free survival. For each biomarker, a threshold value was identified, which proved useful to classify patients into groups having titers above or below the thresholds. We then stratified patients according to the two dichotomous variables into good-, intermediate- and poor-risk groups and found significantly different progression-free survivals, ranging from 3.5 to 11.6 months. Both VEGF and NGAL maintained their predictive significance at bivariate analysis. Our study shows that serum levels of VEGF and NGAL are significant predictors of progression-free survival in patients with renal cell carcinoma treated with Sunitinib.

I.F. = 6,105

N. citazioni = 91

141. **Porta C**. Regarding: 'Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-a2a compared with sunitinib'. *Br J Cancer* 2010;102:1196-7.

ABSTRACT - Mickisch et al. report a comparison of the costs of managing side effects due to the treatment with either sunitinib or bevacizumab plus interferon, the two presently available standards of care for the 1st line treatment of advanced kidney cancer, in four European Countries, i.e., Germany, UK, France, and Italy. This analysis is of value for clinical practice given the recent availability of several molecularly-targeted therapies for the treatment of advanced kidney cancer, including bevacizumab and sunitinib, which have radically changed the natural history of the disease. These therapies have made - at least in the vast majority of cases - this once orphan tumour more likely a chronic disease. Such relative long-term disease stabilisation is inevitably accompanied by increasing costs and, even though these new therapies are usually quite well tolerated, side effects may nevertheless occur which lead to the need for further resources such as extra medical treatment or hospitalisation. As we don't presently have predictive features which could help us to a priori select responders to treatments such as bevacizumab and sunitinib, it is important that one should take into account both the primary costs of each of these treatments - in some countries artificially made uniform by regulatory authorities - but also secondary costs, such as related to the management of these therapy-induced side effects. Mickisch et al used pivotal trial data and financial figures obtained from the healthcare systems of each of the four countries; a linear decision analytic model then calculated the cost comparison. The average cost per patient for the management of grade 3 and 4 side effects with sunitinib or bevacizumab plus interferon was markedly higher with sunitinib, as compared to bevacizumab plus interferon. Despite a relevant cost variability among the four countries, sunitinib treatment led to an average increase in the costs of treatment, due to the management of therapy-related grade 3 and 4 side effects, of 637.5 € (ranging from 418 € for Germany to 972 € for France). Notably, such a difference could also be considered as an underestimation; indeed, we already know that lowering the dose of interferon can lead to a reduction in side effects experienced by patients receiving the bevacizumab-interferon combination, while efficacy seems to be maintained, therefore potentially leading to further savings. These savings are both in terms of a reduction in the amount of interferon used, as well as in the resources necessary for the management of interferon-related side effects. Moreover, toxicities such as hypothyroidism and cardiotoxicity may have been grossly underestimated in the sunitinib registrative trial compared to levels indicated from other recent studies of sunitinib while the safety profile of bevacizumab plus interferon do not seem to have changed so much over time. When considering these additional facts, the indirect economic advantage of bevacizumab plus interferon seems even more evident and convincing. In sum, the report by Mickisch et al highlights that when deciding the ideal treatment for each given patient affected by advanced kidney cancer entering our hospitals, we should take into account economic factors (secondary costs) in addition to the efficacy and safety profiles of available treatments.

I.F. = 4,831

N. citazioni = 2

142. Motzer RJ, Escudier B, Oudard S, Hutson TE, **Porta C**, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Kay A, Ravaud A, for the RECORD-1 Study Group. Phase 3 trial of Everolimus for metastatic renal cell carcinoma. Final results and analysis of prognostic factors. *Cancer* 2010;116:4256-65.

ABSTRACT - Background: A phase 3 trial demonstrated superiority at interim analysis for everolimus over placebo in patients with metastatic renal cell carcinoma (mRCC) progressing on vascular endothelial growth factor receptor-tyrosine kinase inhibitors. Final results and analysis of prognostic factors are reported. Methods: Patients with mRCC (N = 416) were randomized (2:1) to everolimus 10 mg/d (n = 277) or placebo (n = 139) plus best supportive care. Progression-free survival (PFS) and safety were assessed to the end of double-blind treatment. Mature overall survival (OS) data were analyzed, and prognostic factors for survival were investigated by multivariate analyses. A rank-preserving structural failure time model estimated the effect on OS, correcting for crossover from placebo to everolimus. Results: The median PFS was 4.9 months (everolimus) versus 1.9 months (placebo) (hazard ratio [HR], 0.33; P < .001) by independent central review and 5.5 months (everolimus) versus 1.9 months (placebo) (HR, 0.32; P < .001) by investigators. Serious adverse events with everolimus, independent of causality, in >/=5% of patients included infections (all types, 10%), dyspnea (7%), and fatigue (5%). The median OS was 14.8 months (everolimus) versus 14.4 months (placebo) (HR, 0.87; P = .162), with 80% of patients in the placebo arm crossed over to everolimus. By the rank-preserving structural failure time model, the survival corrected for crossover was 1.9-fold longer (95% confidence interval, 0.5-8.5) with everolimus compared with placebo only. Independent prognostic factors for shorter OS in the study included low performance status, high corrected calcium, low hemoglobin, and prior sunitinib (P < .01). Conclusions: These results established the efficacy and safety of everolimus in patients with mRCC after progression on sunitinib and/or sorafenib.

I.F. = 5,131

N. citazioni = 989

143. Hutson TE, Bellmunt J, **Porta C**, Szczylik C, Staehler M, Nadel A, Anderson S, Bukowski R, Eisen T, Escudier B for the Sorafenib TARGET Clinical Trial Group. Long-term safety of sorafenib in advanced renal cell carcinoma: follow-up of patients from phase III TARGET. *Eur J Cancer* 2010;46:2432-40.

ABSTRACT - Background: The phase III Treatment Approaches in Renal cancer Global Evaluation Trial (TARGET) indicated that sorafenib is effective and well tolerated in advanced renal cell carcinoma patients. However, few data have been published on the safety of long-term sorafenib treatment. A retrospective subgroup analysis was performed to evaluate the efficacy and safety of sorafenib in patients in TARGET who received treatment for >1 year. Methods: The present subgroup analysis (based on the September 2006 database with updated safety analysis) evaluated the efficacy and safety of sorafenib in all patients in the sorafenib arm of TARGET who were treated for >1 year. The assessments included the overall survival, progression-free survival (PFS), disease control rate (DCR), and safety. The patients remained on therapy post-progression at the discretion of the investigator. Results: In TARGET, 169 patients received treatment with sorafenib for >1 year. The median PFS of patients in this subpopulation was 10.9 months from the date of randomisation, with a DCR of 92%. The most commonly reported treatment-related adverse events of any grade were diarrhoea (74%), rash/desquamation (51%), hand-foot skin reaction (49%), alopecia (39%), and fatigue (38%). Adverse events were mild to moderate, and presented early in the course of the treatment; there were no unexpected toxi-

cities associated with the long-term administration of sorafenib. Conclusions: Results of this subgroup analysis of patients enrolled in TARGET who received treatment for >1 year indicate that long-term treatment with sorafenib is associated with continued efficacy and a well-tolerated safety profile.
I.F. = 4,944
N. citazioni = 69

144. **Porta C**, Paglino C. Medical treatment of unresectable hepatocellular carcinoma: going beyond sorafenib. *World J Hepatol* 2010;2:103-13.

ABSTRACT - Even though Sorafenib has radically changed the natural history of those hepatocellular carcinoma patients who are not amenable for curative treatments, further therapeutic improvements are badly needed. As it was for Sorafenib, our increasingly refined understanding of the complex mechanisms underlying HCC carcinogenesis are the starting point for the future development of such treatments. Presently, a number of molecularly targeted agents are in different stages of development for this once orphan cancer. Indeed, several pathways are presently being explored to identify potentially active drugs, including epidermal growth factor receptor, vascular endothelial growth factor/vascular endothelial growth factor receptors, mammalian target of rapamycin, phosphatidyl-inositol-3-kinase/Akt, insulin growth factor, Aurora kinase, Wnt/?-catenin, retinoic acid receptor and hepatocyte growth factor/C-Met. This review is aimed at addressing the results obtained so far with these newer drugs, also considering the challenges we shall face in the near future, including the issue of response evaluation and identification of predictive/prognostic biomarkers.
I.F. = n.r.
N. citazioni = 13

145. Bellmunt J, Eisen T, Szczylik C, Mulders P, **Porta C**. A new patient-focused approach to the treatment of metastatic renal cell carcinoma: establishing customized treatment options. *BJU Int* 2011;107:1190-9.

ABSTRACT - Randomized controlled trials (RCTs) show that six targeted agents - sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab and pazopanib - improve outcome in advanced renal cell carcinoma (RCC). The populations enrolled in the pivotal phase III studies differed, and, to date, no head-to-head comparisons allow us to judge relative efficacy and tolerability. Populations recruited to RCTs under-represent certain patient subtypes, notably the elderly and those with comorbidities. Choosing the agent most appropriate in a specific case requires that we take into account the characteristics of the patient, the nature of their disease, and the history and aims of therapy. Data from expanded access programmes and clinical experience may be as relevant as the results of RCTs when making this difficult decision. To show how different sources of data can be integrated, we propose a schema that acknowledges nine patient-, disease-, and treatment-related factors relevant to clinical decision-making and provides an easily understood visual indication of the strength with which a particular agent can be recommended for use in specific subgroups of patients. As an example, we show how this tool shows the suitability of sorafenib in RCC subpopulations of differing age, prognosis, performance status, tumour burden and distribution, treatment history, and comorbidity. This patient-focused approach has broad application to other agents and tumour types.
I.F. = 3,19
N. citazioni = 19

146. Gore ME, Hariharan S, **Porta C**, Bracarda S, Hawkins R, Bjarnason GA, Oudard S, Lee SH, Cartenì G, Nieto A, Yuan J, Szczylik C. Sunitinib in metastatic renal cell carcinoma patients with brain metastases. *Cancer* 2011;117:501-9.

ABSTRACT - Background: In a broad patient population with metastatic renal cell carcinoma (RCC), enrolled in an open-label, expanded access program (EAP), the safety profile of sunitinib was manageable, and efficacy results were encouraging. Here, the authors report results for patients with baseline brain metastases participating in this global EAP. Methods: Previously treated and treatment-naive metastatic RCC patients ≥18 years received sunitinib 50 mg orally, once daily, on Schedule 4/2. Safety was assessed regularly, tumor measurements done per local practice, and survival data collected where possible. Analyses were done in the modified intention-to-treat (ITT) population, consisting of all patients who received ≥1 dose of sunitinib. Results: As of December 2007, 4564 patients had enrolled in 52 countries. Of these enrollees, 4371 were included in the modified ITT population, of whom 321 (7%) had baseline brain metastases and had received a median of 3 treatment cycles (range 1-25). Reasons for their discontinuation included lack of efficacy (32%) and adverse events (8%). The most common grade 3-4 treatment-related adverse events were fatigue and asthenia (both 7%), thrombocytopenia (6%), and neutropenia (5%), the incidence of which were comparable to that for the overall EAP population. Of 213 evaluable patients, 26 (12%) had an objective response. Median progression-free survival and overall survival were 5.6 months (95% CI, 5.2-6.1) and 9.2 months (95% CI, 7.8-10.9), respectively. Conclusions: In patients with brain metastases from RCC, the safety profile of sunitinib was comparable to that in the general metastatic RCC population, and sunitinib showed evidence of antitumor activity.
I.F. = 5,131
N. citazioni = 115

147. Santini D, Perrone G, Roato I, Godio L, Pantano F, Grasso D, Russo A, Vincenzi B, Elisabetta Fratto M, Sabbatini R, Pepa CD, **Porta C**, Del Greco A, Schiavon G, Berruti A, Tomasino RM, Papotti M, Papapietro N, Onetti Muda A, Denaro V, Tonini G. Expression pattern of receptor activator of NFκB (RANK) in a series of primary solid tumors and related bone metastases. *J Cell Physiol* 2011;226:780-4.

ABSTRACT - Background: Receptor activator of NFκB ligand (RANKL), RANK and Osteoprotegerin (OPG) represent the key regulators of bone metabolism both in normal and pathological conditions, including bone metastases. To our knowledge, no previous studies investigated and compared RANK expression in primary tumors and in bone metastases from the same patient. Methods: We retrospectively examined RANK expression by immunohistochemistry in 74 bone metastases tissues from solid tumors, mostly breast, colorectal, renal, lung and prostate cancer. For 40 cases, tissue from the corresponding primary tumor was also analyzed. Results: 66 (89%) of the 74 bone metastases were RANK-positive and, among these, 40 (59.5%) showed more than 50% of positive tumor cells. The median percentage of RANK-positive cells was 60% in primary tumors and metastases, without any statistically significant difference between the two groups (p=0.194). The same percentage was obtained by considering only cases with availability of samples both from primary and metastasis. Conclusion: Our study shows that RANK is expressed by solid tumors, with high concordance between bone metastasis and corresponding primary tumor. These data highlight the central role of RANK/RANKL/OPG pathway as potential therapeutic target not only in bone metastasis management, but also in the adjuvant setting.
I.F. = 3,986
N. citazioni = 100

148. Di Lorenzo G, **Porta C**, Bellmunt J, Sternberg C, Kirkali Z, Staehler M, Joniau S, Montorsi F, Buonerba C. Toxicities of Targeted Therapy and Their Management in Kidney Cancer. *Eur Urol* 2011;59:526-40.

ABSTRACT - Context The therapeutic scenario for metastatic renal cell carcinoma (mRCC) has been evolving rapidly, with sunitinib, sorafenib, bevacizumab, everolimus, pazopanib, and temsirolimus being successfully tested and approved in a short period of time. Oncologists must be familiar with the management of toxicity that these biologic agents cause, as such toxicity is different from that of conventional chemotherapeutic agents. Objective: To describe toxic effects associated with targeted therapy of mRCC and their proper management on the basis of currently available evidence. Evidence acquisition: We conducted a systematic analysis of the literature on 15th October 2010 by performing a search of Medical Subject Headings (MeSH) on PubMed using the words sorafenib, sunitinib, bevacizumab, everolimus, pazopanib, or temsirolimus combined with the MeSH term kidney neoplasms. Consideration for inclusion was given to articles providing data concerning (1) incidence and grading and (2) management of targeted therapy-related toxic effects. A separate search was conducted on PubMed to retrieve meta-analyses using each drug name and the word meta-analysis. Evidence synthesis: Hypertension, fatigue, bone marrow toxicity, skin toxicity, and gastrointestinal side-effects are common with the six targeted agents. Everolimus and temsirolimus are associated with immunosuppression, metabolic alterations, and interstitial pneumonitis, while sunitinib is associated with hypothyroidism. Recommendations for treating these conditions usually follow those for the general population because of the lack of experimental data in this setting (eg, for management of sunitinib-induced hypertension). Conclusions: The treating oncologist should try to manage side-effects associated with targeted therapy using supportive and pharmacologic interventions. Severe toxicity requires external specialist consultation and treatment suspension and/or dose reduction. Experimental data about the management of targeted therapy-related toxicity in mRCC is lacking and required in this setting.

I.F. = 8,843

N. citazioni = 99

149. **Porta C**, Paglino C. Editorial comment: 'Treatment of metastatic renal carcinoma patients with the combination of Gemcitabine, Capecitabine and Bevacizumab at a tertiary cancer center'. *BJU Int* 2011;107:747-8.

ABSTRACT - Treatment options for advanced RCC have dramatically multiplied in relatively few years, rendering a once orphan disease an 'overcrowded' one, with six molecularly targeted agents that have proved to benefit patients from different treatment settings within randomized controlled phase III trials. Despite these successes, advanced RCC should still be regarded as incurable. Besides the highly perceived problem of how best exploiting all the agents presently available, i.e., how best sequencing them, another emerging issue is that of those patients who have failed more than one anti-vascular endothelial growth factor (receptor) [VEGF(R)] inhibitor, as well as an mammalian target of rapamycin (mTOR) inhibitor. Indeed, with the exception of those 20–25% of unlucky patients with advanced RCC who unfortunately and dramatically will not respond to any of the available treatments, an increasing number of patients will ultimately receive several lines of active, molecularly targeted treatments. Consequently, also increasing is the number of patients who, after receiving three, four, or more lines of treatment, are still candidates to further treatment options. This intriguing preliminary report by Jonasch et al. suggests that a combination of the anti-VEGF monoclonal antibody bevacizumab plus two relatively old chemotherapeutic agents (i.e., capecitabine and gemcitabine) endowed with some (even though limited) activity against kidney cancer could benefit patients with advanced RCC, mainly from the intermediate- and poor-risk groups according to the Motzer's classification, already pre-treated also with tyrosine kinase inhibitors. Furthermore, the authors selected individuals to receive the combination of capecitabine, gemcitabine and bevacizumab based on the presence of aggressive tumour characteristics, including multiple negative risk factors, multiple sites of disease, sarcomatoid features, and refractoriness to anti-angiogenic therapies. The rationale for this courageous choice lies in some provocative preclinical works suggesting that remodelling of the endothelium occurring over time, with resistant subsets of endothelial cells replacing those who are dependent on VEGF signalling, being responsible for the development of resistance to anti-angiogenic agents. In such a hypothetical scenario, the use of agents that may alter epithelial tumour function and decrease paracrine factor secretion may potentiate the activity of anti-angiogenic therapy, or re-sensitise tumour cells (as well as endothelial cells) to their action. Furthermore, interest in the use of traditional cytotoxic chemotherapy in advanced RCC has bounced back because of a recent provocative finding from a phase III trial of immunotherapy; indeed, we have seen that the use of chemotherapy after a first progression on immunotherapy was significantly associated with a longer time from first progression to death. Should chemotherapy, eventually given in association with anti-VEGF(R) drugs, be revitalized in RCC in the peculiar setting of molecularly targeted agents-refractory patients? Realistically, it is too early to say, but the experience of Jonasch et al. deserves attention and, especially, warrants further studies.

I.F. = 3,19

N. citazioni = 3

150. **Porta C**, Paglino C, Imarisio I, Canipari C, Chen K, Neary M, Duh MS. Safety and treatment patterns of multikinase inhibitors in patients with metastatic renal cell carcinoma at a tertiary oncology center in Italy. *BMC Cancer* 2011;11:105-8.

ABSTRACT - Background: Multikinase inhibitors (MKIs) sunitinib and sorafenib have become a standard of care for metastatic renal cell carcinoma (mRCC). This study assessed safety and treatment patterns for these agents in a real-world clinical practice setting in Italy. Methods: A retrospective medical record review was performed at a tertiary oncology center in Italy. The study included MKI-naive non-trial patients [greater than or equal to]18 years old, with a histological diagnosis of mRCC, and who received sunitinib or sorafenib as first MKI during 9/2005-7/2008. Data were collected on adverse events (AEs), treatment modifications (discontinuations, interruptions, dose changes), and reasons for these modifications. Results: 145 patients were included; 85 received sunitinib and 60 received sorafenib as first-line MKI. Median treatment duration was 6.6 (sunitinib) and 5.8 (sorafenib) months. 97.6% and 70.0% of patients receiving sunitinib and sorafenib, respectively, experienced [greater than or equal to]1 AE; 27.1% and 31.7% had [greater than or equal to]1 grade 3/4 AE. The most common any grade AE for sunitinib was fatigue/asthenia (81.2%), followed by mucositis/stomatitis (58.8%) and decreased taste sensation (42.4%), while for sorafenib this was fatigue/asthenia (43.3%) followed by hand-foot syndrome (38.3%) and diarrhea (31.7%). Treatment discontinuation, interruption, and dose reduction due to AEs occurred in 11.8%, 23.5%, and 30.6%, respectively, of patients receiving sunitinib, and 5.0%, 23.3%, and 36.7%, respectively, of patients receiving sorafenib. Conclusions: In this retrospective study, most patients experienced [greater than or equal to]1 AE during first-line MKI treatment. AEs were reported frequently and resulted in treatment modifications in 40% of 3 patients receiving sunitinib and 45% of patients receiving sorafenib. These results suggest a need for additional effective and more tolerable treatments for mRCC.

I.F. = 3,153

N. citazioni = 29

151. Procopio G, Verzoni E, Bracarda S, Ricci S, Sacco C, Ridolfi L, **Porta C**, Miceli R, Zilembo N, Bajetta E. Sorafenib with Interleukin-2 vs Sorafenib alone in metastatic renal cell carcinoma: the ROSORC trial. *Br J Cancer* 2011;104:1256-61.

ABSTRACT - Background: preclinical investigations support combining sorafenib with IL-2 in the treatment of metastatic renal cell carcinoma (mRCC).

Methods: in this open-label, phase II study, 128 patients with mRCC were randomised to receive oral sorafenib, 400 mg twice daily, plus subcutaneous IL-2, 4.5 million international units (MIU) five times per week for 6 in every 8 weeks, or sorafenib alone. After enrolment of the first 40 patients, IL-2 dose was reduced to improve the tolerability. Results: after a median follow-up of 27 months, median progression-free survival (PFS) was 33 weeks with sorafenib plus IL-2, and 30 weeks with sorafenib alone (P=0.109). For patients receiving the initial higher dose of IL-2, median PFS was 43 weeks vs 31 weeks for those receiving the lower dose. The most common adverse events were asthenia, hand-foot syndrome, hypertension, and diarrhoea. Grade 3-4 adverse events were reported for 38 and 25% of patients receiving combination and single-agent treatment, respectively. Conclusion: the combination of sorafenib and IL-2 did not demonstrate improved efficacy vs sorafenib alone. Improvements in PFS appeared greater in patients receiving higher-dose IL-2.
I.F. = 4,831
N. citazioni = 61

152. Manchen E, Robert C, **Porta C**. Management of tyrosine kinase inhibitor-induced hand-foot skin reaction: viewpoints from the Medical Oncologist, Dermatologist, and Oncology Nurse. *J Support Oncol* 2011;9:13-23.

ABSTRACT - One significant toxicity associated with the anticancer tyrosine kinase inhibitors (TKIs) is hand-foot skin reaction (HFSR). We provide an overview of HFSR, emphasizing experience-based prevention techniques and nursing management strategies from the viewpoints of a medical oncologist, a dermatologist, and an oncology nurse. Supporting data include (1) published preclinical and phase I-III clinical studies and (2) published abstracts of phase II-III clinical trials of sorafenib and sunitinib. HFSR has been reported in up to 60% of patients treated with sorafenib or sunitinib. TKI-induced HFSR may lead to dose reductions or treatment interruptions and reduced quality of life. Symptoms of TKI-associated HFSR can be managed by implementing supportive measures and aggressive dose modification. Patients educated about HFSR can work with their health-care teams to proactively detect and help manage this cutaneous toxicity, thus preventing or reducing the severity of TKI-associated HFSR. Successful prevention and management of TKI-associated HFSR can help to ensure that patients achieve optimal therapeutic outcomes. Implementation of such measures may increase the likelihood that therapy is continued for the appropriate interval at an appropriate dose for each patient. Optimal management of TKI-associated HFSR is predicated on establishing appropriate partnerships amongmedical oncologists, dermatologists, oncology nurses, and patients.
I.F. = n.r.
N. citazioni = 36

153. **Porta C**, Pedrazzoli P, Paglino C. Is immunotherapy re-entering the kidney cancer arena from the back door? Considerations from the Phase I/II study of Siltuximab. *Immunotherapy* 2011;3:487-90.

ABSTRACT - Evaluation of: Rossi JF, Negrier S, James ND et al.: A Phase I/II study of siltuximab (CNTO 328), an anti-interleukin-6 monoclonal antibody, in metastatic renal cell cancer. Br. J. Cancer 103, 1154-1162 (2010). For years, immunotherapy was the mainstay of treatment for advanced kidney cancer. The recent development of molecularly targeted agents, and of antiangiogenic agents in particular, has completely changed this scenario, leaving immunotherapy with a minor role in treatment, if any. Recent insights in the mechanisms of resistance to these drugs suggest that the immune system could play a relevant role. In particular, IL-6 appears to cooperate with other growth factors in the recruitment of bone marrow-derived immune cells, ultimately leading to resistance to antiangiogenic agents. Furthermore, it is now clear that monoclonal antibodies actively interact with the immune system and show significant immune-modulating effects per se. Further translation research on this issue is much needed.
I.F. = 0,542
N. citazioni = 3

154. **Porta C**, Osanto S, Ravaud A, Climent MA, Vaishampayan U, White DA, Creel P, Dickow B, Fischer P, Gornell SS, Meloni F, Motzer RJ. Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma. *Eur J Cancer* 2011;47:1287-98.

ABSTRACT - Purpose: In April 2009, an expert group of 11 physicians and clinical nurses met to discuss the management of selected adverse events associated with the use of everolimus for the treatment of metastatic renal cell carcinoma (mRCC). Everolimus is an orally administered inhibitor of the mammalian target of rapamycin that recently received approval from the European Medicines Agency for the treatment of advanced RCC that has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy, and from the United States Food and Drug Administration for treatment of advanced RCC after failure of sorafenib or sunitinib. Before the approval of everolimus, no standard therapy existed for the treatment of mRCC after failure of VEGF-targeted therapy. RECORD-1 (Renal Cell cancer treatment with Oral RAD001 given Daily) was the pivotal multicenter, phase III, randomised, double-blind, placebo-controlled trial of everolimus that led to approval for patients with disease progression on or after treatment with VEGF-targeted agents. Safety data from RECORD-1 were reviewed by these clinicians, all of whom had experience using everolimus in patients with mRCC. Adverse events discussed were non-infectious pneumonitis, infections, stomatitis and metabolic abnormalities. Results: The outcome of this discussion is summarised here. Guidance for management of these adverse events is provided. Both clinicians and patients should be aware of the potential side-effects of everolimus and understand that these side-effects are manageable with standard care to optimise patient benefit.
I.F. = 4,944
N. citazioni = 121

155. Santini D, Schiavon G, Vincenzi B, Gaeta L, Pantano F, Russo A, Ortega C, **Porta C**, Galluzzo S, Armento G, La Verde N, Caroti C, Treilleux I, Ruggiero A, Perrone G, Addeo R, Clezardin P, Muda AO, Tonini G. Receptor activator of NF-κB (RANK) expression in primary tumors associates with bone metastasis occurrence in breast cancer patients. *PLoS One* 2011;6:e19234.

ABSTRACT - Background: Receptor activator of NFκB (RANK), its ligand (RANKL) and the decoy receptor of RANKL (osteoprotegerin, OPG) play a pivotal role in bone remodeling by regulating osteoclasts formation and activity. RANKL stimulates migration of RANK-expressing tumor cells in vitro, conversely inhibited by OPG. Materials and Methods: We examined mRNA expression levels of RANKL/RANK/OPG in a publicly available microarray dataset of 295 primary breast cancer patients. We next analyzed RANK expression by immunohistochemistry in an independent series of 93 primary breast cancer specimens and investigated a possible association with clinicopathological parameters, bone recurrence and survival. Results: Microarray analysis showed that lower RANK and high OPG mRNA levels correlate with longer overall survival (p=0.0078 and 0.0335, respectively) and disease-free survival (p=0.059 and 0.0402, respectively). Immunohistochemical analysis of RANK showed a positive correlation with the development of bone metastases (p=0.023) and a shorter skeletal disease-free survival (SDFS, p=0.037). Specifically, univariate analysis of survival showed that "RANK-negative" and "RANK-positive" patients had a SDFS of 105.7 months (95% CI: 73.9-124.4) and 58.9 months (95% CI: 34.7-68.5), respectively. RANK protein expression was also associated with accelerated

bone metastasis formation in a multivariate analysis (p=0.029). Conclusions: This is the first demonstration of the role of RANK expression in primary tumors as a predictive marker of bone metastasis occurrence and SDFS in a large population of breast cancer patients.
I.F. = 4,411
N. citazioni = 1

156. **Porta C**, Procopio G, Cartenì G, Sabbatini R, Bearz A, Chiappino I, Ruggeri EM, Re GL, Ricotta R, Zustovich F, Landi L, Calcagno A, Imarisio I, Verzoni E, Rizzo M, Paglino C, Guadalupi V, Bajetta E. Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma (RCC): an Italian multicentre retrospective analysis of 189 patient cases. *BJU Int* 2011;108(8 Pt 2):E250-7.

ABSTRACT - Objective: To conduct a retrospective, multicentre, cohort analysis to assess the sequential use of the tyrosine kinase inhibitors (TKIs) sorafenib and sunitinib. Patients and Methods: Records of 189 patients with renal-cell carcinoma (RCC) who were treated with sorafenib and sunitinib sequentially between March 2004 and April 2009 at 12 Italian study centres were analysed. Patients were treated under European Expanded Access Programmes or, following market approval, in general clinical practice. Interventions were sorafenib (800 mg/day) and sunitinib (50 mg every day; 4 weeks on and 2 weeks off). Progression-free survival (PFS) during treatment with the first and second TKI was evaluated. Results: In all, 99 patients were treated with sunitinib followed by sorafenib (SuSo) and 90 were treated with sorafenib followed by sunitinib (SoSu); 104 (55%) patients had received prior systemic therapy, mostly with cytokines. The median (range) PFS on the first TKI was similar between treatment groups [sorafenib 8.4 (1.1-28.9) months; sunitinib 7.8 (0.5-30.4) months; hazard ratio (HR) 1.05, 95% confidence interval (CI) 0.78-1.40, p=0.758]. Multivariate analysis showed that good Memorial Sloan-Kettering Cancer Center status was associated with increased PFS. After the second TKI, patients in the SoSu group had a longer median PFS than those in the SuSo group (7.9 months vs 4.2 months, respectively; HR 0.54, 95% CI 0.39-0.74, p<0.001). Multivariate analysis showed only treatment and Eastern Cooperative Oncology Group performance status (and not age, gender, study centre or previous treatment) were significantly associated with duration of PFS. Conclusions: Our findings suggest a limited cross-resistance between sorafenib and sunitinib and that the sequence SoSu may result in a longer combined PFS than SuSo. This is the largest retrospective study to date, though its findings are limited in part by the retrospective nature.
I.F. = 3,19
N. citazioni = 69

157. Ravasio R, Ortega C, Sabbatini R, **Porta C**. Bevacizumab plus interferon-α versus sunitinib for first-line treatment of renal cell carcinoma in Italy: a cost-minimization analysis. *Clin Drug Investig* 2011;31:507-17.

ABSTRACT - Background: Renal cell carcinoma (RCC) is the most common form of kidney cancer. Immunotherapy with interferon-α (IFNα) and interleukin-2 (IL-2) has been the historical therapy of choice for the treatment of locally advanced or metastatic RCC prior to the more recent development of targeted therapies, including sunitinib and bevacizumab (combined with IFNα). Clinically and statistically significant advantages have been shown with both sunitinib and the combination of bevacizumab + IFNα versus IFNα alone in the treatment of advanced or metastatic RCC. The present study evaluated the incremental costs of bevacizumab + IFNα versus sunitinib for the first-line treatment of advanced or metastatic RCC assuming similar efficacy for these treatments. Methods: The efficacy profiles of bevacizumab + IFNα or sunitinib alone have been shown (indirectly) to be similar in patients with RCC; indeed, median progression-free survival (PFS) with either treatment is in the 10- to 11-month range. Therefore, a cost-minimization analysis was performed, focusing on direct medical costs only (drugs, administration and management of adverse events). The analysis considered the perspective of the Italian National Health Service (NHS), comparing the cost of bevacizumab (10 mg/kg) plus IFNα (9, 6 or 3 million IU [MIU]) versus sunitinib (50 mg) as first-line therapies for advanced or metastatic clear-cell RCC. The average cost per treated patient (year 2010 values) was assessed for the two treatment options at 11 months (median PFS). Results: Assuming a PFS of 11 months for both treatment options, bevacizumab + IFNα (9 MIU) would be a lower cost strategy (cost savings of €2052 per patient) than sunitinib. This difference arises mainly from the reduction in the acquisition cost of bevacizumab to the NHS (risk-sharing agreement). The cost advantages for bevacizumab would increase in parallel with a reduction in IFNα dosing; for example, with IFNα 6 MIU the corresponding cost savings would be €4185, and with 3 MIU the cost advantage would be €6320 per patient. Conclusion: This analysis suggests that bevacizumab + IFNα is a cost-saving alternative to sunitinib in the treatment of first-line metastatic RCC. Its superior safety profile also meant that the cost of managing adverse events was lower for bevacizumab + IFNα than for sunitinib.
I.F. = 1,622
N. citazioni = 12

158. Escudier B, Osanto S, Ljungberg B, **Porta C**, Wagstaff J, Mulders P, Gore M, Bex A, Bellmunt J, Bracarda S, Franklin A, Honoré PH, Ravaud A, Steijn JV, Aziz Z, Akaza H. Multidisciplinary management of metastatic renal cell carcinoma in the era of targeted therapies. *Cancer Treat Rev* 2011;38:127-32.

ABSTRACT - The use of targeted agents to treat metastatic renal cell carcinoma (mRCC) has significantly extended progression-free and overall survival but raises issues relating to the long-term delivery of care and the sustained monitoring of efficacy and toxicities, certain of which have not previously been experienced. In this paper, an expert group of medical oncologists, urologists and oncology nurses and pharmacists review and make informal recommendations on the multidisciplinary management of mRCC in the light of progress made and problems that have arisen. Decentralisation of care, with a shift in emphasis from large to small hospitals and possibly to the community, may offer advantages of cost and convenience. However, the major responsibility for care should continue to lie with clinicians (either medical oncologists or urologists) with extensive experience in mRCC, assisted by specialist nurses, and working in centres with facilities adequate to monitor efficacy and manage toxicities. That said, the extended survival of patients emphasises the importance of compliance and the long-term prevention, detection and management of side effects. Much of this will take place in the community. There is therefore a need for multidisciplinary working to extend beyond specialist centres to include general practitioners, community nurses and pharmacists. Although this paper focuses on mRCC, many of the considerations discussed are also relevant to the management of more common solid tumours in the era of targeted therapy.
I.F. = 6,811
N. citazioni = 7

159. **Porta C**, Paglino C, Imarisio I, Ganini C, Pedrazzoli P. Immunological effects of multikinase inhibitors for kidney cancer: a clue for integration with cellular therapies? *J Cancer* 2011;2:333-8.

ABSTRACT - The multikinase inhibitors Sunitinib and Sorafenib not only inhibit angiogenesis and tumor growth, but also have the potential of interacting with the function of the immune system. Presently available data seem to suggest that Sorafenib may exert immune suppressive effects, whilst the effects of Sunitinib are not so clear, being immune stimulatory in the vast majority – but not all – the studies reported. Trials of combination of these multikinase inhibitors with different types of immune manipulation – and cel-

lular therapies in particular – should be rationally designed taking into account all these complex effects, which ultimately deserve further insights.
I.F. = n.r.
N. citazioni = 34

160. Ridolfi L, Bertetto O, Santo A, Naglieri E, Lopez M, Recchia F, Lissoni P, Galliano M, Testore F, **Porta C**, Maglie M, Dall'Agata M, Fumagalli L, Ridolfi R. Chemotherapy with or without low-dose interleukin-2 in advanced non-small cell lung cancer: results from a phase III randomized multicentric trial. *Int J Oncol* 2011;39:1011-7.

ABSTRACT - Non-small cell lung cancer (NSCLC) is associated with IL-2-dependent cell-mediated immunodeficiency. As IL-2 is the main lymphocyte growth factor, a phase III randomized multicenter trial was conducted to evaluate the impact of subcutaneous low-dose IL-2 added to standard chemotherapy (CT) on overall survival (OS) in advanced NSCLC patients. Patients (n=241) with histologically confirmed stage IIIb or IV non-operable NSCLC underwent stratified randomization on the basis of center, ECOG PS, stage of disease and percentage of weight loss. Patients received gemcitabine (1000 mg/m2) on days 1 and 8 + cisplatin (100 mg/m2) on day 2 every 21 days for a maximum of 6 cycles [chemotherapy (CT) arm]. In the CT+IL-2 arm, patients also received low-dose subcutaneous IL-2 3,000,000 IU/die on days 3-5, 9-11, 15-17. The study had 90% power to detect a 20% absolute increase in 1-year OS with 118 patients/arm. An overall response (OR) rate of 12.8% (14% in the CT+IL-2 arm and 11.4% in CT arm) was observed. Stable disease was 70 and 66.7%, and progressive disease 16 and 21.8% in the CT+IL-2 and CT arms, respectively. No differences in response were found in any subgroup analysis. At a median follow-up of 32 months, 1-year OS was 45% for the CT+IL-2 arm vs. 51% for the CT arm (p=0.456 log-rank). Median progression-free survival was 6.6 months in the CT+IL-2 arm vs. 6.9 months in the CT arm (p=0.573, log-rank). A higher number of grade 4 toxicities were reported with CT+IL-2. The most common grade ≥3 adverse events were gastrointestinal toxicity (mainly nausea and diarrhea) and myelosuppression. No relevant differences in clinical outcome were observed from the addition of IL-2 to CT. Future studies investigating the role of T-regulators in chemoimmunotherapeutic regimens could be performed.
I.F. = 2,571
N. citazioni = 29

161. **Porta C**. Entropy increases in kidney cancer treatment, but a bit of simplicity may emerge from chaos. *Eur Urol* 2011;60:1171-2 (Editorial).

We know from the second law of thermodynamics that the spontaneous evolution of an isolated system can never lead to a decrease of its entropy (ie, its intrinsic disorder), as entropy always increases as long as the system evolves. Even though kidney cancer (the "system") cannot be regarded as a purely isolated system, and even though we are actively attempting to modify it with all our therapeutic weapons, it is clear that this system has evolved dramatically in the past few years and that complexity (if not entropy/disorder) is the direct consequence of this evolution. What has happened in the past 6 years in the field of kidney cancer is both exceptional and unprecedented. Starting in 2005, when the results of the sorafenib TARGET trial were first disclosed at the American Society of Clinical Oncology (ASCO) annual meeting, almost each subsequent year saw the presentation of one novel drug or more for this once-orphaned disease. Subsequent to the recent presentation of the axitinib trial results, seven molecularly targeted agents have proven their activity against this tumor within large, randomized, phase 3 trials: the four multikinase inhibitors sorafenib, sunitinib, pazopanib, and axitinib; the anti–vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (given together with interferon-α [IFN-α]); and the two mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus. This list excludes compounds likely to enter the field soon (eg, tivozanib). The picture is complicated further by the lack of randomized, head-to-head, comparative trials and the limited time we had to synthesize all of the data we have gathered. As a measure of such a huge complexity, several issues remain still open, none trivial: 1) the ideal first-line treatment, 2) the role of combinations, and especially 3) how to better sequence the drugs we now have to maximize the clinical benefit for the vast majority of our patients. As far as the first-line treatment for patients with good or intermediate prognosis (for poor prognosis patients, the situation seems a little more clear), sunitinib is by far the most commonly prescribed drug. However, phase 3 data suggest that a similar benefit, at least in terms of progression-free survival (PFS), also may be achieved with bevacizumab plus IFN-α or with pazopanib. In addition, recent data, although not coming from phase 3 trials, seem to challenge these few certainties. The results of the TORAVA randomized phase 2 trial—the only first-line comparison trial presently available—showed that bevacizumab plus IFN-α performed definitively better than sunitinib, especially in terms of resulting PFS. Several drawbacks from the design of this phase 2 study may account for such a difference, but the data—and the relative doubts—remain. As for the combination of bevacizumab plus IFN-α, the recently presented results of the BEVLiN single-arm phase 2 trial are very provocative and, in some ways, in concordance with a well-known subanalysis of the AVOREN trial. This concordance suggests that the combination of bevacizumab with low doses of IFN-α may lead to enhanced (although not well understood mechanistically) antitumor activity. Sorafenib lost almost all of its attractiveness in first-line treatment after it proved not to be superior to IFN-α in a highly criticized randomized phase 2 trial. However, it recently proved able—also within a randomized phase 2 trial—to achieve PFS of 9 mo, almost doubling the PFS reported in the first-line trial against IFN-α. This finding moved sorafenib closer to the other treatment options commonly used in first-line treatment. Again, huge biases exist but also the clear-cut feeling that we simply do not know all that we should about these drugs. As far as combinations of molecularly targeted agents, the few data we have from several phase 1 and 2 trials and the above-mentioned randomized phase 2 TORAVA trial, suggest that, besides economical issues, tolerability appears to be the most relevant limitation of such an approach. What to do after the failure of a first-line anti–VEGF receptor (anti-VEGFR) therapy is still a matter of debate. Physicians are lined up in opposite camps, the supporters of shifting to an mTOR inhibitor facing those convinced by the opportunity of continuing inhibition of the same pathway using a different multikinase inhibitor. In this issue of European Urology, Busch and colleagues have added another piece of evidence (albeit retrospective) to this already long-lasting quarrel. Their data show no relevant differences in terms of PFS (or overall survival) between the use of an mTOR inhibitor and a multikinase inhibitor after failure of a first multikinase inhibitor. This finding is absolutely in agreement with other similar reports that clearly suggest that, besides those unfortunate patients who will not respond to anything from the very beginning (the primary refractory patients), all others may achieve some kind of benefit from almost all available drugs, and this benefit may be enhanced by the use of the higher number of possible of agents in sequence, even though the "ideal" sequence is still unknown. Second-line treatment was a particular object of controversy, despite several attempts to identify which patients will benefit from which second-line treatment, with the ultimate aim of helping physicians make reasonable choices in the real world of everyday clinical practice. Interestingly, the mainly retrospective reports suggesting that continuous inhibition of the VEGFR pathway could be of benefit for advanced kidney cancer patients may not contradict the results of the prospective, randomized, phase 3 RECORD-1 trial, which demonstrated the activity of the mTOR inhibitor everolimus after one (or even two) multikinase inhibitors. The peculiar molecular pathogenesis of kidney cancer is heavily dependent on angiogenesis, due to the frequent mutation of the von Hippel-Lindau tumor suppressor gene in sporadic cases. This makes it possible that presently available mTOR inhibitors (which indeed are just TORC1 complex inhibitors) could be active in this cancer due to their indirect inhibition of angiogenesis. But is this really true in clinical practice? Nobody really knows. Once again, apparently chaos is still ruling the system. Physics tells us that chaos can be, and often is, a property of very simple systems, meaning that simple questions usually have complicated answers. However, our only way out could be by turning this concept upside-down: In a complex system (eg, kidney cancer) we should look for an easy—and credible—answer to our questions.

Such an answer is probably Chris Ryan's "simplified algorithm" statement, courageously made during the educational program at the 2010 ASCO annual meeting: "Choose any agent you want. Use it well." This is a statement on which we should all agree. It is a shortcut, for sure, but a smart one and also a bit of simplicity to move out from the fogs of chaos.
I.F. = 8,843
N. citazioni = 8

162. Mickisch GH, Schwander B, Escudier B, Bellmunt J, Maroto JP, **Porta C**, Walzer S, Siebert U. Indirect treatment comparison of bevacizumab + interferon-α-2a vs tyrosine kinase inhibitors in first-line metastatic renal cell carcinoma therapy. *Clinicoeconomics Outcomes Res* 2011;3:19-27.

ABSTRACT - Background: The vascular endothelial growth factor inhibitor bevacizumab (BEV) given in combination with interferon-α-2a (IFN), and the tyrosine kinase inhibitors (TKIs) sunitinib (SUN) and pazopanib (PAZ), have all shown significant increase in progression-free survival (PFS) in first-line metastatic renal-cell carcinoma (mRCC) therapy. These targeted therapies are currently competing to be primary choice; hence, in the absence of direct head-to-head comparison, there is a need for valid indirect comparison assessment. Methods: Standard indirect comparison methods were applied to independent review PFS data of the pivotal Phase III trials, to determine indirect treatment comparison hazard-ratios (HR) with 95% confidence intervals (95% CI). As BEV+IFN and SUN have been compared to IFN, indirect comparison was enabled by the common IFN comparator arms. As PAZ was compared to placebo (PLA), a connector trial (IFN vs PLA) was required for the indirect comparison to BEV+IFN. Sensitivity analyses taking into account real-life influence of patient compliance on clinical outcomes were performed. Results: The indirect efficacy comparison resulted in a statistically non-significant PFS difference of BEV+IFN vs SUN (HR: 1.06; 95% CI: 0.78-1.45; p = 0.73) and of BEV+IFN vs PAZ (range based on different connector trials; HR: 0.74-1.03; p = 0.34-0.92). Simulating real-life patient compliance and its effectiveness impact showed an increased tendency towards BEV+IFN without reaching statistical significance. Conclusions: There is no statistically significant PFS difference between BEV+IFN and TKIs in first-line mRCC. These findings imply that additional treatment decision criteria such as tolerability and therapy sequencing need to be considered to guide treatment decisions.
I.F. = n.r.
N. citazioni = 10

163. Ganini C, Rovereto B, **Porta C**. Surgery and target agents for renal cell carcinoma treatment: the path between proper interaction. *Urologia* 2011;78(Suppl.):9-15.

ABSTRACT - Background: Renal cell carcinoma accounts for 3% of all solid tumors and currently causes about 3,500 deaths/year in the UK. Once an orphan disease, it has undergone an impressive change in its natural history with an improvement in overall survival, thanks to the development of new target agents. Introduction: In its management, renal cell carcinoma has been treated with both surgical and medical approaches. Nowadays, many more drugs are available, especially in the metastatic setting, so that we should reconsider the peculiar role of surgery and its interaction with target agents. Conclusions: Cytoreductive nephrectomy still plays a major role in the management of the disease, though no really solid data have been still obtained. Adjuvant and neoadjuvant settings, instead, are still under evaluation, especially new adjuvant therapies involving the numerous target agents we have. Finally, metastasectomy has a controversial role, with some evidence of more efficacy than the medical treatment, though it shows too many biases to be considered certain. The picture that comes out suggests a complex frame, in which we have great power to act, but in which we need to better comprehend the interactions that could be created between surgery and medical therapies, to achieve an optimal multimodal treatment for renal cell carcinoma.
I.F. = n.r.
N. citazioni = 1

164. Patard JJ, **Porta C**, Wagstaff J, Gschwend JE. Optimizing treatment for metastatic renal cell carcinoma. *Expert Rev Anticancer Ther* 2011;11:1901-11.

ABSTRACT - With the advent of targeted antiangiogenic therapies for renal cell carcinoma (RCC), the prognosis for patients with locally advanced or metastatic disease has significantly improved. Indeed, the results of several randomized clinical trials have demonstrated that targeted therapies, such as tyrosine kinase inhibitors (TKIs), provide superior efficacy and tolerability compared with traditional cytokine-based treatments. However, TKI therapy is still associated with significant toxicities related to off-target inhibition that are detrimental to patient quality of life. The results of ongoing head-to-head trials will determine how these agents compare with each other in terms of efficacy, and whether TKIs that interact with fewer off-target kinases have improved tolerability profiles. Furthermore, examining how these agents could be integrated with surgery to provide a multimodal approach to the treatment of metastatic RCC could further improve the outlook for RCC patients.
I.F. = 2,976
N. citazioni = 5

165. **Porta C**. The European Multidisciplinary Cancer Congress (ECCO 16, ESMO 36 and ESTRO 30). *Future Oncol* 2012;8:13-5.

ABSTRACT - For years, both the European Cancer Organization (ECCO) and the European Society of Medical Oncology (ESMO) congresses have been alternatively held every 2 years, someway in competition with one another. Finally, starting in 2009, ECCO and ESMO launched the ECCO/ESMO joint European Multidisciplinary Cancer Congress, which, this year, has also been joined by the European Society for Therapeutic Radiology and Oncology (ESTRO), with the aim of promoting the need for a multidisciplinary approach to cancer. Indeed, according to the organizers, this is the only congress in Europe that covers the entire spectrum of cancer, ranging from the basic science and translational research, to prevention, treatment, nursing and supportive care. Continuing a positive trend that dates back to the very first ECCO/ESMO joint meeting in Berlin, Germany, breakthrough studies were first presented at the European meeting this year, once again clearly showing all the potentialities of an unified European Oncological Community. Here are the studies that interested me the most at the meeting.
I.F. = 2,455
N. citazioni = 2

166. **Porta C**, Bracarda S. 3rd Pavia international symposium on advanced kidney cancer. *Expert Opin Pharmacother* 2012;13:445-53.

ABSTRACT - Kidney cancers' natural history has radically changed in the past few years, due to the development of novel targeted agents. Despite these improvements, several unanswered questions still remain on the table, regarding the best first-line treatment, the ideal sequence of treatments, the management of specific subgroups of patients (e.g., elderly patients or those with comorbidities) and the relevance of prognostic factors, among many

others. To foster discussions among clinicians and investigators working in this field, and to exchange different viewpoints concerning the newest advances in kidney cancer pathogenesis and treatment, the 3rd Pavia International Symposium on Advanced Kidney cancer was held in Pavia (Italy) between 30 June and 1 July 2011. The aim of this report is to summarize the most significant advances in the different disciplines applied to advanced kidney cancer, which were presented and discussed during the meeting, and how these advances will be changing the perspective of patients with this disease.

I.F. = 2.403

167. **Porta C**, Tortora G, Linassier C, Papazisis K, Awada A, Berthold D, Maroto JP, Powles T, De Santis M. Maximising the duration of disease control in metastatic renal cell carcinoma with targeted agents: an expert agreement. *Med Oncol* 2012;29:189-207**.**

ABSTRACT - With six targeted agents approved (sorafenib, sunitinib, temsirolimus, bevacizumab [+ interferon], everolimus and pazopanib), many patients with metastatic renal cell carcinoma (mRCC) will receive multiple therapies. However, the optimum sequencing approach has not been defined. A group of European experts reviewed available data and shared their clinical experience to compile an expert agreement on the sequential use of targeted agents in mRCC. To date, there are few prospective studies of sequential therapy. The mammalian target of rapamycin (mTOR) inhibitor everolimus was approved for use in patients who failed treatment with inhibitors of vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFR) based on the results from a Phase III placebo-controlled study; however, until then, the only licensed agents across the spectrum of mRCC were VEGF(R) inhibitors (sorafenib, sunitinib and bevacizumab + interferon), and as such, a large body of evidence has accumulated regarding their use in sequence. Data show that sequential use of VEGF(R) inhibitors may be an effective treatment strategy to achieve prolonged clinical benefit. The optimal place of each targeted agent in the treatment sequence is still unclear, and data from large prospective studies are needed. The Phase III AXIS study of second-line sorafenib vs. axitinib (including post-VEGF(R) inhibitors) has completed, but the data are not yet published; other ongoing studies include the Phase III SWITCH study of sorafenib-sunitinib vs. sunitinib-sorafenib (NCT00732914); the Phase III 404 study of temsirolimus vs. sorafenib post-sunitinib (NCT00474786) and the Phase II RECORD 3 study of sunitinib-everolimus vs. everolimus-sunitinib (NCT00903175). Until additional data are available, consideration of patient response and tolerability to treatment may facilitate current decision-making regarding when to switch and which treatment to switch to in real-life clinical practice.

I.F. = 2,21

N. citazioni = 17

168. **Porta C**, Powles T. Sequential therapy in metastatic renal cell carcinoma: what comes next? *Med Oncol* 2012;29:1914-5.

ABSTRACT - Metastatic renal cell carcinoma (mRCC) is a fast-moving therapeutic field with multiple targeted agents approved and many more in development. In our expert agreement article, we evaluated available data together with our clinical experience to consider how we might optimize using targeted therapies in sequence, emphasizing the need continually to address the question, "what comes next?" Crucially, new phase III data presented at the American Society of Clinical Oncology (ASCO) 2011 annual meeting provide level 1 evidence that patients can receive continued clinical benefit when VEGF-targeted tyrosine kinase inhibitors (TKIs) are used sequentially. The randomized, open-label, phase III AXIS study compared second-line axitinib 5 mg bid (titrated to 7, then 10 mg bid, if tolerated) with sorafenib 400 mg bid in 723 patients with mRCC, more than half of whom had previously received the TKI sunitinib (n = 389). The study met the primary endpoint of superiority for axitinib, with median PFS 6.7 months, compared with 4.7 months for sorafenib (P < 0.0001). Median PFS was lower in post-sunitinib than in the total patient population for both axitinib (4.8 months) and sorafenib (3.4 months; P < 0.05 versus axitinib). Notably, and as discussed in our expert agreement article, this phenomenon was also seen in the phase III RECORD-1 study of everolimus in patients previously treated with sorafenib and/or sunitinib—prior sunitinib was prognostic of lower PFS and overall survival in a multivariate analysis. The AXIS and RECORD-1 data, therefore, suggest that pre-treatment with effective VEGF-TKI therapy, such as sunitinib, has a detrimental effect on subsequent outcome with both VEGF-TKI therapy and mTOR inhibition. Therefore, cross-resistance between these two classes may be apparent. A further noteworthy publication at ASCO 2011, from Dr. Mhd Al-Marrawi on behalf of the International mRCC Database Consortium, showed that response to initial TKI therapy did not predict response to further TKI therapy. This study did not report whether the sequence of TKIs received was important, but this question could be addressed in part by performing a similar analysis using the AXIS data—i.e., were ORR/stable disease/PFS with axitinib or sorafenib related to ORR/stable disease/PFS with sunitinib and were there differences between axitinib and sorafenib in this regard? Overall, the findings from AXIS, RECORD-1, and the International mRCC Database Consortium do not support the hypothesis that switching mode of action from VEGF inhibition to mTOR is the logical first step in the face of VEGF resistance. Re-challenging with VEGF-TKI therapy appears to be more attractive as the first treatment manipulation at present. Switching to mTOR as 3rd line or later, which is supported by randomized phase III data, gives us multiple lines of therapy with proven efficacy. On a further note, though it may be tempting to compare the efficacy data from AXIS with those for RECORD-1, there are a number of key differences between the studies, including patient population and study design, and so such comparisons are fundamentally flawed. Patient-reported outcomes from AXIS were also presented at ASCO. Dr. David Cella showed that health-related quality of life (HRQoL) was similar for sorafenib and axitinib, based on Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI)-15 and FKSI disease-related symptoms (DRS) scores. This similarity was observed, despite differences between sorafenib and axitinib in terms of their toxicity profiles—as reported by Dr. Brian Rini at ASCO, grade 3/4 AEs that were numerically more frequent in sorafenib-treated patients than in axitinib-treated patients were hand-foot syndrome (16% vs. 5%) and rash (4% vs. <1%), and grade 3/4 AEs numerically more frequent with axitinib than with sorafenib included diarrhea (11% vs. 7%), hypertension (16% vs. 11%), and fatigue (11% vs. 5%; for all AEs, the significance of between-treatment differences was not reported). All AEs can be troublesome, but their impact may vary between patients based on their individual needs and disease characteristics. For example, elderly patients, who make up the majority of patients with mRCC, are particularly prone to suffer from AEs that are usually more tolerated by younger patients (e.g., fatigue), reiterating the need for a patient-focused approach to treatment. While the AXIS data answer some important questions and support the use of sequential TKI therapy in mRCC, there are still some unanswered considerations. These include the choice between VEGF-targeted therapy and an mTOR inhibitor in patients who have progressed on previous VEGF-targeted treatment, the identification of specific patients who benefit from each targeted agent, and what to use in axitinib-refractory disease. The implications for clinical practice of findings from ongoing studies will be of great interest.

I.F. = 2,21

N. citazioni = 1

169. **Porta C**, Szczylik C, Escudier B. Combination or sequencing strategies to improve the outcome of metastatic renal cell carcinoma patients: A critical review. *Crit Rev Oncol Hematol* 2012;82:323-7.

ABSTRACT - The introduction of novel anti-angiogenic therapies has greatly improved the outcome of patients with metastatic renal cell carcinoma (mRCC). The use of these therapies in combination or sequentially is propo-

sed to provide greater efficacy. We have reviewed completed and ongoing clinical trials in mRCC that have reported efficacy and/or safety data of novel therapies used in combination or sequentially. Bevacizumab appears to be a useful partner when combined with interferon (IFN), while controversial results have been reported when combined with temsirolimus and everolimus. Other combinations appear to have unacceptable tolerability or require dose or schedule optimization. Sequencing data provide a clear indication that multiple lines of treatment may extend survival. The 'ideal' sequence, however, is still unknown. In conclusion, novel therapies used in combination or sequentially have potential to provide optimised treatment and patient outcomes in mRCC. The results from ongoing/planned trials are expected to help shape future therapy.

I.F. = 4,689

N. citazioni = 31

170. Calvo E, Escudier B, Motzer RJ, Oudard S, Hutson TE, **Porta C**, Bracarda S, Grünwald V, Thompson JA, Ravaud A, Kim D, Panneerselvam A, Anak O, Figlin RA. Everolimus in metastatic renal cell carcinoma: subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. *Eur J Cancer* 2012;48:333-9.

ABSTRACT - Introduction - In the phase III RECORD-1 trial (ClinicalTrials.gov: NCT00410124), patients with metastatic renal cell carcinoma (mRCC) who progressed on previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) therapy were randomised 2:1 to everolimus 10mg once daily (n=277) or placebo (n=139). Median progression-free survival (PFS) was 4.9 months with everolimus and 1.9 months with placebo (hazard ratio [HR], 0.33; p <.001). This preplanned, prospective sub-analysis evaluated PFS benefit of everolimus versus placebo in patients who had previously received 1 or 2 VEGFr-TKIs. Patients and Methods - Median PFS was estimated using the Kaplan-Meier method, and Cox proportional hazards model was used to analyse differences in PFS. Results - All patients (100%) received ≠ 1 previous VEGFr-TKI; 26% of patients received 2 previous VEGFr-TKIs. Among patients who received 1 previous VEGFr-TKI, median PFS was 5.4 months with everolimus and 1.9 months with placebo (HR, 0.32; 95% confidence interval [CI], 0.24-0.43; p <.001). Among patients who received 2 previous VEGFr-TKIs, median PFS was 4.0 months with everolimus and 1.8 months with placebo (HR, 0.32; 95% CI, 0.19-0.54; p <.001). The everolimus safety profile was similar for both groups. Conclusions - Everolimus was associated with prolonged PFS relative to placebo in patients who received 1 or 2 previous VEGFr-TKIs. Patients who received only 1 previous VEGFr-TKI had apparently longer PFS with everolimus in reference to those who received 2 previous VEGFr-TKIs. These results support the use of everolimus as the standard of care in patients who fail initial VEGFr-TKI therapy.

I.F. = 4,944

N. citazioni = 105

171. **Porta C**, Calvo E, Climent MA, Vaishampayan U, Osanto S, Ravaud A, Bracarda S, Hutson TE, Escudier B, Grünwald V, Kim D, Panneerselvam A, Anak O, Motzer RJ. Efficacy and safety of Everolimus in elderly patients with metastatic renal cell carcinoma: an exploratory analysis of the outcomes of elderly patients in the RECORD-1 trial. *Eur Urol* 2012;61:826-33.

ABSTRACT - Background: Elderly patients with metastatic renal cell carcinoma (mRCC) may require special treatment considerations, particularly when comorbidities are present. An understanding of the efficacy and safety of targeted agents in elderly patients with mRCC is essential to provide individualized therapy. Objective: To evaluate the efficacy and safety of everolimus in elderly patients (those 65 and 70 yr of age) enrolled in RECORD-1. Design, setting, and participants: The multicenter randomized RECORD-1 phase 3 trial (Clinicaltrials.gov identifier, NCT00410124; http://www.clinicaltrials.gov) enrolled patients with mRCC who progressed during or within 6 mo of stopping sunitinib and/or sorafenib treatment (n = 416). Intervention: Everolimus 10 mg once daily (n = 277) or placebo (n = 139) plus best supportive care. Treatment was continued until disease progression or unacceptable toxicity. Measurements: Median progression-free survival (PFS), median overall survival (OS), and time to deterioration in Karnofsky performance status (TTD-KPS) were assessed using the Kaplan-Meier method; the log-rank test was used to compare treatment arms. Other outcomes evaluated included reduction in tumor burden, overall response rate, and safety. Results and limitations: In RECORD-1, 36.8% of patients were 65 yr and 17.5% were 70 yr of age. PFS, OS, TTD-KPS, reduction in tumor burden, and ORR were similar in the elderly and the overall RECORD-1 population. Everolimus was generally well tolerated in elderly patients, and most adverse events were grade 1 or 2 in severity. The toxicity profile of everolimus was generally similar in older patients and the overall population; however, peripheral edema, cough, rash, and diarrhea were reported more frequently in the elderly regardless of treatment. The retrospective nature of the analyses was the major limitation. Conclusions: Everolimus is effective and tolerable in elderly patients with mRCC. When selecting targeted therapies in these patients, the specific toxicity profile of each agent and any patient comorbidities should be considered.

I.F. = 8,843

N. citazioni = 52

172. **Porta C**, Paglino C, Imarisio I. Sorafenib rechallenge in metastatic renal cell carcinoma (Editorial Comment). *BJU Int* 2012;110(Pt B):E235.

Nozawa et al . report on the activity of Sorafenib rechallenge in patients with advanced RCC. Their data, even though retrospective and therefore intrinsically biased, confirm those of another report, suggesting that rechallenging patients with the vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFRTKI) sunitinib could help achieve a further survival benefit. At first sight, their results could be regarded as just more retrospective observations, potentially useful (not taking into account local regulatory issues) only in those countries where not all the novel agents are
available, or after their use, in those patients who are still clinically suitable for further treatments. Yet, if we take these data together with the recently published results of the AXIS trial, which showed the activity of axitinib, another VEGFR-TKI, as a second-line treatment (mainly, but not exclusively, after first-line sunitinib) and also with the retrospective series of the International Metastatic RCC Database Consortium, suggesting that VEGFR-TKI primary-refractory patients will achieve no further benefit from either changing TKI, or shifting to an mTOR inhibitor (with the latter option being even less efficaceous), a couple of key questions are raised. Firstly, how long should we continue to inhibit the VEGF/VEGFRs pathway and, secondly, and equally importantly, does shifting from a VEGFR-TKI to an mTOR inhibitor really mean changing the mechanism of action? The presently available data suggest that continuing to inhibit angiogenesis is a smart strategy in RCC, and that, shifting from a VEGFR-TKI to a mTOR inhibitor, does not necessarily mean hitting another target. Indeed, we should always take into account that in RCC, a neoplasm that depends heavily on VEGF-driven angiogenesis, owing to the frequent mutation of the VHL tumour suppressor gene, the inhibition of mTOR could ultimately be just a dif-

ferent way to inhibit angiogenesis. If this is true, the only reasonable way to deal with the treatment of advanced RCC patients is by trying to personalize treatment as much as possible, i.e. by trying to simplify a hugely complex scenario, which will be even more complex when the results of several ongoing trials are available.

I.F. = 3,19

N. citazioni = 6

173. Masini C, Sabbatini R, **Porta C**, Procopio G, Di Lorenzo G, Onofri A, Buti S, Iacovelli R, Invernizzi R, Moscetti L, Aste MG, Pagano M, Grosso F, Lucia Manenti A, Ortega C. Use of tyrosine kinase inhibitors in patients with metastatic kidney cancer receiving haemodialysis: a retrospective Italian survey. *BJU Int* 2012;110:692-8.

ABSTRACT - Objective - To investigate the safety and efficacy of tyrosine kinase inhibitors (TKIs) in patients with metastatic renal cell carcinoma (mRCC) and end-stage renal disease requiring haemodialysis (HD). Patients and Methods - Between July 2006 and December 2010, 24 patients undergoing HD were treated with sunitinib and/or sorafenib for mRCC in 14 Italian institutions. We retrospectively reviewed the medical records of these patients to evaluate the administered doses of TKIs, treatment-related toxicities and the clinical response to therapy. Results - Sunitinib was administered at 50 mg daily for 4-6 weeks in six patients, 37.5 mg daily for 4-6 weeks in seven patients (one patient subsequently increased the dose to 50 mg daily), 25 mg daily for 4-6 weeks in two patients and 12.5 mg daily for 4-6 weeks in one patient. Among the eight patients treated with sorafenib, four patients received 800 mg daily (400 mg every 12 h), three patients 400 mg daily and one patient 200 mg daily with a continuous schedule. The estimated median progression-free and overall survival periods of this cohort of patients were 10.3 months and 22.6 months, respectively. With regard to tolerability and safety, no unexpected adverse events were registered and no grade 4 haematological or non-haematological toxicities were reported. Conclusions - Sunitinib and sorafenib treatment is not contraindicated in patients with mRCC undergoing HD. The outcome of this patient population is similar to that observed in patients with normal renal function treated with TKIs. These results merit further confirmation by a larger prospective trial.

I.F. = 3,19

N. citazioni = 40

174. Gore ME, Bellmunt J, Eisen T, Escudier B, Mickisch G, Patard J, **Porta C**, Ravaud A, Schmidinger M, Schöffski P, Sternberg C, Szczylik C, De Nigris E, Wheeler C, Kirpekar S. Evaluation of treatment options for patients with advanced renal cell carcinoma: assessment of appropriateness, using the validated semi-quantitative RAND corporation/University of California, Los Angeles methodology. *Eur J Cancer* 2012;48:1038-47.

ABSTRACT - A diverse range of treatment options and interventions are available for the management of renal cell carcinoma (RCC), allowing clinicians to tailor therapy to best meet their patient's needs and situation. However, choosing from the plethora of options can be problematic. RCC treatment guidelines advise on the most efficacious agents based upon specific clinical trial populations, but these do not always take into account all the patient factors that influence the suitability of treatment options for individual patients. This study used the validated RAND/UCLA (RAND corporation/University of California, Los Angeles) 'appropriateness methodology' to integrate clinical efficacy data with expert opinion concerning the use of specific RCC treatment options for particular patient scenarios, in an attempt to facilitate the widespread implementation of patient-focussed treatment choices. Use of the methodology has allowed us to develop treatment algorithms for patients with locally-advanced RCC and for those with metastatic disease post-nephrectomy or with primary tumour in situ. The algorithms take into account patient-specific characteristics such as tumour histology, prior treatment and known risk factors to advise whether a particular treatment intervention is appropriate, not appropriate or of uncertain appropriateness. Use of this methodology aims to develop a formalised process by which expert opinion can be integrated with clinical data and used as an additional source of information that can provide further guidance concerning difficult treatment decisions when data are absent or sparse.

I.F. = 4,944

N. citazioni = 15

175. Bracarda S, Hutson TE, **Porta C**, Figlin RA, Calvo E, Grünwald V, Ravaud A, Motzer R, Kim D, Anal O, Panneerselvam A, Escudier B. Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: a RECORD-1 subgroup analysis. *Br J Cancer* 2012;106:1475-80.

ABSTRACT - Background - A relevant percentage of patients with metastatic renal cell carcinoma develop intolerance to vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFr-TKIs) and require careful selection of subsequent treatment. This retrospective analysis evaluated the safety and efficacy of everolimus in patients enrolled in the phase-III RECORD-1 trial who discontinued previous VEGFr-TKI therapy because of toxicity. Methods - Patients with an adverse event (AE) as their primary reason for discontinuation of previous VEGFr-TKI therapy were included. Median progression-free survival (PFS) for VEGFr-TKI-intolerant patients in each arm was estimated using the Kaplan-Meier method, and effect on PFS (hazard ratio (HR)) was calculated using the Cox proportional hazard model. Results - In VEGFr-TKI-intolerant patients (n=58, 14%), median PFS was 5.4 months with everolimus and 1.9 months with placebo (HR: 0.32; P=0.004). In sunitinib-intolerant patients (n=26), median PFS was 5.1 months with everolimus and 2.8 months with placebo (HR: 0.28; P=0.033). Grade 3/4 AEs reported with everolimus in VEGFr-TKI-intolerant patients included infections (16%), fatigue (7%) and stomatitis (4%). The toxicity profile of everolimus was similar in the VEGFr-TKI-intolerant and overall study populations. Conclusion - Everolimus is well tolerated and efficacious with no increased toxicity in patients intolerant to VEGFr-TKI therapy.

I.F. = 4,831

N. citazioni = 19

176. **Porta C**, Motzer RJ. Reply to Giuseppe Procopio, Elena Verzoni and Filippo De Braud's Letter to the Editor re: Camillo Porta, Emiliano Calvo, Miguel A. Climent, et al. Efficacy and Safety of Everolimus in Elderly Patients with Metastatic Renal Cell Carcinoma: An Exploratory Analysis of the Outcomes of Elderly Patients in the RECORD-1 Trial. 2012;61:826-33. *Eur Urol* 2012;62:e7-e8.

ABSTRACT - We appreciate the response from Procopio to our article reporting on the subgroup analysis of elderly patients with metastatic renal cell carcinoma (mRCC) in the RECORD-1 phase 3 trial, and we acknowledge that subgroup analyses of multiple pivotal trials have demonstrated the efficacy

of different targeted agents in elderly patients with mRCC. However, clinical practice guidelines in the United States and Europe recommend everolimus for use in patients with mRCC who have failed initial vascular endothelial growth factor receptor–tyrosine kinase inhibitor therapy, and high-level evidence from the RECORD-1 trial supports use of everolimus in this patient population. We should then acknowledge that for everolimus and other targeted agents, evidence of efficacy and safety in elderly patients with mRCC has been derived from retrospective, and therefore some- what biased, studies, and there are currently no prospective data to support these findings. Until prospective data on the use of targeted agents in elderly patients with mRCC are available, we must rely on these retrospective findings when deciding on a treatment strategy. We agree with Procopio that the characteristics of each available agent and individual patient profiles should be carefully considered in determining an optimal treatment strategy. When weighing risks and benefits of targeted therapies, toxicity profiles of available agents and the patient's comorbidities and quality of life should be taken into consideration. The toxicity profiles of mammalian target of rapamycin inhibitors and inhibitors of the vascular endothelial growth factor–signaling pathway differ; thus, the patient's comorbidities and age-related physiologic changes are important factors in deciding which class of targeted agent may have the lower risk. A useful tool for detection of geriatric conditions is the Comprehensive Geriatric Assessment (CGA). The CGA assesses comorbidity, activities of daily living, cognition, psychological state, nutritional status, and medication use, and it accounts for patients' physiologic age. Information garnered from the CGA can detect significant unsuspected conditions, and this information can help to determine if an elderly patient with mRCC is a good candidate for treatment with a specific targeted agent. The CGA ultimately provides information about patients' prognoses and could be a valuable tool in designing future prospective studies to specifically assess the efficacy and safety of targeted agents in elderly patients wit mRCC, a task that is definitely worthwhile in a globally aging population.
I.F. = 8,843

177. Stenner F, Chastonay R, Liewen H, Haile SR, Cathomas R, Rothermundt C, Siciliano RD, Stoll S, Knuth A, Buchler T, **Porta C**, Renner C, Samaras P. A pooled analysis of sequential therapies with Sorafenib and Sunitinib in metastatic renal cell carcinoma. *Oncology* 2012;82:333-40.

ABSTRACT - Objective: To evaluate the optimal sequence for the receptor tyrosine kinase inhibitors (rTKIs) sorafenib and sunitinib in metastatic renal cell cancer. Methods: We performed a retrospective analysis of patients who had received sequential therapy with both rTKIs and integrated these results into a pooled analysis of available data from other publications. Differences in median progression-free survival (PFS) for first- (PFS1) and second-line treatment (PFS2), and for the combined PFS (PFS1 plus PFS2) were examined using weighted linear regression. Results: In the pooled analysis encompassing 853 patients, the median combined PFS for first-line sunitinib and 2nd-line sorafenib (SuSo) was 12.1 months compared with 15.4 months for the reverse sequence (SoSu; 95% CI for difference 1.45-5.12, p = 0.0013). Regarding first-line treatment, no significant difference in PFS1 was noted regardless of which drug was initially used (0.62 months average increase on sorafenib, 95% CI for difference -1.01 to 2.26, p = 0.43). In second-line treatment, sunitinib showed a significantly longer PFS2 than sorafenib (average increase 2.66 months, 95% CI 1.02-4.3, p = 0.003). Conclusion: The SoSu sequence translates into a longer combined PFS compared to the SuSo sequence. Predominantly the superiority of sunitinib regarding PFS2 contributed to the longer combined PFS in sequential use.
I.F. = 2,538
N. citazioni = 29

178. Blayney JK, Ceresoli GL, Castagneto B, O'Brien ME, Hasan B, Sylvester R, Rudd R, Steele J, Busacca S, **Porta C**, Mutti L, O'Byrne KJ, Scullin P, Gaafar R, Baas P, Van Meerbeeck J, Fennell DA. Response to chemotherapy is predictive in relation to longer overall survival in an individual patient combined-analysis with pleural mesothelioma. *Eur J Cancer* 2012;48:2983-92.

ABSTRACT - Background: There is currently no early predictive marker of survival for patients receiving chemotherapy for malignant pleural mesothelioma (MPM). Tumour response may be predictive for overall survival (OS), though this has not been explored. We have thus undertaken a combined-analysis of OS, from a 42day landmark, of 526 patients receiving systemic therapy for MPM. We also validate published progression-free survival rates (PFSRs) and a progression-free survival (PFS) prognostic-index model. Methods: Analyses included nine MPM clinical trials incorporating six European Organisation for Research and Treatment of Cancer (EORTC) studies. Analysis of OS from landmark (from day 42 post-treatment) was considered regarding tumour response. PFSR analysis data included six non-EORTC MPM clinical trials. Prognostic index validation was performed on one non-EORTC data-set, with available survival data. Results: Median OS, from landmark, of patients with partial response (PR) was 12·8 months, stable disease (SD), 9·4 months and progressive disease (PD), 3·4 months. Both PR and SD were associated with longer OS from landmark compared with disease progression (both p<0·0001). PFSRs for platinum-based combination therapies were consistent with published significant clinical activity ranges. Effective separation between PFS and OS curves provided a validation of the EORTC prognostic model, based on histology, stage and performance status. Conclusion: Response to chemotherapy is associated with significantly longer OS from landmark in patients with MPM.
I.F. = 4,944
N. citazioni = 22

179. Escudier B, Szczylik C, **Porta C**, Gore M. Treatment selection in metastatic renal cell carcinoma: expert consensus. *Nat Rev Clin Oncol* 2012;9:327-37.

ABSTRACT - In metastatic renal cell carcinoma (mRCC), many factors influence clinical decisions, including histology, tumour burden, prognostic factors, comorbidities, and the ability of the patient to tolerate treatment. Progression-free survival (PFS) durations reported from randomized trials of targeted therapies vary considerably, in part because of differences in patient characteristics. For first-line therapy, an estimate of PFS with sunitinib, bevacizumab plus interferon, or sorafenib in a 'general' population is 8-9 months, but each regimen is suitable for different patient categories. For example, sunitinib is suitable for all-prognosis groups, particularly younger, fitter patients; pazopanib for patients with a good or intermediate prognosis; bevacizumab plus interferon for good-prognosis patients or those with indolent disease; and sorafenib for patients at all prognostic risk levels, particularly the elderly and those with comorbidities. Sequential therapy with targeted agents provides significant benefit, and should be considered in all patients who can tolerate such treatment. Level 1 evidence supports sequential use of tyrosine kinase inhibitors, as well as these agents followed by everolimus. We consider how patient characteristics have influenced the results of studies of first-line therapy, and we provide expert opinion on the most appropriate treatment choices for particular patient groups receiving first-line and second-line therapy.
I.F. = 10.787
N. citazioni = 114

180. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, **Porta C**, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012;57:821-9.

ABSTRACT - Background and aims: The Sorafenib Hepatocellular Carcinoma (HCC) Assessment Randomized Protocol (SHARP) trial demonstrated that sorafenib improves overall survival and is safe for patients with advanced HCC. In this trial, 602 patients with well-preserved liver function (>95% Child-Pugh A) were randomized to receive either sorafenib 400mg or matching placebo orally b.i.d. on a continuous basis. Because HCC is a heterogeneous disease, baseline patient characteristics may affect individual responses to treatment. In a comprehensive series of exploratory subgroup analyses, data from the SHARP trial were analyzed to discern if baseline patient characteristics influenced the efficacy and safety of sorafenib. Methods: Five subgroup domains were assessed: disease etiology, tumor burden, performance status, tumor stage, and prior therapy. Overall survival (OS), time to progression (TTP), disease control rate (DCR), and safety were assessed for subgroups within each domain. Results: Subgroup analyses showed that sorafenib consistently improved median OS compared with placebo, as reflected by hazard ratios (HRs) of 0.50-0.85, similar to the complete cohort (HR=0.69). Sorafenib also consistently improved median TTP (HR, 0.40-0.64), except in HBV-positive patients (HR, 1.03), and DCR. Results are limited by small patient numbers in some subsets. The most common grade 3/4 adverse events included diarrhea, hand-foot skin reaction, and fatigue; the incidence of which did not differ appreciably among subgroups. Conclusions: These exploratory subgroup analyses showed that sorafenib consistently improved median OS and DCR compared with placebo in patients with advanced HCC, irrespective of disease etiology, baseline tumor burden, performance status, tumor stage, and prior therapy.

I.F. = 9,334

N. citazioni = 564

181. **Porta C**. How to identify active novel agents in rare cancers and then make them available: a need for a paradigm shift. *Eur Urol* 2012;62:1020-1 (Editorial).

In this issue of European Urology, Tannir and colleagues reported the results of a prospective phase 2 study of sunitinib in patients with non–clear cell renal cell carcinoma (RCC), an extremely heterogeneous group of biologically different, and rare, tumor types. This study confirmed what has already been suggested by few prospective studies and, which is that sunitinib works also in these rare cancers, but that its activity and efficacy are less evident than in the classical clear cell histotype. A differential histotype-driven activity of sunitinib (apparently superior in the chromophobe histotype) was also postulated by the authors but could not be proved due the limited number of patients with chromophobe cancer included in the study and the design of the study itself. Notably, this study indirectly raises two other questions that are more general but nevertheless key: 1) Do we need innovative study designs to test novel agents in rare cancer types? 2) In case of success, how do we make active novel agents, which are also very costly, available to patients with rare cancers (for which use these drugs are usually not registered) in a global situation characterized by a dramatic shortage of economic resources? I will start by addressing the issue of clinical trial design in rare cancers. The main goal of clinical trials is to try to reduce as much as possible the uncertainty surrounding the activity of new treatments, to move them to everyday clinical practice, and consequently to accept paying their costs for the community. Traditional clinical trials use statistical methodologies that need considerable numbers of patients, which are difficult to collect in rare cancers, to minimize the so-called random error and the frequent low magnitude of the expected effect. The small differences in favor of new treatments observed in many clinical trials may be due, among other reasons, to the frequent lack of patient selection. Research on biomarkers should thus be an inherent part of research on new drugs, especially in rare cancers. Finding a biomarker could also indirectly help reduce the number of patients needed in a trial. If, for example, we treat patients with a given mutation with an agent targeting the specific product of that mutation rather than treating a general unselected population, the achievable gain is expected to be huge, and if the expected difference is so high, the sample size can be lower. Besides trying to rely on biomarkers, which may or may not be available, rare cancers would greatly benefit from novel trial designs, such as the so-called adaptive trials, or the use of Bayesian statistics. Adaptive trials permit changing aspects of the study or its statistical procedures while the study is ongoing. The overall development of a new drug for a rare cancer may be made easier and faster thanks to adaptive mechanisms such as the intensive use of stopping rules (for safety or for futility), the transformation of a phase 2 into a phase 3 study (in case the early stage of the study was positive), or the use of drop-the-loser or play-the-winner designs. Bayesian statistics is an approach to exploit all available evidence. In clinical trials, traditional (or frequentist) statistical methods may use information from previous studies only to make an estimate of the expected outcome. However, the amount of previously available data does not change the number of patients required. In contrast, the Bayesian approach uses Bayes' theorem to formally combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream in which inferences are being updated each time new data become available. In addition, the theory of Bayesian experimental design fits the theory for making optimal decisions under uncertainty, something that perfectly fits the rare tumor scenario. Before a Bayesian trial begins and data are obtained, probabilities are given to all the possible values (or ranges of values) of an unknown quantity of interest. These probabilities, taken together, constitute the prior distribution for that quantity. After data from the trial become available, the prior distribution is updated according to Bayes' theorem. This updated distribution is called the posterior distribution, from which one obtains the probabilities for values of the unknown quantity after data are observed. This approach is a scientifically valid way of combining previous information (the prior probabilities) with current data. The approach can be used in an iterative fashion as knowledge accumulates: today's posterior probabilities become tomorrow's prior probabilities. A Bayesian trial provides the clinician with a probability distribution that can be directly used in the clinical decision-making process, for example, in a formal decision analysis. There is an ongoing initiative, Rare Cancers Europe (http://www.rarecancerseurope.org), launched by the European Society of Medical Oncology, which is trying to achieve a consensus in the community of experts on these innovative trial designs in the setting of the development of novel agents in rare cancers. Notably, the US Food and Drug Administration started to suggest the use of Bayesian statistics in medical device clinical trials back in 2006. Another key point is the off-label use of novel agents in rare cancers, a use that is more widespread than in common cancers. An interesting idea comes from the United Kingdom, where the lack of reimbursement for several novel agents, including some for treatment of kidney cancer, already gave rise to much controversy. Despite these previous controversies, a cancer drug fund (CDF) recently has been established. The CDF is a government initiative to provide access to drugs to treat cancer while they are still going through the National Institute for Clinical Excellence (NICE) process and sometimes also after NICE has turned them down (eg, everolimus for RCC is not NICE approved but is available through the CDF). Decisions about which drugs to fund are made at a local level of 10 strategic health authorities (SHAs) throughout England (but not Scotland or Wales). The criteria for access to the fund should be based primarily on evidence of clinical effectiveness and anticipated delivery of

measurable outcomes, such as improved overall survival, progression-free survival, or improved quality of life. SHAs should also consider cost effectiveness if there are robust data to support decision making. Where treatments are similarly clinically effective or where ranking scores of clinical effectiveness do not differentiate between different therapies, panels should consider cost effectiveness to maximize the number of patients treated from the available funding. As a whole, the issue of how to deal with rare cancer types in an era of molecularly targeted agents and in a situation of global economical crisis is a key priority for both the world of academics and that of politics. Presently, no clear-cut answers are available, but a paradigm shift is urgently needed.
I.F. = 8,843
N. citazioni = 12

182. Imarisio I, Paglino C, Ganini C, Magnani L, Caccialanza R, **Porta C**. The effect of sorafenib treatment on the diabetic status of patients with renal cell or hepatocellular carcinoma. *Future Oncol* 2012;8:1051-7.

ABSTRACT - Aim: To evaluate the effect of sorafenib on the glucose tolerance and diabetic status of patients with metastatic renal cell carcinoma (RCC) or advanced hepatocellular carcinoma (HCC). Materials & methods: Eighty patients with metastatic RCC or advanced HCC received 400 mg sorafenib twice daily for an average of approximately 8 and 5 months, respectively; 22 had diabetes mellitus and three had prediabetes. Results: One of 55 nondiabetic patients, and one of three patients with impaired fasting glucose or impaired glucose tolerance developed diabetes mellitus, one of 12 patients on oral antihyperglycemic agents switched to insulin and no patient treated with insulin needed to increase their dose. Conclusion: Sorafenib has the potential to be a feasible and safe treatment option for patients with advanced HCC or metastatic RCC and comorbid diabetes mellitus or prediabetes.
I.F. = 2,455
N. citazioni = 9

183. Escudier B, Eisen T, **Porta C**, Patard JJ, Khoo V, Algaba F, Mulders P, Kataja V on behalf of the ESMO Guidelines Working Group. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012;23(Suppl. 7):vii65-vii71.
I.F. = 6,425
N. citazioni = 230

184. Procopio G, Sabbatini R, **Porta C**, Verzoni E, Galligioni E, Ortega C. Optimizing further treatment choices in short- and long-term responders to first-line therapy for patients with advanced renal cell carcinoma. *Exp Rev Anticancer Ther* 2012;12:1089-96.

ABSTRACT - Sequencing decisions in advanced renal cell carcinoma are likely to become more difficult when new targeted agents are approved for first and subsequent lines of therapy. Approximately 70% of patients benefit from targeted therapy before progression, of which 20% can be described as short-term responders (progression-free survival: <6 months) and 50% as long-term responders (progression-free survival: >6 months). The remaining 30% show either no response (20%) or are intolerant to treatment (10%). The challenge is to establish the optimal second-line agent for over 70% of patients who progress following initial response to a first-line tyrosine kinase inhibitor. As it is impossible to define the optimal second-line therapy for every patient, it is suggested that age and comorbidities of the patient, the sites of disease and the side effects of previous therapies be taken into account in order to optimize the use of different agents sequentially.
I.F. = 2.976
N. citazioni = 6

185. Lodola F, Laforenza U, Bonetti E, Lim D, Dragoni S, Bottino C, Ong HL, Guerra G, Ganini C, Massa M, Manzoni M, Ambudkar IS, Genazzani AA, Rosti V, Pedrazzoli P, Tanzi F, Moccia F, **Porta C**. Store-operated Ca^{++} entry is remodelled and controls in vitro angiogenesis in endothelial progenitor cells isolated from tumoral patients. *PLoS One* 2012;7:e42541.

ABSTRACT - Background: Endothelial progenitor cells (EPCs) may be recruited from bone marrow to sustain tumor vascularisation and promote the metastatic switch. Understanding the molecular mechanisms driving EPC proliferation and tubulogenesis could outline novel targets for alternative anti-angiogenic treatments. Store-operated Ca(2+) entry (SOCE), which is activated by a depletion of the intracellular Ca(2+) pool, regulates the growth of human EPCs, where is mediated by the interaction between the endoplasmic reticulum Ca(2+)-sensor, Stim1, and the plasmalemmal Ca(2+) channel, Orai1. As oncogenesis may be associated to the capability of tumor cells to grow independently on Ca(2+) influx, it is important to assess whether SOCE regulates EPC-dependent angiogenesis also in tumor patients. Methodology/Principal Findings: The present study employed Ca(2+) imaging, recombinant sub-membranal and mitochondrial aequorin, real-time polymerase chain reaction, gene silencing techniques and western blot analysis to investigate the expression and the role of SOCE in EPCs isolated from peripheral blood of patients affected by renal cellular carcinoma (RCC; RCC-EPCs) as compared to control EPCs (N-EPCs). SOCE, activated by either pharmacological (i.e. cyclopiazonic acid) or physiological (i.e. ATP) stimulation, was significantly higher in RCC-EPCs and was selectively sensitive to BTP-2, and to the trivalent cations, La(3+) and Gd(3+). Furthermore, 2-APB enhanced thapsigargin-evoked SOCE at low concentrations, whereas higher doses caused SOCE inhibition. Conversely, the anti-angiogenic drug, carboxyamidotriazole (CAI), blocked both SOCE and the intracellular Ca(2+) release. SOCE was associated to the over-expression of Orai1, Stim1, and transient receptor potential channel 1 (TRPC1) at both mRNA and protein level The intracellular Ca(2+) buffer, BAPTA, BTP-2, and CAI inhibited RCC-EPC proliferation and tubulogenesis. The genetic suppression of Stim1, Orai1, and TRPC1 blocked CPA-evoked SOCE in RCC-EPCs. Conclusions: SOCE is remodelled in EPCs from RCC patients and stands out as a novel molecular target to interfere with RCC vascularisation due to its ability to control proliferation and tubulogenesis.
I.F. = 4,411
N. citazioni = 128

186. Ganini C, Lasagna A, Ferraris E, Gatti P, Paglino C, Imarisio I, Morbini P, Benazzo M, **Porta C**. Lingual metastasis from renal cell carcinoma: a case report and literature review. *Rare Tumors* 2012;4:e41.

ABSTRACT - Renal cell carcinoma (RCC) accounts for the 3% of all solid tumors. Despite continuous improvement in the therapy regimen, less has been achieved in terms of enabling an earlier diagnosis: the neoplasia usually reveals its presence at an advanced stage, obviously affecting prognosis. The most frequent sites of secondary disease are shown to be lungs

(50-60%), bone (30-40%), liver (30-40%) and brain (5%); while the head and neck district seems to account for less than 1% of patients with primary kidney lesion. We report here the case of a 70-year old man who presented with acute renal failure due to abdominal recurrence of RCC 18 years post nephrectomy. After a few months of follow up without any systemic therapy due to the renal impairment, the patient presented a vascularized tongue lesion that was demonstrated to be a secondary localization of the RCC. This lesion has, therefore, been treated with microsphere embolization to stop the frequent bleeding and to lessen the unbearable concomitant symptoms it caused, such as dysphagia and pain. A tongue lesion that appears in a RCC patient should always be considered suspect and a multidisciplinary study should be conducted both to assess whether it is a metastasis or a primary new lesion and to understand which method should be selected, if necessary, to treat it (surgery, radiation or embolization). Lingual metastasis should be examined accurately not only because they seem to implicate a poor prognosis, but also because they carry a burden of symptoms that not only threatens patients' lives but also has a strong impact on their quality of life.
I.F. = n.r.
N. citazioni = 15

187. **Porta C**, Sabbatini R, Procopio G, Paglino C, Galligioni E, Ortega C. Primary resistance to tyrosine kinase inhibitors in patients with advanced renal cell carcinoma: state-of-the-science. *Expert Rev Anticancer Ther* 2012;12:1571-7.

ABSTRACT - Although over 70% of patients with metastatic renal cell carcinoma (RCC) respond to initial therapy with tyrosine kinase inhibitors (disease control rate 70-80%), approximately 20-30% of patients do not respond to first-line therapy and progress within ≤3 months. Understanding the mechanisms of resistance to targeted therapies is vital in the development of prospectively defined sequences and because the choice of first-line therapy determines that of second and subsequent line therapy, identification of the optimal first-line therapy is a priority for clinicians treating patients with metastatic RCC. By preselecting those patients most likely to respond to antivascular endothelial growth factor therapy, clinicians can begin to optimize therapeutic strategies. This review focuses on primary antivascular endothelial growth factor-refractory patients and the move towards individualizing treatment for RCC. The authors include a review of the growing number of studies, as yet retrospective, which provide important information on the group of primary refractory patients with advanced RCC for whom the prognosis is not good. First, the percentage of primary refractory patients (26%) is in agreement with disease control rate - the sum of objective responses and disease stabilization, observed in registration studies for a range of tyrosine kinase inhibitors. Second, the prognosis for these patients is poor as they do not respond to first-line nor to second-line therapy, and changing the mechanism of action (with inhibition of mTOR pathway) does not appear to produce additional benefits. Third and most importantly, the results of these studies demonstrate the need to better characterize the mechanism of primary resistance to current therapeutic agents with the ultimate aim of developing a therapeutic strategy for this important subgroup of patients.
I.F. = 2.976
N. citazioni = 32

188. Paglino C, Imarisio I, Ganini C, Morbini P, Vercelli A, Bregant C, **Porta C**. Sunitinib in advanced metastatic non-clear cell renal cell carcinoma: a single institution retrospective study. *Future Oncol* 2012;8:1605-12.

ABSTRACT - Aim: Sunitinib is an orally active multi-targeted tyrosine kinase inhibitor that exerts its antitumor effects primarily through the selective inhibition of VEGF. Novel targeted therapies such as sunitinib have transformed the treatment of advanced metastatic renal cell carcinomas, particularly those with clear cell histology. Here, our experience in patients with non-clear cell kidney cancer treated as part of the sunitinib Expanded Access Program is reported. Materials & methods: This was a retrospective assessment of 21 patients with non-clear cell renal cell carcinoma who were treated with oral sunitinib 50 mg/day in repeated 6 weekly cycles (4 weeks on and 2 weeks off). Disease assessment and physical examination were recorded at baseline and tumor assessments were performed every 3 months, according to Response Evaluation Criteria In Solid Tumors. The primary outcome measure was progression-free survival. Results: Patients received an average of 6.38 cycles of sunitinib; one patient was classified as a complete responder and two as partial responders. The overall response rate was 14.3% and clinical benefit was attained by 52.4%. The median progression-free survival was 4.1 months while median overall survival was 14.6 months. In general, sunitinib was well tolerated and only three patients experienced a grade 3 toxicity, which resolved with dosage reduction. Conclusion: As expected, sunitinib exerted lower antitumor activity in patients with non-clear cell renal cell carcinoma than was achieved in the general population with metastatic kidney cancer. However, responses (one complete and two partial) were documented and clinical benefit was observed in more than half of all patients.
I.F. = 3,163
N. citazioni = 9

189. **Porta C**, Ganini C, Paglino C. Modifying Sunitinib schedule in advanced kidney cancer patients: reflections from the results of the renal EFFECT trial. *Transl Androl Urol* 2012;1:120-2
I.F. = n.r.
N. citazioni = 1

190. **Porta C**, Paglino C, Imarisio I, Ganini C, Sacchi L, Quaglini S, Giunta V, De Amici M. Changes in circulating pro-angiogenic cytokines, other than VEGF, before progression to Sunitinib therapy in advanced renal cell carcinoma patients. *Oncology* 2013;84:115-122.

ABSTRACT - Objectives: This study included a cohort of advanced renal cell carcinoma patients treated with sunitinib. Since resistance to sunitinib may be mediated through angiogenic cytokines other than VEGF, we measured the circulating levels of three pro-angiogenic cytokines: basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and interleukin (IL)-6. Methods: Cytokines were measured at baseline and on the first day of each treatment cycle until progression in 85 advanced kidney cancer patients treated with sunitinib using a quantitative sandwich enzyme immunoassay (ELISA) technique. Results: Even though no statistically significant differences in the titers of the three cytokines were observed between baseline and the time of progression in the whole patient cohort, in 45.3, 46.6, and 37.3% of the patients a more than 50% increase between baseline and the time of progression was shown in circulating IL-6, bFGF, and HGF, respectively. Furthermore, this increase was more than 100% in 37.3, 44, and 30.6% of the patients, respectively. We also demonstrated that, in these patients, cytokines tended to increase and to remain high immediately before progression. Conclusions: In a large percentage of kidney cancer patients, progression is preceded by a significant increase in pro-angiogenic cytokines other than VEGF.
I.F. = 2.267
N. citazioni = 66

191. **Porta C**, Paglino C. Experience gathered from retrospective series on renal cell carcinoma is useful, but now it is time for a global claim for academically driven prospective studies. *Eur Urol* 2013;64:71-2.

ABSTRACT - What has happened in the past 8 yr with regard to advanced renal cell carcinoma is something new and unprecedented in the field of urologic oncology and in medical oncology as a whole. In such a limited timespan, seven novel molecularly targeted agents—sorafenib, sunitinib, temsirolimus, bevacizumab plus interferon, pazopanib, everolimus, and axitinib—have been licensed, and one more (tivozanib) is presently under consideration by the regulatory authorities. This means that since 2005, when Bernard Escudier presented the results of the phase III TARGET trial at the American Society of Clinical Oncology meeting, a novel agent was made available each year for the treatment of this once "orphan" disease. This situation has led to the "embarrassment of riches" that was the title of a brilliant editorial by Vogelzang in the Journal of Clinical Oncology, in which he there and then addressed some of the issues deriving from this complex scenario. One of these issues is that we simply have not had enough time to really comprehend the data gathered in each drug's registration trial. Moreover, after licensing, many pharmaceutical companies simply gave up the idea of developing their drug further. Even worse, some started designing marketing-oriented trials aimed at better positioning the drug in a rapidly evolving scenario or trials aimed at putatively quicker and easier registration. Consequently, we had to start to dissect the results of these registrative trials, as well as expanded access programs, with an intellectual microtome. We have tried to learn as much as possible about these drugs in specific, clinically relevant settings (eg, elderly patients, pretreated patients, patients with specific metastatic sites) from both retrospective series, as well as subanalyses of the registrative studies. As a clear example of such an approach, in this issue of the Platinum Journal, Busch and colleagues reported an interesting retrospective comparison of triple-sequence therapies in metastatic renal cell carcinoma. A manuscript retrospectively reporting the outcome of two different three-drug sequences on an extremely limited number of patients (just 103 in total) has been accepted for publication in a top journal, and despite its limitations—honestly discussed by the authors themselves—its results will ultimately affect the way advanced kidney cancer patients are treated. This is something on which we should start reflecting. Although presently inevitable, the idea of translating into everyday clinical practice what has emerged from retrospective, uncontrolled study is against the evidence-based medicine we continue to teach in medical schools. We have simply skipped the key step of doing confirmatory prospective studies of relevant clinical questions and issues, using the retrospective data we gathered as we should: to generate hypotheses, not to drive clinical practice. As an academic community, it is time to stop for awhile and cooperate to push companies to do smart studies, not marketing-oriented studies, with the aim of addressing clinically and academically relevant questions. It will not be easy, for sure, but it is mandatory to fully exploit the potentialities (and peculiarities) of all these drugs, which are only partially recognized, and to offer our patients really tailored treatments supported by level A evidence. Another key issue is the unprocrastinating quest for biomarkers. This quest that should not be left to pharmaceutical companies, for practical reasons as well as ethical ones, and should be coupled, whenever possible, with well-designed clinical trials. Even though many of us, as clinical researchers, will probably agree on these goals, a completely different issue is how to achieve them. The costs of a clinical trial today, especially if coupled with some biological insight, are almost unaffordable in academia. Trials with molecularly targeted agents are simply impossible to perform without the support of the pharmaceutical companies. A possible solution is to support the development of an international network of academic centers devoted to the management of this disease and then make them really work together to create a "critical mass" in the complex, and presently unbalanced, relationship with pharmaceutical companies. The revitalization of already existing sovra-national cooperative groups (eg, the European Organization for Research and Treatment of Cancer in Europe) could be a first step in such a direction. Coparticipation of different entities (eg, academic centers, pharmaceutical companies, regulatory authorities, and governments) in these efforts will also probably be required, as will be the use of novel trial designs for the next generation of trials. This effort is huge and definitely not easy to perform but should be regarded as crucial to really improve the way we treat patients, without losing money and resources unnecessarily in an unprecedented global economic crisis like the present one.

I.F. = 8,493
N. citazioni = 1

192. Bracarda S, **Porta C**, Boni C, Santoro A, Mucciarini C, Pazzola A, Cortesi E, Gasparro D, Labianca R, Di Costanzo F, Falcone A, Cinquini M, Caserta C, Paglino C, De Angelis V. Could Interferon still play a role in metastatic renal cell carcinoma? a randomized study of two schedules of Sorafenib plus Interferon-alpha 2a (RAPSODY). *Eur Urol* 2013;63:254-61.

ABSTRACT - Background: Sorafenib has proven efficacy in metastatic renal cell carcinoma (mRCC). Interferon (IFN) has antiangiogenic activity that is thought to be both dose- and administration-schedule dependent. Objective: To compare two different schedules of IFN combined with sorafenib. Design,setting, and particpants: Single-stage, prospective, noncomparative, randomized, open-label, multicenter, phase 2 study on previously untreated patients with mRCC and Eastern Cooperative Oncology Group performance status 0-2. Intervention: Sorafenib 400 mg twice daily plus subcutaneous IFN, 9 million units (MU) three times a week (Arm A) or 3 MU five times a week (Arm B). Outcome measurements and statistical analysis: Primary end points were progression-free survival (PFS) for each arm and safety. Data were evaluated according to an intent-to-treat analysis. Results and limitations: A total of 101 patients were evaluated. Median PFS was 7.9 mo in Arm A and 8.6 mo in Arm B (p=0.049) and the median duration of response was 8.5 and 19.2 mo, respectively (p=0.0013). Nine partial responses were observed in Arm A, and three complete and 14 partial responses were observed in Arm B (17.6% vs 34.0%; p=0.058); 24 and 21 patients (47% and 42%), respectively, achieved stable disease. The most common grade 3-4 toxicities were fatigue plus asthenia (28% vs 16%; p=0.32) and hand-foot skin reactions (20% vs 18%). Conclusions: Sorafenib plus frequent low-dose IFN showed good efficacy and tolerability. Further investigations should be warranted to identify a possible positioning of this intriguing regimen (6% complete response rate) in the treatment scenario of mRCC.

I.F. = 8,493
N. citazioni = 28

193. Pressiani T, Boni C, Rimassa L, Labianca R, Fagiuoli S, Salvagni S, Ferrari D, Cortesi E, **Porta C**, Mucciarini C, Latini L, Carnaghi C, Banzi M, Fanello S, De Giorgio M, Lutman FR, Torzilli G, Tommasini MA, Ceriani R, Covini G, Tronconi MC, Giordano L, Locopo N, Naimo S, Santoro A. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. *Ann Oncol* 2013;24:406-11.

ABSTRACT - Background: Sorafenib has shown survival benefits in patients

with advanced hepatocellular carcinoma (HCC) and Child-Pugh (CP) class A liver function. There are few prospective data on sorafenib in patients with HCC and CP class B. Patients and methods: A consecutive prospective series of 300 patients with CP class A or B HCC were enrolled in a dual-phase trial to determine survival and safety data according to liver function (class A or B) in patients receiving oral sorafenib 800 mg daily. [Results of this study were presented in part at the ASCO 2012 Gastrointestinal Cancers Symposium, 19-21 January 2012. J Clin Oncol 2012; 30 (Suppl 4): abstract 306.] Results: Overall progression-free survival (PFS), time to progression (TTP) and overall survival (OS) were 3.9, 4.1 and 9.1 months, respectively. For patients with CP class A versus B status, PFS was 4.3 versus 2.1 months, TTP was 4.2 versus 3.8 months and OS was 10.0 versus 3. 8 months. Extrahepatic spread was associated with worse outcomes but taken together with CP class, liver function played a greater role in reducing survival. Adverse events for the two CP groups were similar. Conclusion: Although patients with HCC and CP class B liver function have poorer outcomes than those with CP class A function, data suggest that patients with CP class B liver function can tolerate treatment and may still benefit from sorafenib.
I.F. = 6,425
N. citazioni = 94

194. Santoro A, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem L, Van Vlierberghe, Trojan J, Kolligs FT, Weiss A, Miles S, Gasbarrini A, Lencioni M, Cicalese L, Sherman M, Gridelli C, Buggisch P, Gerken G, Schmid RM, Boni C, Personeni N, Hassoun Z, Abbadessa G, Schwartz B, Von Roemeling, Lamar ME, Chen Y, **Porta C**. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. *Lancet Oncol* 2013;14:55-63.

ABSTRACT - Background: Tivantinib (ARQ 197), a selective oral inhibitor of MET, has shown promising antitumour activity in hepatocellular carcinoma as monotherapy and in combination with sorafenib. We aimed to assess efficacy and safety of tivantinib for second-line treatment of advanced hepatocellular carcinoma. Methods: In this completed, multicentre, randomised, placebo-controlled, double-blind, phase 2 study, we enrolled patients with advanced hepatocellular carcinoma and Child-Pugh A cirrhosis who had progressed on or were unable to tolerate first-line systemic therapy. We randomly allocated patients 2:1 to receive tivantinib (360 mg twice-daily) or placebo until disease progression. The tivantinib dose was amended to 240 mg twice-daily because of high incidence of treatment-emergent grade 3 or worse neutropenia. Randomisation was done centrally by an interactive voiceresponse system, stratified by Eastern Cooperative Oncology Group performance status and vascular invasion. The primary endpoint was time to progression, according to independent radiological review in the intention-to-treat population. We assessed tumour samples for MET expression with immunohistochemistry (high expression was regarded as ≥2+ in ≥50% of tumour cells). This study is registered with ClinicalTrials.gov, number NCT00988741. Findings: 71 patients were randomly assigned to receive tivantinib (38 at 360 mg twice-daily and 33 at 240 mg twicedaily); 36 patients were randomly assigned to receive placebo. At the time of analysis, 46 (65%) patients in the tivantinib group and 26 (72%) of those in the placebo group had progressive disease. Time to progression was longer for patients treated with tivantinib (1.6 months [95% CI 1.4–2.8]) than placebo (1.4 months [1.4–1.5]; hazard ratio [HR] 0.64, 90% CI 0.43–0.94; p=0.04). For patients with MET-high tumours, median time to progression was longer with tivantinib than for those on placebo (2.7 months [95% CI 1.4–8.5] for 22 MET-high patients on tivantinib vs 1.4 months [1.4–1.6] for 15 MET-high patients on placebo; HR 0.43, 95% CI 0.19–0.97; p=0.03). The most common grade 3 or worse adverse events in the tivantinib group were neutropenia (ten patients [14%] vs none in the placebo group) and anaemia (eight [11%] vs none in the placebo group). Eight patients (21%) in the tivantinib 360 mg group had grade 3 or worse neutropenia compared with two (6%) patients in the 240 mg group. Four deaths related to tivantinib occurred from severe neutropenia. 24 (34%) patients in the tivantinib group and 14 (39%) patients in the placebo group had serious adverse events. Interpretation: Tivantinib could provide an option for second-line treatment of patients with advanced hepatocellular carcinoma and well-compensated liver cirrhosis, particularly for patients with MET-high tumours. Confirmation in a phase 3 trial is needed, with a starting dose of tivantinib 240 mg twice-daily.
I.F. = 22.589
N. citazioni = 455

195. **Porta C**, Ganini C, Paglino C. From the Zeno's paradoxes to novel immunotherapeutic agents for kidney cancer; moving from an era of wrong premises and conclusions to a better comprehension of immunology. *Exp Opin Biol Ther* 2013;13:813-5.

ABSTRACT - In the 5th century B.C., Zeno of Elea offered arguments that led to conclusions contradicting what we all know from our experience. The arguments were paradoxes for the ancient philosophers and it took centuries to demonstrate that they were not true. For example, in his Achilles and the tortoise paradox, fast running Achilles races to catch a slower tortoise that has a head start; so, if Achilles hopes to overtake the tortoise, he must run first to the place where the tortoise presently is, but by the time he arrives there, it would have crawled to a new place, so then Achilles must run to this new place, but the tortoise meanwhile will have crawled on, and so forth Achilles will never catch the tortoise, concludes Zeno. From this well known paradox, it appears clearly that from wrong premises come wrong conclusions, something that for years has affected our perception of the role of immunotherapy in kidney cancer.
I.F. = 3,505

196. Bracarda S, Montironi R, **Porta C**, Szczylic C, Bearz A, Cartenì G, Bellmunt J. The treating scenario in genitourinary oncology: what is new? Part 1. *Future Oncol* 2013;9:797-801.

ABSTRACT - The objectives of this innovative meeting were to discuss developments in the management of genitourinary cancer worldwide and how Italian clinicians could harness these innovations in their everyday practice. The 2-day meeting was divided into two sessions covering kidney and prostate cancer, and a large part was given over to the presentation and discussion of new recently presented data at major international congresses in 2012. There were no restrictions on content and all subjects from pathology, surgery and genetics to therapy and patient outcomes were covered.
I.F. = 3,163

197. Bracarda S, Montironi R, **Porta C**, Szczylic C, Bearz A, Cartenì G, Bellmunt J. The treating scenario in genitourinary oncology: what is new? Part 2. *Future Oncol* 2013;9:803-6.

ABSTRACT - The objectives of this innovative meeting were to discuss developments in the management of genitourinary cancer worldwide and how Italian clinicians could harness these innovations in their everyday practice. The 2-day meeting was divided into two sessions covering kidney and

prostate cancer, and a large part was given over to the presentation and discussion of new recently presented data at major international congresses in 2012. There were no restrictions on content and all subjects from pathology, surgery and genetics to therapy and patient outcomes were covered.
I.F. = 3,163

198. Sabbatini R, Ortega C, Procopio G, Masini C, Galligioni E, **Porta C**. Metastatic renal cell carcinoma: how to make the best sequencing decision after withdrawal for intolerance to a tyrosine kinase inhibitor. *Future Oncol* 2013;9:831-43.

ABSTRACT - With seven agents approved for metastatic renal cell carcinoma (RCC) within the past few years, there has undoubtedly been progress in treating this disease. The treatment safety of these new agents, however, now represents a crucial concern, which requires a search for the best possible balance between the minimization of the treatment burden and the need for maintaining appropriate drug dosages able to induce the best clinical benefit. In this review we have analyzed safety data of all approved targeted agents for metastatic RCC available as first- or second-line therapy to provide suggestions aimed at establishing the most appropriate second-line or later treatment on the basis of toxicities that have arisen in therapy. Based on the characteristics and comorbidities of the patients and on the toxicity profile of each treatment, it is possible to plan different therapeutic options. We, therefore, have compiled a list of points that are important to keep in mind when considering the use of the targeted drugs for the treatment of advanced RCC.
I.F. = 3,163
N. citazioni = 7

199. Massari F, Bria E, Maines F, Milella M, Giannarelli D, Cognetti F, Pappagallo G, Tortora G, **Porta C**. Adjuvant treatment for resected Renal Cell Carcinoma: are all strategies equally negative? Potential implications for trial design with targeted agents. *Clin Genitourin Cancer* 2013;11:471-6.

ABSTRACT - Background: Although data from ongoing trials with targeted agents are awaited, we used a meta-analytical approach to explore whether cytokines (CK), vaccines (VAX), or other therapies may differentially influence patients' outcomes. Materials and Methods: The objective was to determine whether significant interactions exist according to treatment (CK vs. VAX vs. other), in the context of a literature-based meta-analysis. Fourteen trials (3380 patients) were identified, with 10 randomized clinical trials (RCTs) (2257 patients) providing data for the primary outcome-5-year relapse-free survival (RFS). The primary selected end point was 5-year RFS; secondary end points were 5- and 2-year overall survival (OS) and 2-year RFS. Event-based relative risk (RR) ratios with 95% confidence intervals (CI) were extracted and cumulated according to a random-effect model from articles/presentations. Testing for heterogeneity was performed as well. Results: Although not statistically significant, an effect in favor of a qualitative interaction according to treatment was found for 5-year RFS, with a likely detrimental effect in CK (P = .42) in contrast to that found in VAX subpopulation (P = .76). For the secondary end points, a similar effect in favor of a quantitative significant interaction according to treatment was found for 5-year OS, regardless of the approach adopted, with a different magnitude of treatment effect. In addition, a borderline significant (P = .05) detrimental effect in terms of 2-year OS against the use of adjuvant treatment was determined in the CK subpopulation (RR, 1.24; 95% CI, 0.99, 1.54). Conclusion: The effect in favor of a qualitative interaction according to the adopted strategy is intriguing and suggests potential implications for trial design with targeted agents.
I.F. = 2.605
N. citazioni = 21

200. Zustovich F, Landi L, Lombardi G, **Porta C**, Galli L, Fontana A, Amoroso D, Galli C, Andreuccetti M, Falcone A, Zagonel V. Sorafenib plus Daily Low-dose Temozolomide for Relapsed Glioblastoma: A Phase II Study. *Anticancer Res* 2013;33:3487-94.

ABSTRACT - Background: Bevacizumab has provided encouraging results in relapsed glioblastoma multiforme (GBM). Pre-clinical and clinical investigations also showed that continuous low-dose temozolomide has some antiangiogenic activity. Based on this evidence, a phase II trial was designed to investigate an oral regimen of sorafenib, an oral multikinase inhibitor, and metronomic temozolomide for relapsed GBM. Patients and methods: Forty-three patients (median age=60.0 years) naive for antiangiogenic agents received 400 mg sorafenib twice daily plus TMZ 40 mg/m(2)/day until disease progression. Results: Toxicity, mostly grade 1-2, was manageable. Grade 3-4 toxicities were hand-foot syndrome (n=4), hypertension (n=2), and fatigue (n=3). Five patients (12%) achieved partial response, 18 (43%) stable disease, 20 (48%) showed progression. The median time-to-progression was 3.2 months, 6-month progression-free survival was 26%, and median overall survival was 7.4 months. Conclusion: This combination of sorafenib and temozolomide was feasible and safe, showing some activity in patients with relapsed GBM.
I.F. = 1,725
N. citazioni = 53

201. Stenner-Liewen F, Grünwald V, Greil R, **Porta C**. The clinical potential of temsirolimus in second or later lines of treatment for metastatic renal cell carcinoma. *Expert Rev Anticancer Ther* 2013;13:1021-33.

ABSTRACT - An impressive variety of targeted therapies has been approved for the treatment of metastatic renal cell carcinoma (mRCC). Despite promising progress, there are still unmet clinical needs. The optimal sequence of these agents in the therapeutic setting has not yet been determined. Most available data address first- and second-line therapy of clear cell RCC. The mTOR inhibitor temsirolimus has been approved for first-line treatment of mRCC, and there are new data addressing the use of temsirolimus in later therapeutic lines. Temsirolimus has discerning features compared with other currently registered drugs, such as its intravenous administration route-providing predictable bioavailability and adherence to treatment-and potential benefit in nonclear cell histologies. Here, we review the available literature on temsirolimus, with reference to data also available for everolimus, to determine its clinical potential in mRCC.
I.F. = 2,652
N. citazioni = 14

202. Procopio G, Verzoni E, Bracarda S, Ricci S, Sacco C, Ridolfi L, **Porta C**, Miceli R, Zilembo N, Bajetta E, on behalf of Italian Trials in Medical Oncology (ITMO) group. Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): final results of the ROSORC trial. *Ann Oncol* 2013;24:2967-71.

ABSTRACT - Background: The ROSORC trial, a randomised, phase II trial

comparing sorafenib plus interleukin (IL-2) versus sorafenib alone as first-line treatment of metastatic renal cell carcinoma (mRCC) failed to demonstrate differences in progression-free survival (PFS). Updated overall survival (OS) results are reported. Patients and Methods: In this study, 128 patients were randomised to receive sorafenib 400 mg twice daily plus subcutaneous IL-2 4.5 million international units (MIU) five times per week for 6 weeks every 8 weeks (arm A) or sorafenib alone (arm B). OS was estimated with the Kaplan-Meier method and compared with the two-sided log-rank test. Results: After a median follow-up of 58 months (interquartile range: 28-63 months), the median OS was 38 and 33 months in arms A and B, respectively (P = 0.667). The 5-year OS was 26.3% [95% confidence interval (CI) 15.9-43.5) and 23.1% (95% CI 13.2-40.5) for the combination- and single-agent arm, respectively. Most of the patients who were refractory to first-line treatment were subsequently treated with different targeted agents; they had a median survival greater than expected. Conclusions: This outcome suggests a synergistic effect of the subsequent therapies following sorafenib failure. Clinicaltrials.gov identifier: NCT00609401.

I.F. = 6,425

N. citazioni = 23

203. Buti S, **Porta C**. Axitinib dose titration: what's the limiting factor? *Lancet Oncol* 2013;14:1152-4 [Editorial].

Pharmacokinetic data suggest that for patients with metastatic renal-cell carcinoma an increased exposure to tyrosine kinase inhibitors could be associated with improved clinical outcome. To date, four approaches to increase drug exposure have been proposed. First, simple dose escalation until unacceptable toxic effects is reached (a strategy which has ultimately failed); second, changing the schedule from the beginning of treatment, or according to toxicity; third, adapting the dose according to evidence of specific polymorphisms in genes involved in drug pharmacokinetics; or, fourth, dose titration in patients who do not have substantial toxic effects during a lead-in period, when the drug is given at standard dose. This last approach has been chosen by Brian Rini and colleagues in The Lancet Oncology. They report the results of an intriguing randomised phase 2 study testing the activity of axitinib dose titration in treatment-naive patients with metastatic renal-cell carcinoma. Patients were initially placed on a 4 week lead-in period with a flat dose of axitinib of 5 mg twice daily. Those patients without uncontrolled hypertension (blood pressure 150/90 mm Hg or lower), grade 3 or 4 axitinib-related toxic effects, or dose reductions, and who were being treated with no more than two concurrent antihypertensive drugs, were eligible for titration, and were randomly assigned to receive either titration with axitinib (an initial dose of 7 mg twice daily, to be increased to a maximum of 10 mg twice daily) or placebo; both patients and investigators were blinded to titration group. Those patients not meeting the eligibility criteria continued to receive 5 mg of axitinib twice daily. The primary endpoint of the study was the proportion of patients achieving a partial or complete response in randomised groups. Of the 213 patients enrolled, just 112 (52%) patients were dose titrated; of these patients, 30 (54%, 95% CI 40–67) of 56 patients from the axitinib titration group achieved an objective response, compared with 19 (34%, 22–48) of 56 patients in the placebo titration group (one-sided p=0·019). Unfortunately (and someway surprisingly), achieving an objective response had no effect on progression-free survival; indeed, median progression-free survival was 14·5 months with axitinib titration, compared with 15·7 months with placebo titration (hazard ratio 0·85; 95% CI 0·54–1·35; one-sided stratified p=0·24). Higher, but manageable, treatment-related toxic effects were noted in the axitinib titration group. Available pharmacokinetic data showed lower drug exposure in those patients who were eligible for dose titration, and that dose titration conferred proportionally increased drug exposure in the active-titration group. This study challenges the concept of giving tyrosine-kinase inhibitors at a flat dose. Toxicity-driven dose titration has been shown to be feasible, and results in increased number of patients achieving an objective response—albeit at the cost of greater toxic effects. In line with data obtained for other drugs, only a small subset of patients were eligible to receive the dose titration; furthermore, only 11% of the randomised patients were Asian, suggesting this strategy is for selected patients only (ie, those without significant toxicity). Axitinib dose titration seemed to only affect those patients with stable disease, who shifted from stable disease to partial response. By contrast, primary refractory patients were unaffected, with about 20% of patients having progressive disease in both the axitinib and placebo titrated groups. This possibility could also explain the similarities between the two progression-free survival curves within the first 2 months of treatment. Moreover, the median duration in the axitinb titration group was short (1·8 months [range 0·1–27·6] with 7 mg, and 3·5 months [<0·1–30·4] with 10 mg), and more common dose reductions in the active titration group than in the placebo titration group (14 [25%] of 56 patients vs five [9%] of 56 patients received dose reductions, respectively) could explain the absence of effect on progression-free survival, and the better progression-free survival in the placebo titration group between months 2 and 6. Beyond these speculations, what clinical relevance does an increased proportion of patients achieving an objective response have, if it has no impact on progression-free survival? Indeed, the confidence interval for the hazard ratio of progression-free survival includes unity, and the progression-free survival curves overlap in several points. This strategy could probably fit just the neoadjuvant setting, especially in cases in which the tumour burden needs to be reduced to facilitate surgery. Another key issue is the acceptability of greater patient toxicity: will the typical unselected (and often, less motivated) patient really accept enduring more, and worse, adverse events in exchange for greater efficacy? Indeed, would the average oncologist be willing to accept the above trade-off? Finally, the lack of patient prognostic data (Heng and MSKCC scores) makes it difficult to compare the results of this study with those of the phase 3 study comparing efficacy of axitinib and sorafenib in the same patient setting reported by Hutson and colleagues. In conclusion, toxicity-driven axitinib dose titration to toxicity improves drug exposure and results in better antitumour activity. Perhaps we should revise our way of thinking about how we administer tyrosine-kinase inhibitors in patients with metastatic renal-cell carcinoma; perhaps these drugs have more in common with chemotherapy than we thought (eg, a dose-response relation). Nevertheless, dose titration to toxicity is not yet ready to become standard practice, given that it does not seem easily applicable to the majority of patients, due to the greater toxicity and subsequent possible resistance by patients and physicians themselves.

I.F. = 22,589

N. citazioni = 5

204. Paglino C, Procopio G, Sabbatini R, Bellmunt J, Schmidinger M, Bearz A, Bamias A, Melichar B, Imarisio I, Tinelli C, **Porta C**. A retrospective analysis of two different sequences of therapy lines for advanced kidney cancer. *Anticancer Res* 2013;33:4999-5004.

ABSTRACT - Background/Aim: the ideal sequence of targeted agents for advanced kidney cancer is still unknown. In the present study we assessed the clinical benefit of two different sequential approaches, namely sorafenib, an inhibitor of mammalian target of rapamycin (mTORi) and sunitinib, or sunitinib (an mTORi) and sorafenib. Patients and Methods: we retrospectively reviewed the outcome of 40 advanced kidney cancer patients treated with one of the two above sequences. Results: a total of 26 patients were treated with the sequence sorafenib-mTORi-sunitinib and 14 with the sequence sunitinib-mTORi-sorafenib. The actuarial overall median progression-free survival (PFS) in the sorafenib-mTORi-sunitinib group and in the sunitinib-mTORi-sorafenib group were 21.9 and 22.8 months, respectively (log-rank test: p=0.928). In the sorafenib-mTORi-sunitinib group, patients in first-,

second- and third-line therapy experienced PFS of 11.7, 5.1 and 9.1 months, respectively, while in the sunitinib-mTORi-sorafenib group PFS was 14.4, 4.3, and 3.9 months, respectively. Conclusion: our results suggest there is no significant difference between the two sequence modalities.
I.F. = 1,725
N. citazioni = 4

205. Santini D, Procopio G, **Porta C**, Ibrahim T, Barni S, Mazzara C, Fontana A, Berruti A, Berardi R, Vincenzi B, Ortega C, Ottaviani D, Carteni G, Lanzetta G, Virzì V, Santoni M, Silvestris N, Satolli MA, Collovà E, Russo A, Badalamenti G, Fedeli SL, Tanca FM, Adamo V, Maiello E, Sabbatini R, Felici A, Cinieri S, Tonini G, Bracarda S. Natural history of malignant bone disease in renal cancer: final results of an italian bone metastasis survey. *PLoS One* 2013;8:e83026.

ABSTRACT - The aim of this study was to assess the treatment patterns and safety of sunitinib, sorafenib and bevacizumab in real-world clinical settings in US, Europe and Asia. Medical records were abstracted at 18 community oncology clinics in the US and at 21 tertiary oncology centers in US, Europe and Asia for 883 patients ≥ 18 years who had histologically/cytologically confirmed diagnosis of advanced RCC and received sunitinib (n=631), sorafenib (n=207) or bevacizumab (n=45) as first-line treatment. No prior treatment was permitted. Data were collected on all adverse events (AEs) and treatment modifications, including discontinuation, interruption and dose reduction. Treatment duration was estimated using Kaplan-Meier analysis. Demographics were similar across treatment groups and regions. Median treatment duration ranged from 6.1 to 10.7 months, 5.1 to 8.5 months and 7.5 to 9.8 months for sunitinib, sorafenib and bevacizumab patients, respectively. Grade 3/4 AEs were experienced by 26.0, 28.0 and 15.6% of sunitinib, sorafenib and bevacizumab patients, respectively. Treatment discontinuations occurred in 62.4 (Asia) to 63.1% (US) sunitinib, 68.8 (Asia) to 90.0% (Europe) sorafenib, and 66.7 (Asia) to 81.8% (US) bevacizumab patients. Globally, treatment modifications due to AEs occurred in 55.1, 54.2 and 50.0% sunitinib, sorafenib and bevacizumab patients, respectively. This study in a large, global cohort of advanced RCC patients found that angiogenesis inhibitors are associated with high rates of AEs and treatment modifications. Findings suggest an unmet need for more tolerable agents for RCC treatment.
I.F. = 3,73
N. citazioni = 48

206. Secondino S, Turin I, Montini E, **Porta C**, Maccario R, Pedrazzoli P, Montagna D. Case report: long-lasting response in a patient with metastatic renal cell cancer receiving antitumor cytotoxic T lymphocytes. *Tumori* 2013;99:e282-4.

ABSTRACT - Aims and background: Adoptive immunotherapy can be a therapeutic option to treat cancer patients with advanced-stage disease refractory to conventional therapies. Methods and study design: We used T-cell therapy with autologous antitumor cytotoxic T lymphocytes (CTLs) in a patient with metastatic renal cell carcinoma. Autologous antitumor CTLs obtained by stimulating CD8-enriched cells with dendritic cells pulsed with irradiated apoptotic tumor cells and expanded in vitro were transfused on days +14 and +28 following chemotherapy and every 2 to 4 months thereafter. Results and conclusions: Treatment with high doses of antitumor CTLs proved to be safe and induced immunological responses and long-lasting clinical benefit in our patient.
I.F. = 1,09

207. Moccia F, Dragoni S, Poletto V, Rosti V, Tanzi F, Ganini C, **Porta C**. Orai1 and transient receptor potential channels as novel molecular targets to impair tumor neovascularisation in Renal Cell Carcinoma and other malignancies. *Anticancer Agents Med Chem* 2014;14:296-312.

ABSTRACT - The term "angiogenic switch" describes one of the earlier events of tumorigenesis, that occurs when the balance between pro- and anti-angiogenic factors shifts towards a pro-angiogenic outcome. This leads to the transition from a microscopic indolent lesion to a macroscopic and vascularised primary tumor, that may eventually metastatize and spread to distant sites. The molecular mechanisms underlying such a critical step in the carcinogenetic process have been extensively investigated. Both local endothelial cells (ECs) and endothelial progenitor cells (EPCs), recruited from bone marrow, have been implicated in the angiogenic switch, which is ultimately triggered by a plethora of growth factors released by cancer cells, pivotal among which is vascular endothelial growth factor (VEGF); indeed, VEGF both activates ECs nearby the growing tumour, and leads to EPC mobilization into the circulation. In kidney, in particular, the frequent mutation of the Von Hippel Lindau tumor suppressor gene leads to an overproduction of pro-angiogenic factors which makes this neoplasm quite sensitive to antiangiogenic drugs. However, it is now evident that the use of VEGF(Rs) inhibitors in everyday clinical practice is not as effective as observed in murine models.The investigation of alternative signalling pathways involved in the angiogenic switch is, therefore, imperative in order to induce tumour regression whereby preventing harmful drawback consequences. Ca2+ entry across the plasma membrane has long been known to stimulate mature ECs to undergo angiogenesis. Recent work from several groups worldwide has then outlined that members of the Transient Receptor Potential (TRP) superfamily of cationic channels and Orai1 provide the pathway for such proangiogenic Ca2+ signal. In addition, Canonical TRP 1 (TRPC1) and Orai1 channels control proliferation and tubulogenesis in both normal EPCs and EPCs isolated from peripheral blood of tumour patients. As a consequence, TRP channels and Orai1 might serve as novel molecular targets to develop alternative and more effective strategies of angiogenesis inhibition.
I.F. = 2,61
N. citazioni = 42

208. **Porta C**, Vercelli A, Paglino C. Slow and steady wins the race: practical (and philosophical) considerations of treatment activity evaluation when novel anticancer agents just slow neoplastic progression. *Eur Urol* 2014;65:721-2 [Editorial].

The question of how to measure antitumor treatment activity in the era of molecularly targeted agents is anything but trivial. This is especially so in diseases like kidney cancer, where, because of the availability of a number of active agents that are often used sequentially, progression-free survival (PFS) has replaced overall survival (OS)—once the holy grail of oncology—as the most reasonable, although not ideal, primary end point of clinical trials. We have learned over the years that many of these novel agents exert more cytostatic than cytotoxic activity or, at least, that they induce limited, albeit discrete, tumor shrinkage. This does not take into account the issue of pseudoprogression (or initial progression followed by tumor shrinkage), a phenomenon once dramatically relevant only in relatively rare cancers such as gastrointestinal stromal tumors but now of interest after the first experiences

with novel immunotherapeutics (eg, anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies), regardless of tumor type. These issues have raised questions about the usefulness of commonly accepted Response Evaluation Criteria in Solid Tumors (RECIST) for patients receiving targeted or novel immunologic agents. In this month's issue of the Platinum Journal, Ferté and colleagues provide evidence that the tumor growth rate (TGR) is associated with prognosis (PFS and OS) in kidney cancer patients treated with two different targeted agents (ie, sorafenib and everolimus), allowing for early and precise evaluation of drug activity compared with RECIST evaluation. TGR is a relatively complex computation that combines the RECIST sums of the target lesions and the time between tumor imaging, including pretreatment, off-treatment, and postprogression periods. Notably, with this method, the authors demonstrated persistent activity of sorafenib at progression and an apparent flare-up effect after drug discontinuation; this pattern was not observed in everolimus-treated patients. Given this finding, a difficult key question arises: When should we really stop treatment if, with some agents (eg, sorafenib), slowing of tumor growth may be observed beyond progression but tumor flare may occur at treatment discontinuation? This pattern of drug activity over time seems to support a very practical approach of some kidney cancer specialists (although not common practice among general oncologists), namely, to continue treatment beyond (limited) progression, changing the drug only in case of numerical or massive dimensional progression. However, those of us who acted this way did not take into account those putative differences between agents suggested in the paper by Ferté and colleagues. Continuing treatment beyond progression is quite difficult, although not impossible, to perform and to explain to patients, especially in the presence of several alternatives; however, this approach could help us optimize some of the drugs within our cancer armamentarium. Yet, the practical application of this strategy is hampered not by the art of medicine but by health economics. In some countries (e.g., Italy), the national health system reimburses high-cost targeted agents only until progression is documented and definitely not beyond. Consequently, continuing treatment despite progression could be quite complicated at best. In conclusion, although the provocative paper by Ferté and colleagues needs validation and probably is not applicable outside referral centers like Institut Gustave Roussy, the authors raise some key questions about how best to evaluate tumor response to targeted agents, when to stop treatment, and how to integrate such decisions with economic issues. To date, none of these questions has a clear-cut, evidence-based answer. Fortunately, medicine is still more art than pure science.
I.F. = 8,493

209. Romero AI, Chaput N, Poirier-Colame V, Rusakiewicz S, Jacquelot N, Chaba K, Mortier E, Jacques Y, Caillat-Zûcman S, Flament C, Caignard A, Messaoudene M, Auperin A, Vielh P, Dessen P, **Porta C**, Mateus C, Ayyoub M, Valmori D, Eggermont A, Robert C, Zitvogel L. Regulation of CD4+NKG2D+ Th1 cells in patients with metastatic melanoma treated with Sorafenib: role of IL-15Rα and NKG2D triggering. *Cancer Res* 2014;64:68-80.

ABSTRACT - Beyond cancer-cell intrinsic factors, the immune status of the host has a prognostic impact on cancer patients and influences the effects of conventional chemotherapies. Metastatic melanoma (MM) is intrinsically immunogenic, thereby facilitating the search for immune biomarkers of clinical responses to cytotoxic agents. Here we show that a multi-tyrosine kinase inhibitor, sorafenib, upregulates IL-15Rα in vitro and in vivo in melanoma patients, and in conjunction with NKG2D ligands, contributes to the Th1 polarization and accumulation of peripheral CD4+NKG2D+T cells. Hence, the increase of blood CD4+NKG2D+T cells after two cycles of sorafenib (combined with temozolomide) was associated with prolonged survival in a prospective phase 1/2 trial enrolling 63 MM patients who did not receive vemurafenib nor immune checkpoint blocking antibodies. In contrast, in MM treated with classical treatment modalities, this CD4+NKG2D+ subset failed to correlate with prognosis. These findings indicate that sorafenib may be used as an "adjuvant" molecule capable of inducing or restoring IL-15Rα/IL-15 in tumors expressing MICA/B and on circulating monocytes of responding patients, hereby contributing to the bioactivity of NKG2D+ Th1 cells.
I.F. = 8,65
N. citazioni = 33

210. Escudier B, Heng DY, Smyth-Medina A, **Porta C**. Considerations for the design of future clinical trials in metastatic Renal Cell Carcinoma. *Clin Genitourin Cancer* 2014;12:1-12.

ABSTRACT - Metastatic renal cell carcinoma (mRCC) remains incurable in most cases, and there is a need to improve outcomes through clinical research, which will include development of novel molecularly targeted or immunotherapeutic agents. There are also many remaining questions regarding the optimization of currently available regimens, including the utility of dose escalation, the benefit of combination therapy, and the optimal sequences of therapies. Addressing these clinical questions will require careful planning and the inclusion of novel elements in trial designs. Future trials should include molecular phenotyping and selection of patients most likely to benefit from targeted therapies. In this article, we consider lessons learned from previous trials in mRCC and discuss how these lessons might be implemented in the design of future trials that focus on clinically useful questions and provide results that can be readily interpreted. The ultimate aim of the next generation of mRCC trials will be rapid cost-effective identification, testing, and approval of agents that can improve prognosis in this challenging disease.
I.F. = 1,429
N. citazioni = 5

211. Oh WK, McDermott D, **Porta C**, Levy A, Elaidi R, Scotte F, Hawkins R, Castellano D, Bellmunt J, Rha SY, Sun JM, Nathan P, Feinberg BA, Scott J, McDermott R, Ahn JH, Wagstaff J, Chang YH, Ou YC, Donnellan P, Huang CY, McCaffrey J, Chiang PH, Chuang CK, Korves C, Neary MP, Diaz JR, Mehmud F, Duh MS. Angiogenesis inhibitor therapies for advanced renal cell carcinoma: toxicity and treatment patterns in clinical practice from a global medical chart review. *Int J Oncol* 2014;44:5-16.

ABSTRACT - The aim of this study was to assess the treatment patterns and safety of sunitinib, sorafenib and bevacizumab in real-world clinical settings in US, Europe and Asia. Medical records were abstracted at 18 community oncology clinics in the US and at 21 tertiary oncology centers in US, Europe and Asia for 883 patients ≥ 18 years who had histologically/cytologically confirmed diagnosis of advanced RCC and received sunitinib (n=631), sorafenib (n=207) or bevacizumab (n=45) as first-line treatment. No prior treatment was permitted. Data were collected on all adverse events (AEs) and treatment modifications, including discontinuation, interruption and dose reduction. Treatment duration was estimated using Kaplan-Meier analysis. Demographics were similar across treatment groups and regions. Median treatment duration ranged from 6.1 to 10.7 months, 5.1 to 8.5 months and 7.5 to 9.8 months for sunitinib, sorafenib and bevacizumab patients, respec-

tively. Grade 3/4 AEs were experienced by 26.0, 28.0 and 15.6% of sunitinib, sorafenib and bevacizumab patients, respectively. Treatment discontinuations occurred in 62.4 (Asia) to 63.1% (US) sunitinib, 68.8 (Asia) to 90.0% (Europe) sorafenib, and 66.7 (Asia) to 81.8% (US) bevacizumab patients. Globally, treatment modifications due to AEs occurred in 55.1, 54.2 and 50.0% sunitinib, sorafenib and bevacizumab patients, respectively. This study in a large, global cohort of advanced RCC patients found that angiogenesis inhibitors are associated with high rates of AEs and treatment modifications. Findings suggest an unmet need for more tolerable agents for RCC treatment.

I.F. = 2,657

N. citazioni = 30

212. Motzer RJ, **Porta C**, Vogelzang NJ, Sternberg CN, Szczylik C, Zolnierek J, Kollmannsberger C, Rha SY, Bjarnason GA, Melichar B, De Giorgi U, Grünwald V, Davis ID, Lee J-L, Esteban E, Urbanowitz G, Squires M, Marker M, Shi MM, Escudier B. Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. *Lancet Oncology* 2014;15:286-96.

ABSTRACT - Background: An unmet medical need exists for patients with metastatic renal cell carcinoma (RCC) who have progressed on a vascular endothelial growth factor (VEGF)-targeted therapy and a mammalian target of rapamycin (mTOR) inhibitor. Fibroblast growth factor (FGF) pathway activation has been proposed as a mechanism of escape from VEGF-targeted therapies. Dovitinib is an oral tyrosine kinase inhibitor that inhibits VEGF and FGF receptors. This multicenter phase 3 study compared dovitinib with sorafenib as a third-line targeted therapy in metastatic RCC. Methods: Patients with clear cell metastatic RCC who received one prior VEGF-targeted therapy and one prior mTOR inhibitor were randomized by interactive voice or web response system to receive open-label dovitinib (500 mg orally on a 5-days-on/2-days-off schedule) or sorafenib (400 mg orally twice daily) in a 1:1 ratio. Randomization was stratified by risk group and region. The primary endpoint was progression-free survival (PFS) by blinded central review. Efficacy was evaluated in all randomized patients and safety was assessed in patients who received at least one dose of study drug. The ongoing study, NCT01223027, is registered on www.clinicaltrials.gov. Findings: A total of 570 patients were enrolled in the trial, with a median follow up of 11·3 months (interquartile range 7·9-14·6 months). The median PFS was 3·7 months (95% CI, 3·5-3·9) for dovitinib (n = 284) and 3·6 months (95% CI, 3·6-3·7) for sorafenib (n = 286) (hazard ratio [HR], 0·86; 95% CI, 0·72-1·04; one-sided P = 0·063). Two hundred-eighty patients in the dovitinib arm and 284 patients in the sorafenib arm received at least one dose of study drug. Common grade 3/4 adverse events included fatigue (28[10%]), hypertension (22[8%]), and diarrhea (20[7%]) in the dovitinib arm, and hypertension (47[17%]), fatigue (24[8%]), and palmar-plantar erythrodysesthesia (18[6%]) in the sorafenib arm. The most common serious adverse event was dyspnea (16[6%] and 15 [5%] in the dovitinib and sorafenib arms, respectively). Interpretation: Dovitinib demonstrated activity but not superior efficacy compared with sorafenib in patients who progressed on prior VEGF-targeted therapies and mTOR inhibitors. This trial provides reference outcome data for future studies in this third-line setting.

I.F. = 25,117

N. citazioni = 211

213. Procopio G, Derosa L, Gernone A, Morelli F, Sava T, Zustovich F, De Giorgi U, Ferrari V, Sabbatini R, Gasparro D, Felici A, Burattini L, Calvani N, Lo Re G, Banna G, Brizzi MP, Rizzo M, Ciuffreda L, Iacovelli R, Ferraù F, Taibi E, Bracarda S, **Porta C**, Galligioni E, Contu A. Sorafenib as first- or second-line therapy in patients with metastatic renal cell carcinoma in a community setting. *Future Oncol* 2014;10:1741-50.

ABSTRACT - Aim: The Italian Retrospective Analysis of Sorafenib as First or Second Target Therapy study assessed the efficacy and safety of sorafenib in metastatic renal cell carcinoma patients treated in the community. Patients & methods: Patients receiving first- or second-line single-agent sorafenib between January 2008 and December 2010 were eligible. Retrospective data collection started in 2012 and covers at least 1-year follow-up. The primary end point was overall survival (OS). Results: Median OS was 17.2 months (95% CI: 15.5-19.6): 19.9 months (95% CI: 15.9-25.3) in patients treated with first-line sorafenib and 16.3 months (95% CI: 13.1-18.2) with second-line sorafenib. Overall median (95% CI) progression-free survival was 5.9 months (95% CI: 4.9-6.7): 6.6 (95% CI: 4.9-9.3) and 5.3 months (95% CI: 4.3-6.0) in first- and second-line patients, respectively. Conclusion: The efficacy and safety of sorafenib in routine community practice was generally good, especially in relation to OS in patients treated in the second line, where results were similar to those seen in recent prospective clinical trials.

I.F. = 3,163

N. citazioni = 14

214. Aapro M, Andre F, Blackwell K, Calvo E, Jahanzeb M, Papazisis K, **Porta C**, Pritchard K, Ravaud A. Adverse event management in patients with advanced cancer receiving oral everolimus: focus on breast cancer. *Ann Oncol* 2014;25:763-73.

ABSTRACT - Background: Everolimus, an orally administered rapamycin analogue, inhibits the mammalian target of rapamycin (mTOR), a highly conserved intracellular serine-threonine kinase that is a central node in a network of signaling pathways controlling cellular metabolism, growth, survival, proliferation, angiogenesis, and immune function. Everolimus has demonstrated substantial clinical benefit in randomized, controlled, phase III studies leading to approval for the treatment of advanced renal cell carcinoma, advanced neuroendocrine tumors of pancreatic origin, renal angiomyolipoma and subependymal giant-cell astrocytoma associated with tuberous sclerosis complex, as well as advanced hormone-receptor-positive (HR(+)) and human epidermal growth factor receptor-2-negative advanced breast cancer. Materials and methods: We discuss clinically relevant everolimus-related adverse events from the phase III studies, including stomatitis, noninfectious pneumonitis, rash, selected metabolic abnormalities, and infections, with focus on appropriate clinical management of these events and specific considerations in patients with breast cancer. Results: The majority of adverse events experienced during everolimus therapy are of mild to moderate severity. The safety profile and protocols for toxicity management are well established. The class-effect adverse event profile observed with everolimus plus endocrine therapy in breast cancer is (as expected) distinct from that of endocrine therapy alone, but is similar to that observed with everolimus in other solid tumors. Information gained from the experience in other carcinomas on prompt diagnosis and treatments to optimize drug exposure, treatment outcomes, and patients' quality of life also applies to the patient population with advanced breast cancer. Conclusions: As with all orally administered agents, education of both physicians and patients in the management of adverse events for patients receiving everolimus is critical to achieving optimal exposure and clinical benefit. Active monitoring for early identification

of everolimus-related adverse events combined with aggressive and appropriate intervention should lead to a reduction in the severity and duration of the event.

I.F. = 7,384

N. citazioni = 65

215. Escudier B, **Porta C**, Bono P, Powles T, Eisen T, Sternberg CN, Gschwend JE, De Giorgi U, Parik O, Hawkins R, Sevin E, Négrier S, Khan S, Diaz J, Redhu S, Mehmud F, Cella D. A randomized, controlled, double-blind, crossover trial assessing treatment preference for Pazopanib versus Sunitinib in patients with metastatic Renal Cell Carcinoma (PISCES study). *J Clin Oncol* 2014;32:1412-8.

ABSTRACT - Purpose: Patient-reported outcomes may help inform treatment choice in advanced/metastatic renal cell carcinoma (RCC), particularly between approved targeted therapies with similar efficacy. This double-blind cross-over study evaluated patient preference for pazopanib or sunitinib and the influence of health-related quality of life (HRQoL) and safety factors on their stated preference. Patients and methods: Patients with metastatic RCC were randomly assigned to pazopanib 800 mg per day for 10 weeks, a 2-week washout, and then sunitinib 50 mg per day (4 weeks on, 2 weeks off, 4 weeks on) for 10 weeks, or the reverse sequence. The primary end point, patient preference for a specific treatment, was assessed by questionnaire at the end of the two treatment periods. Other end points and analyses included reasons for preference, physician preference, safety, and HRQoL. Results: Of 169 randomly assigned patients, 114 met the following prespecified modified intent-to-treat criteria for the primary analysis: exposure to both treatments, no disease progression before cross over, and completion of the preference questionnaire. Significantly more patients preferred pazopanib (70%) over sunitinib (22%); 8% expressed no preference (P < .001). All preplanned sensitivity analyses, including the intent-to-treat population, statistically favored pazopanib. Less fatigue and better overall quality of life were the main reasons for preferring pazopanib, with less diarrhea being the most cited reason for preferring sunitinib. Physicians also preferred pazopanib (61%) over sunitinib (22%); 17% expressed no preference. Adverse events were consistent with each drug's known profile. Pazopanib was superior to sunitinib in HRQoL measures evaluating fatigue, hand/foot soreness, and mouth/throat soreness. Conclusion: This innovative cross-over trial demonstrated a significant patient preference for pazopanib over sunitinib, with HRQoL and safety as key influencing factors

I.F. = 18,038

N. citazioni = 316

216. **Porta C**, Paglino C, Mosca A. Targeting PI3K/Akt/mTOR Signaling in Cancer. *Front Oncol* 2014;4:e64.

ABSTRACT - The phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) signaling pathways are two pathways crucial to many aspects of cell growth and survival, in physiological as well as in pathological conditions (e.g., cancer). Indeed, they are so interconnected that, in a certain sense, they could be regarded as a single, unique pathway. In this paper, after a general overview of the biological significance and the main components of these pathways, we address the present status of the development of specific PI3K, Akt, and mTOR inhibitors, from already registered medicines to novel compounds that are just leaving the laboratory bench.

I.F. = n.r.

N. citazioni = 785

217. **Porta C**, Paglino C, Grunwald. Sunitinib re-challenge in advanced renal-cell carcinoma. *Br J Cancer* 2014;111:1047-53.

ABSTRACT - Despite offering significant benefits in advanced renal-cell carcinoma (RCC), the effectiveness of targeted therapies eventually declines with the development of resistance. Defining optimal sequences of therapy is therefore the focus of much current research. There is also evidence that treatment 're-challenge' may be an effective strategy in some patients. We review evidence to evaluate whether Sunitinib Sunitinib may have value as re-challenge therapy in patients who have progressed on prior targeted therapy with Sunitinib and/or alternative tyrosine kinase inhibitor or mammalian target of Rapamycin inhibitor. Re-challenge with Sunitinib appears to be of clinical benefit, thus representing a feasible therapeutic optionfor patients with advanced RCC who are refractory to other treatments and are able to receive further therapy. These observations support hypotheses that resistance to targeted agents is transient and can be at least partially reversed by re-introduction of the same agent after a treatment break. Median progression-free survival durations appear to be shorter and reponse rates lower on re-challenge than following initial treatment, atough a wider interval between treatments appears to increase response to Sunitinib re-challenge.

I.F. = 5,082

N. citazioni = 32

218. Bellmunt J, Pons F, Foreshew A, Fay AP, Powles T, **Porta C**, Bracarda S, Lampron ME, Cerbone L, Sternberg CN, Hutson TE, Choueiri TK. Sequential targeted therapy after Pazopanib therapy in patients with metastatic renal cell cancer: efficacy and toxicity. *Clin Genitourin Cancer* 2014;12:262-9.

ABSTRACT - Introduction/Background - Patients with metastatic renal cell carcinoma (mRCC) in whom first-line therapies have failed might derive clinical benefit with sequential targeted agents. Limited data are available on the efficacy and toxicity of subsequent therapies after disease progression during pazopanib therapy. Patients and methods - Patients with mRCC who received subsequent systemic treatment after pazopanib treatment failure were identified across 7 institutions. Pazopanib was given as first-line therapy in 28 patients and after cytokines therapy in 7 patients. Clinical outcome and toxicity analyses of 2 sequential treatment options (anti-vascular endothelial growth factor [VEGF] or mammalian target of rapamycin inhibitor [mTORi]) is presented. Results - Subsequent therapy was anti-VEGF in 22 patients and mTORi in 13. One patient who received bevacizumab and temsirolimus combination was excluded. VEGF-targeted therapies included sorafenib (n = 10), sunitinib (n = 3), bevacizumab (n = 2), cediranib (n = 4) and cabozantinib (n = 3). Patients treated with mTORi received everolimus. Median progression-free survival was 5.6 months from the start of subsequent therapy with anti-VEGF and 2.4 months with mTORi (P = .009). Overall survival (OS) was not significantly different (P = .68). Clinical benefit (including partial response and stable disease) on subsequent therapy was observed in 15 patients (64%) and 4 patients (31%) of anti-VEGF- and everolimus-treated patients, respectively (P = .021). Conclusion - In this retrospective study, targeting VEGF was an effective strategy after disease progression during pazopanib treatment, although OS was not different among patients treated with VEGF or mTORi.

I.F. = 1,429

N. citazioni = 9

219. **Porta C**, Levy A, Hawkins R, Castellano D, Bellmunt J, Nathan P, McDermott R, Wagstaff J, Donnellan P, McCaffrey J, Vekeman F, Neary MP, Diaz J, Mehmud F, Duh MS. Impact of adverse events, treatment modifications, and dose intensity on survival among patients with advanced renal cell carcinoma treated with first-line sunitinib: a medical chart review across ten centers in five European countries. *Cancer Med* 2014;3:1517-26.

ABSTRACT - Angiogenesis inhibitors have become standard of care for advanced and/or metastatic renal cell carcinoma (RCC), but data on the impact of adverse events (AEs) and treatment modifications associated with these agents are limited. Medical records were abstracted at 10 tertiary oncology centers in Europe for 291 patients ≥18 years old treated with sunitinib as first-line treatment for advanced RCC (no prior systemic treatment for advanced disease). Logistic regression models were estimated to compare dose intensity among patients who did and did not experience AEs during the landmark periods (18, 24, and 30 weeks). Cox proportional hazard models were used to explore the possible relationship of low-dose intensity (defined using thresholds of 0.7, 0.8, and 0.9) and treatment modifications during the landmark periods to survival. 64.4% to 67.9% of patients treated with sunitinib reported at least one AE of any grade, and approximately 10% of patients experienced at least one severe (grade 3 or 4) AE. Patients reporting severe AEs were statistically significantly more likely to have dose intensities below either 0.8 or 0.9. Dose intensity below 0.7 and dose discontinuation during all landmark periods were statistically significantly associated with shorter survival time. This study of advanced RCC patients treated with sunitinib in Europe found a significant relationship between AEs and dose intensity. It also found correlations between dose intensity and shorter survival, and between dose discontinuation and shorter survival. These results confirm the importance of tolerable treatment and maintaining dose intensity.
I.F. = n.r.
N. citazioni = 47

220. Dragoni S, Turin I, Laforenza U, Potenza DM, Bottino C, Glasnov TN, Prestia M, Ferulli F, Saitta A, Mosca A, Guerra G, Rosti V, Luinetti O, Ganini C, **Porta C**, Pedrazzoli P, Tanzi F, Montagna D, Moccia F. Store-operated Ca^{2+} entry does not control proliferation in primary cultures of human metastatic renal cellular carcinoma. *Biomed Res Int* 2014;2014:739494.

ABSTRACT - Store-operated Ca(2+) entry (SOCE) is activated following depletion of the inositol-1,4,5-trisphosphate (InsP3)-sensitive Ca(2+) pool to regulate proliferation in immortalized cell lines established from either primary or metastatic lesions. The molecular nature of SOCE may involve both Stim1, which senses Ca(2+) levels within the endoplasmic reticulum (ER) Ca(2+) reservoir, and a number of a Ca(2+)-permeable channels on the plasma membrane, including Orai1, Orai3, and members of the canonical transient receptor (TRPC1-7) family of ion channels. The present study was undertaken to assess whether SOCE is expressed and controls proliferation in primary cultures isolated from secondary lesions of heavily pretreated metastatic renal cell carcinoma (mRCC) patients. SOCE was induced following pharmacological depletion of the ER Ca(2+) store, but not by InsP3-dependent Ca(2+) release. Metastatic RCC cells express Stim1-2, Orai1-3, and TRPC1-7 transcripts and proteins. In these cells, SOCE was insensitive to BTP-2, 10 μM Gd(3+) and Pyr6, while it was inhibited by 100 μM Gd(3+), 2-APB, and carboxyamidotriazole (CAI). Neither Gd(3+) nor 2-APB or CAI impaired mRCC cell proliferation. Consistently, no detectable Ca(2+) signal was elicited by growth factor stimulation. Therefore, a functional SOCE is expressed but does not control proliferation of mRCC cells isolated from patients resistant to multikinase inhibitors.
I.F. = 2,706
N. citazioni = 46

221. Escudier B, **Porta C**, Schmidinger M, Algaba F, Patard JJ, Khoo V, Eisen T, Horwich A; ESMO Guidelines Working Group. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25(Suppl. 3):iii49-iii56.
I.F. = 6,578
N. citazioni = 295

222. Escudier B, **Porta C**, Powles T, Eisen T, Sternberg CN, Mehmud F, Cella D. PISCES: Reply to S. Barni et al. and Sun M. et al. *J Clin Oncol* 2014;32:3783-4.

We thank Barni and Petrelli and Sun et al for their interest in our report of the PISCES (Patient Preference Study of Pazopanib Versus Sunitinib in Advanced or Metastatic Kidney Cancer) trial. We certainly agree with our colleagues that efficacy is the primary goal of treatment. The antiangiogenic tyrosine kinase inhibitors (TKIs) pazopanib and sunitinib that were evaluated in PISCES are approved systemic options for advanced renal cell carcinoma. Previous adjusted indirect analysis suggested that their efficacy is comparable. Subsequently, the COMPARZ (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma) study demonstrated that the progression-free survival (PFS) benefit with pazopanib was noninferior to that of sunitinib in the first-line setting. Among agents with comparable efficacy, the choice of treatment may be informed by the relative tolerability of the agents. Thus, the primary objective of PISCES was to evaluate the impact of treatment-related toxicities on the patients, based on their preference for which drug they would choose to continue their treatment; this objective was predicated on the now validated assumption that both drugs (pazopanib and sunitinib) have similar efficacy. Patient preference was an important clinical question to address because of the potential for patients to have prolonged exposure to drug-related toxicitie. In regard to the contention that switching between in-class drugs may have compromised clinical benefit to the patient, we know of no molecular rationale or clinical observational data to suggest that this may be a risk. First, there is no evidence that the use of sequential vascular endothelial growth factor (VEGF) TKIs in the first-line metastatic renal cell carcinoma setting has a negative effect on PFS either for patients with stable or responding disease at the time of cross-over. Second, there is no evidence to suggest cross-resistance, given that disease control has been demonstrated with VEGF TKIs in patients progressing during receipt of other VEGF TKIs. In view of the similar potency of both drugs for VEGF receptor 2 (VEGFR2), the primary therapeutic target, it was thought unlikely that there would be a loss of efficacy resulting from a significant change in the suppression of the activity of this receptor. Finally, the risk of changing the biology of a tumor by switching TKIs before progression is even more unlikely, given the fact that VEGFR inhibitors primarily target tumor vessels and not tumor cells. It should also be noted that the study protocol was reviewed and approved by several institutional review boards and ethics committees. The authors also note that previous oncology studies to assess patient preference for agents with similar mechanisms of action employed a similar cross-over design before disease progression and have provided important data for the treating clinician. Indeed, other studies such as EVERSUN are currently evaluating preplan-

ned shifts from one agent to another in the absence of progression, translating to renal cell carcinoma an approach that was previously quite successful in lymphoma. Finally, all patients were informed of the result of their disease assessment scan before crossing over to the next drug, and patients had the option to withdraw from the study, be unblinded, and continue to receive treatment with either drug or another off-study second-line treatment at the discretion of the treating physician. Thus, there were no limitations with respect to options for second-line therapy, precluding ethical concerns that could affect the overall treatment plan. The clinical question addressed in PISCES necessitated a novel study design. The key aspect of this patient preference study was to expose the same patient to both drugs within a time frame that was short enough to avoid significant changes in disease status but long enough for the patient to experience the common adverse events associated with both drugs. The 10-week treatment period with each drug separated by a 2-week washout period was deemed an appropriate time to balance sufficient treatment duration, being able to cross over in a comparable health state (ie, minimize symptoms from increasing tumor burden and decrease in performance status), and to ascertain a preference among patients who had not experienced disease progression (per protocol) - hence, the restriction of the study duration to within half of the expected median PFS in this setting. We acknowledge that the inherent limitation of treatment exposure to just under 3 months may not reflect long-term patient experience because toxicities may become less bothersome over time as a result of patient tolerance or dose modifications. However, PISCES did capture the effects of treatment-related toxicity over a significant period of time in the lives of patients with advanced renal cell cancer, and the findings are consistent with the results of the COMPARZ study, which demonstrated that over a longer period of time (6 to 12 months), differences in quality of life remain in favor of pazopanib.

I.F. = 17,960

223. Passalacqua R, Caminiti C, Buti S, **Porta C**, Camisa R, Braglia L, Tomasello G, Vaglio A, Labianca R, Rondini E, Sabbatini R, Nastasi G, Artioli F, Prati A, Potenzoni M, Pezzuolo D, Oliva E, Alberici F, Buzio C; POLAR-01 Trial Investigators. Adjuvant Low-Dose Interleukin-2 (IL-2) Plus Interferon-α (IFN-α) in Operable Renal Cell Carcinoma (RCC): A Phase III, Randomized, Multicentre Trial of the Italian Oncology Group for Clinical Research (GOIRC). *J Immunother* 2014;37:440-7.

ABSTRACT - There is currently no standard therapy to reduce the recurrence rate after surgery for renal cell carcinoma (RCC). The aim of this study was to assess efficacy and safety of adjuvant treatment with low doses of interleukin-2 (IL-2)+interferon-[alpha] (IFN-[alpha]) in operable RCC. The patients were randomized 1:1 to receive a 4-week cycle of low-dose IL-2+IFN-[alpha] or observation after primary surgery for RCC. Treatment cycles were repeated every 4 months for the first 2 years and every 6 months for the subsequent 3 years. The primary endpoint was recurrence-free survival (RFS); safety; and overall survival (OS) were secondary endpoints. ClinicalTrials.gov registration number was NCT00502034. 303/310 randomized patients (156 in the immunotherapy arm and 154 in the observation group) were evaluable at the intention-to-treat analyses. The 2 arms were well balanced. At a median follow-up of 52 months (range, 12–151 mo), RFS, and OS were similar, with an estimated hazard ratio (HR) of 0.84 [95% confidence interval (CI), 0.54–1.31; P=0.44] and of 1.07 (95% CI, 0.64–1.79; P=0.79), respectively in the 2 groups. Unplanned, subgroup analysis showed a positive effect of the treatment for patients with age 60 years and younger, pN0, tumor grades 1-2, and pT3a stage. Among patients with the combined presence of >=2 of these factors, immunotherapy had a positive effect on RFS (HR=0.44; 95% CI, 0.24–0.82; P<=0.01), whereas patients with <2 factors in the treatment arm exhibited a significant poorer OS (HR=2.27; 95% CI, 1.03–5.03 P=0.037). Toxicity of immunotherapy was mild and limited to World Health Organization grade 1-2 in most cases. Adjuvant immunotherapy with IL-2+IFN-[alpha] showed no RFS or OS improvement in RCC patients who underwent radical surgery. The results of subset analysis here presented are only hypothesis generating.

I.F. = 3,354

N. citazioni = 51

224. Gore ME, Bellmunt J, Eisen T, Escudier B, Mickisch G, Patard J, **Porta C**, Ravaud A, Schmidinger M, Schöffski P, Sternberg CN, Szczylik C, Lewis S, Kirpekar S. Assessing the impact of evolving evidence in renal cell carcinoma treatment: an update of the Renal Cell Carcinoma Appropriateness-based Treatment Toolkit (ReCATT). *Eur J Cancer* 2014;50:3153-60.

ABSTRACT - The appropriateness of the numerous therapeutic options available for patients with advanced or metastatic renal cell carcinoma (RCC) was evaluated in 2011, using the RAND/University of California, Los Angeles (UCLA) appropriateness methodology to match treatment suitability to a range of patient scenarios. However, the RCC therapeutic area evolves rapidly and a body of new clinical data has accrued in the intervening years; as a result the exercise was repeated in 2013 using the same methodology, expert panel and patient scenarios. The aim of the updated assessment was to update the guidance to clinicians and use it to develop an interactive web-based application, the Renal Cell Carcinoma Appropriateness-based Treatment Toolkit (ReCATT). This round of assessment achieved greater concordance concerning the appropriateness of treatments/interventions for the clinical scenarios tested; this higher level of agreement is likely to reflect the body of scientific evidence accrued since the previous assessment exercise. Many of the areas of disagreement in 2011 related to the suitability of pazopanib or sunitinib treatment; in the 2013 assessment both agents were considered appropriate treatment options for many of the clinical scenarios assessed. Uncertain scenarios often are related to the optimal management of metastatic RCC with clear cell histology. The use of the RAND/UCLA RCC assessment findings to develop the ReCATT support tool will help to disseminate expert opinion concerning best treatment practice and guide the clinical management of RCC patients treated in the community setting.

I.F. = 4,819

N. citazioni = 5

225. Fiorini C, Massari F, Pedron S, Sanavio S, Ciccarese C, Porcaro AB, Artibani W, Bertoldo F, Zampini C, Sava T, Ficial M, Caliò A, Chilosi M, D'Amuri M, Sanguedolce F, Tortora GP, Scarpa A, Delahunt B, **Porta C**, Martignoni G, Brunelli M. Methods to identify molecular expression of mTOR pathway: a rationale approach to stratify patients affected by clear cell renal cell carcinoma for more likely response to mTOR inhibitors. *Am J Cancer Res* 2014;4:907-15.

ABSTRACT - Since target therapy with mTOR inhibitors plays an important role in the current management of clear cell renal cell carcinoma (RCC), there is an increasing demand for predictive biomarkers, which may help to select patients that are most likely to benefit from personali-

zed treatment. When dealing with formalin-fixed paraffin-embedded (FFPE) cancer tissue specimens, several techniques may be used to identify potential molecular markers, yielding different outcome in terms of accuracy. We sought to investigate and compare the capability of three main techniques to detect molecules performing an active function in mTOR pathway in RCC. Immunohistochemistry (IHC), Western blot (WB) and immunofluorescence (IF) analyses were performed on FFPE RCC tissue specimens from 16 patients by using the following mTOR pathway-related: mTOR (Ser235/236), phospho-mTOR (p-mTOR/Ser2448), phospho-p70S6k (p-p70S6k/Thr389), both monoclonal and polyclonal, phospho-S6Rb (p-S6Rb) and phospho-4EBP1 (p-4EBP1/Thr37/46). No single molecule was simultaneously revealed by all three techniques. Only p-p70S6k was detected by two methods (IHC and IF) using a monoclonal antibody. The other molecules were detected exclusively by one technique, as follows: p-mTOR and polyclonal p-p70S6K by IHC, p70S6K, p-S6Rb and p-4EBP1 by WB, and, finally, mTOR by IF. We found significant differences in detecting mTOR pathway-related active biomarkers by using three common techniques such as IHC, WB and IF on RCC samples. Such results have important implications in terms of predictive biomarker testing, and need to be related to clinical end-points such as responsiveness to targeted drugs by prospective studies.

I.F.: 3,968

N. citazioni = 8

226. Fusco V, **Porta C**, Saia G, Paglino C, Bettini G, Scoletta M, Bonacina R, Vescovi P, Merigo E, Lo Re G, Guglielmini P, Di Fede O, Campisi G, Bedogni A. Osteonecrosis of the jaw in patients with metastatic Renal Cell Cancer treated with Bisphosphonates and targeted agents: results of an Italian multicenter study and review of the Literature. *Clin Genitourin Cancer* 2015;13:287-94.

ABSTRACT - Osteonecrosis of the jaw (ONJ) associated with the use of bisphosphonates has been rarely reported in metastatic renal cell cancer (RCC) patients. Since the introduction of combined therapies consisting of nitrogen-containing bisphosphonates (NBPs) and targeted agents, an increasing number of RCC patients were reported to develop ONJ, suggesting that therapeutic angiogenesis suppression might increase the risk of ONJ in NBPs users. We performed a multicenter retrospective study and reviewed literature data to assess the occurrence and to investigate the nature of ONJ in RCC patients taking NBPs and targeted agents. Nine Italian Centers contributed to the data collection. Patients with exposed and nonexposed ONJ were eligible for the study if they had been taking NBPs and were receiving targeted agents at the time of ONJ diagnosis. Forty-four RCC patients were studied. Patients were mostly male (82%), with a median age of 63 years (range, 45-85 years). Zoledronic acid (93%) and sunitinib (80%) were the most frequently used NBP and antiangiogenic agent, respectively. Other agents included Pamidronate, ibandronate, sorafenib, bevacizumab, mammalian target of rapamycin inhibitors. Forty-nine sites of ONJ were encountered, with the mandible being the preferred site of ONJ (52%); both jaws were affected in 5 cases (12%). The most common precipitating event was dental/periodontal infection (34%), followed by tooth extraction (30%). Oral triggers of ONJ were missing in 10 cases (23%). This unexpectedly high number of ONJ cases, in comparison with literature data, suggests that frequency of ONJ in RCC patients might be largely underestimated and suggests a potential role for targeted agents in the incremental risk of ONJ.

I.F.: 1,693

N. citazioni = 37

227. **Porta C**, Bracarda S, Danesi R. Steroids in prostate cancer: the jury is still out ... and even more confused. *Eur Urol* 2015;67:680-1.

In cancer patients, steroids are often used to palliate symptoms related to coexisting inflammation due to the presence of the tumor itself in some metastatic sites (eg, the spine) or to certain anticancer treatments (eg, radiation therapy). They are also used as adjuvants to painkiller drugs or to antiemetics, as anabolizing agents, as lympholytic agents (in some hematologic malignancies), or as replacement therapy (eg, in patients with hypocorticosurrenalism due to different causes). The most exploited mechanism of action (MOA) of steroids remains the anti-inflammatory MOA. However, from other medical specialties (eg, rheumatology), we have learned that the relative anti-inflammatory potency of steroids varies greatly. Taking cortisol (ie, hydrocortisone), for example, as the standard reference and considering just the oral route of administration, the glucocorticoid potency of dexamethasone is reportedly 25–80 but is just 4 for prednisolone. In castration-resistant prostate cancer (CRPC), steroids may act as anticancer drugs; in this case, the MOA of corticosteroids has been linked putatively to inhibition of the pituitary production of adrenocorticotropic hormone, leading to reduced synthesis of adrenal androgens. However, the pharmacologic activity of glucocorticoids on cell proliferation is more complex and involves inhibition of transcription of multiple genes (including cyclooxygenase 2, cytokines, cell adhesion molecules, and nitric oxide synthase), blockage of genomic effects of vitamin D3, and increased synthesis of annexin-1. All of these effects are proportional to glucocorticoid potency. In addition, steroids are able to inhibit the production of vascular endothelial growth factor by tumor cells, thus reducing neoangiogenesis and lymphangiogenesis. In this issue of the Platinum Journal, Venkitaraman and colleagues reported the results of a randomized phase 2 trial comparing continuous low-dose dexamethasone, intermittent high-dose dexamethasone, and prednisolone in CRPC patients. With prostate-specific antigen (PSA) response rate as the primary end point of their study, the authors observed higher efficacy for dexamethasone in this setting. Furthermore, the intermittent high-dose dexamethasone arm was dropped after no response was seen in the first patients treated, suggesting that intermittent dexamethasone (given as premedication or as an antiemetic) does not have significant antitumor activity in CRPC. Beyond some methodological limitations (mainly relative to the small size of the population studied), the main result of this study—the superiority of dexamethasone—is somewhat expected, especially if we consider the above-reported different potency of the two steroids. What this study does not help us understand is the role of corticosteroids in prostate cancer—"friend or foe," as another recent editorial published in the Platinum Journal asked, without finding a clear-cut answer. What it is difficult to understand is why, according to the study of Venkitaraman and colleagues, the two steroids tested demonstrated activity against CRPC in terms of confirmed PSA response rates, time to PSA progression, and overall response rates, at least in those patients with measurable disease; in the subgroup analyses of the abiraterone and enzalutamide registrative studies, the use of corticosteroids was associated with poorer prognosis. Several mechanisms have been proposed over time and have been the subjects of a number of recent, authoritative papers, but the contradiction outlined above remains unresolved. In fact, the multifaceted role of corticosteroids is underscored by evidence that they may also promote androgen-independent growth. Indeed, induction of glucocorticoid receptor (GR) expression is a common feature of anti–androgen-resistant tumors in preclinical models and patient samples. GR may replace androgen receptor (AR) signaling and activate a number of genes associated with maintenance of the anti–androgen-resistant phenotype. Dexamethasone drives enzalutami-

de resistance, and short-term AR inhibition results in GR upregulation in prostate cancer cells due to AR-mediated negative feedback. Moreover, Carreira et al showed a temporal association between clinical progression and appearance of AR mutations selected by glucocorticoids in about 20% of patients progressing on abiraterone. Before the availability of novel agents such as abiraterone and enzalutamide, this issue could have been regarded as trivial. Today, this uncertainty is no longer acceptable. Translational research aimed at elucidating the complex effect of steroids on prostate cancer cells (eg, the potential to inhibit or promote prostate cancer cell proliferation), their role in modifying tumor milieu (with the coparticipation of other cell populations), and better understanding of the interaction between the AR and the GR pathways will be key to solving the above-mentioned contradiction and, more importantly, to understanding the results of recent and future trials of novel hormonal agents for CRPC.

I.F.: 10,476

N. citazioni = 3

228. Elaidi R, Harbaoui A, Beuselinck B, Eymard JC, Bamias A, De Guillebon E, **Porta C**, Vano Y, Linassier C, Debruyne PR, Gross-Goupil M, Ravaud A, Aitelhaj M, Marret G, Oudard S. Outcomes from second-line therapy in long-term responders to first-line tyrosine kinase inhibitor in clear-cell metastatic renal cell carcinoma. *Ann Oncol* 2015;26:378-85.

ABSTRACT - Background: Although sequential targeted therapy is standard in patients with metastatic clear-cell renal cell carcinoma (m-ccRCC), the choice of drugs and optimal administration sequence have yet to be established. The objective of this study was to explore whether it is preferable to rechallenge a long-term responder to a first-line tyrosine kinase inhibitor (TKI) with a TKI or whether to switch to a mammalian target of rapamycin inhibitor (mTORi); to determine whether second-line treatment response depends on duration of first-line response (TD1). Patients and methods: Retrospective multicenter study (2004-2011) of 241 consecutive mRCC patients (clear-cell histology) who received a first-line TKI for ≥6 months followed by a second-line TKI (n=118) or mTORi (n=123). Endpoints: Progression-free survival (PFS) and time-to-treatment-failure (TTF) on second-line therapy. Multivariable full-model covariables: second-line drug, TD1, ECOG-PS prior to first- and second line, best objective response (first-line), Fuhrman grade, number of metastatic sites, and presence of bone metastases. Adjustment covariable: International mRCC Database Consortium (IMDC) risk score. Multiple propensity score and missing data methods were used. Any correlation between first-line and second-line PFS was investigated using censored quantile regression models (CQRM). Results: Sequence effect in the overall cohort was in favor of the TKI-TKI sequence over the TKI-mTORi sequence on using TD1 as continuous covariable (HR≈0.75 for PFS and TTF). TKI-TKI superiority was attributed in large part to the 11-22 month (TD1) subgroup of patients which displayed significantly better outcomes (HR≈0.5; median PFS (months): 9.4 (5.9-12.2) vs 3.9 (3.0-5.5), p=0.003; TTF(months): 8.0 (5.5-11.0) versus 3.6 (3.0-4.6), p=0.009). Upon full CQRM, long-term second-line responders were more likely to have received a second TKI than an mTORi and to have been long-term responders to first-line TKI. Conclusions: m-ccRCC patients who remained on first-line TKI between 11 and 22 months benefited from a TKI rechallenge rather than from second-line mTORi.

I.F. = 6,578

N. citazioni = 23

229. Santoni M, Conti A, Partelli S, **Porta C**, Sternberg CN, Procopio G, Bracarda S, Basso U, De Giorgi U, Derosa L, Rizzo M, Ortega C, Massari F, Iacovelli R, Milella M, Di Lorenzo G, Buti S, Cerbone L, Burattini L, Montironi R, Santini D, Falconi M, Cascinu S. Surgical resection does not improve survival in patients with renal metastases to the pancreas in the era of tyrosine kinase inhibitors. *Ann Surg Oncol* 2015;22:2094-100.

ABSTRACT - Background: The aim of this study was to compare survival of resected and unresected patients in a large cohort of patients with metastases to the pancreas from renal cell carcinoma (PM-RCC). Methods: Data from 16 Italian centers involved in the treatment of metastatic RCC were retrospectively collected. The Kaplan-Meier and log-rank test methods were used to evaluate overall survival (OS). Clinical variables considered were sex, age, concomitant metastasis to other sites, surgical resection of PM-RCC, and time to PM-RCC occurrence. Results: Overall, 103 consecutive patients with radically resected primary tumors were enrolled in the analysis. PM-RCCs were synchronous in only three patients (3 %). In 56 patients (54 %), the pancreas was the only metastatic site, whereas in the other 47 patients, lung (57 %), lymph nodes (28 %), and liver (21 %) were the most common concomitant metastatic sites. Median time for PM-RCC occurrence was 9.6 years (range 0-24 years) after nephrectomy. Surgical resection of PM-RCC was performed in 44 patients (median OS 103 months), while 59 patients were treated with tyrosine kinase inhibitors (TKIs; median OS 86 months) (p = 0.201). At multivariate analysis, Memorial Sloan Kettering Cancer Center risk group was the only independent prognostic factor. None of the other clinical variables, such as age, sex, pancreatic surgery, or the presence of concomitant metastases, were significantly associated with outcome in PM-RCC patients. Conclusions: The presence of PM-RCC is associated with a long survival, and surgical resection does not improve survival in comparison with TKI therapy. However, surgical resection leads to a percentage of disease-free PM-RCC patients.

I.F. = 3,943

N. citazioni = 53

230. Sternberg CN, Calabrò F, Bracarda S, Cartenì G, Lo Re G, Ruggeri EM, Conte P, Monfardini S, Gasparini G, Ciuffreda L, Marini G, Bonetti A, Heouaine A, Ardizzoni A, Ravaioli A, Labianca R, Masini C, Fly K, Zhang K, Hariharan S, Capaccetti B, **Porta C**. Safety and efficacy of Sunitinib in patients from Italy with metastatic renal cell carcinoma: final results from an expanded-access trial. *Oncology* 2015;88:273-80.

ABSTRACT - Objectives: Patients with metastatic renal cell carcinoma (mRCC) received sunitinib in a global expanded-access program (EAP). Here, we report the efficacy and safety results for the EAP subpopulation in Italy. Methods: Patients ≥18 years old with previously treated or treatment-naïve mRCC received oral sunitinib 50 mg/day on a 4-weeks-on/2-weeks-off schedule. Tumor measurements were scheduled per local practice (using Response Evaluation Criteria in Solid Tumors). Safety was regularly assessed. Results: A total of 521 patients participated, including 40% aged ≥65 years, 11% with an Eastern Cooperative Oncology Group performance status ≥2, 14% with non-clear cell RCC, and 11% with brain metastases. The median treatment duration and posttreatment follow-up were 7.4 and 12.3 months, respectively. The objective response rate was 12%, and the median progression-free and overall survival was 9.1 and 27.2 months, respectively. 514 patients

(99%) discontinued treatment; reasons included death (17%), nonresponse (46%), or adverse events (AEs; 13%). The most common any-grade treatment-related AEs were asthenia (44%, plus 15% reporting fatigue), thrombocytopenia and stomatitis (both 37%), diarrhea (36%), mucosal inflammation (29%), hypertension (26%), and dysgeusia (25%). The most common grade 3/4 treatment-related AEs were thrombocytopenia (10%), asthenia (9%, plus 3% reporting fatigue), neutropenia, stomatitis (both 6%), and hypertension (5%). Conclusion: In a large population of Italian mRCC patients, sunitinib had a manageable safety profile and encouraging efficacy.

I.F.: 2,613

N. citazioni = 25

231. Bria E, Massari F, Maines F, Pilotto S, Bonomi M, **Porta C**, Bracarda S, Heng D, Santini D, Sperduti I, Giannarelli D, Cognetti F, Tortora G, Milella M. Progression-free survival as primary endpoint in randomized clinical trials of targeted agents for advanced renal cell carcinoma. Correlation with overall survival, benchmarking and power analysis. *Crit Rev Oncol Hematol* 2015;93:50-9.

ABSTRACT - Purpose: A correlation, power and benchmarking analysis between progression-free and overall survival (PFS, OS) of randomized trials with targeted agents or immunotherapy for advanced renal cell carcinoma (RCC) was performed to provide a practical tool for clinical trial design. Results: For 1st-line of treatment, a significant correlation was observed between 6-month PFS and 12-month OS, between 3-month PFS and 9-month OS and between the distributions of the cumulative PFS and OS estimates. According to the regression equation derived for 1st-line targeted agents, 7859, 2873, 712, and 190 patients would be required to determine a 3%, 5%, 10% and 20% PFS advantage at 6 months, corresponding to an absolute increase in 12-month OS rates of 2%, 3%, 6% and 11%, respectively. Conclusions: These data support PFS as a reliable endpoint for advanced RCC receiving up-front therapies. Benchmarking and power analyses, on the basis of the updated survival expectations, may represent practical tools for future trial' design.

I.F. = 4,046

N. citazioni = 11

232. Albiges L, Choueiri T, Escudier B, Galsky M, George D, Hofmann F, Lam T, Motzer R, Mulders P, **Porta C**, Powles T, Sternberg C, Bex A. A systematic review of sequencing and combinations of systemic therapy in metastatic renal cancer. *Eur Urol* 2015;67:100-10.

ABSTRACT - Context - The introduction of novel molecular-targeted agents has revolutionised the management of patients with metastatic renal cell carcinoma (mRCC). However, uncertainties remain over sequential or simultaneous combination therapies. Objective - To systematically review relevant literature comparing the clinical effectiveness and harms of different sequencing and combinations of systemic targeted therapies for mRCC. Evidence acquisition - Relevant databases (including Medline, Cochrane Library, trial registries, and conference proceedings) were searched (January 2000 to September 2013) including only randomised controlled trials (RCTs). Risk of bias assessment was performed. A qualitative and quantitative synthesis of the evidence was presented. Evidence synthesis - The literature search identified 5149 articles. A total of 24 studies reporting on 9589 patients were eligible for inclusion; data from four studies were included for meta-analysis. There were generally low risks of bias across studies; however, clinical and methodological heterogeneity prevented pooling of data for most studies. Overall, the data showed several targeted therapies were associated with an improvement in progression-free survival in patients with mRCC. There were limited data from RCTs regarding the issue of sequencing; studies on combination therapies have been hampered by difficulties with tolerability and safety. Conclusions - Although the role of vascular endothelial growth factor/vascular endothelial growth factor receptor targeting therapies and mammalian target of rapamycin inhibition in the management of mRCC is now established, limited reliable data are available regarding sequencing and combination therapies. Although data from retrospective cohort studies suggest a potential benefit for sequencing systemic therapies, significant uncertainties remain. Presently, mRCC systemic treatment should follow international guidelines (such as the European Society for Medical Oncology, National Comprehensive Cancer Network, and European Association of Urology) for patients fit to receive several lines of systemic therapies. Patient summary - We thoroughly examined the literature on the benefits and harms of combining drugs for the treatment of kidney cancer that has spread and on the sequence in which the drugs should be given.

I.F. = 10,476

N. citazioni = 111

233. Bracarda S, **Porta C**, Sisani M, Marrocolo F, Paglino C, Hamzaj A, D Buono S, Sternberg CN. Comparing comparators: a look at control arms in kidney cancer studies over the years. *Br J Cancer* 2015;112:14-19.

ABSTRACT - In the past decade, an increasing number of frequently positive randomised clinical trials have been completed, allowing new consideration of the present therapeutic armamentarium for advanced renal cell carcinoma. These studies were predominantly designed to compare the experimental drugs with 1 of 2 active control arms: interferon alpha-2a or sorafenib. Different from expectations, the final results of some of these studies were not in line with the predictions, and the reasons have not been fully investigated. Consequently, there is a great need for careful analysis of the studies carried out so far, chiefly the role and validity of the control arms. In this regard, the examination of patient baseline characteristics and other factors of potential interest seems fundamental for a correct analysis of the results of these trials and consequent optimal use of the available targeted agents.

I.F. = 4,817

N. citazioni = 4

234. Santoni M, Conti A, **Porta C**, Procopio G, Sternberg CN, Basso U, De Giorgi U, Bracarda S, Rizzo M, Ortega C, Massari F, Iacovelli R, Derosa L, Masini C, Milella M, Di Lorenzo G, Atzori F, Pagano M, Buti S, De Vivo R, Mosca A, Rossi M, Paglino C, Verzoni E, Cerbone L, Muzzonigro G, Falconi M, Montironi R, Burattini L, Santini D, Cascinu S. Sunitinib, pazopanib or sorafenib for the treatment of patients with late relapsing (>5 years) metastatic renal cell carcinoma. *J Urol* 2015;193:41-7.

ABSTRACT - Purpose: Late recurrence of renal cell carcinoma (RCC) is not a rare event. The aim of this retrospective study was to investigate the clinico-pathological features and the outcome of patients (pts) treated with sorafenib, sunitinib and pazopanib for late-relapsing renal cell carcinoma (LR-RCC). Material and methods: Data were collected from 21 Italian centers

involved in the treatment of metastatic RCC. Late relapse was defined as >5 yrs after initial radical nephrectomy. Results: 2490 pts were screened and 269 pts (11%) were included. First-line therapy was sunitinib in 190 pts (71%), sorafenib in 58 pts (21%) and pazopanib in 21 pts (8%). The median progression-free survival (PFS) was 20.0 months (95% CI 17.0-25.1) for sunitinib and 14.1 months for both sorafenib (95% CI 11.0-29.0) and pazopanib (95% CI 11.2-NR). On multivariate analysis, MSKCC score and metastases to lymph nodes, liver, and brain were associated with worst overall survival, while pancreatic metastases were associated with longer survival. Furthermore, age, MSKCC score and brain metastases were associated with worst Progression-free survival. Conclusions: Pts with LR-RCC seem to present a characteristic pattern of metastatic spread, without showing significant differences in terms of PFS among sorafenib, sunitinib and pazopanib.
I.F. = 3,753
N. citazioni = 44

235. Kaminska K, Szczylik C, Bielecka ZF, Bartnik E, **Porta C**, Czarnecka AM. The role of the cell-cell interaction in cancer progression. *J Cell Mol Med* 2015;19:283-96.

ABSTRACT - In the field of cancer research, scientific investigations are based on analysing differences in the secretome, the proteome, the transcriptome, the expression of cell surface molecules, and the deregulation of signal transduction pathways between neoplastic and normal cells. Accumulating evidence indicates a crucial role in carcinogenesis concerning not only stromal cells but also normal cells from target organs and tissue where tumours emerge. The tumour microenvironment (TME) definitively plays an important role in regulating neighbouring cell behaviour. To date, limited attention has been focused upon interactions between cancer cells and normal cells. This review concentrates on the interactions between stromal and healthy cells from the TME in cancer development. In the article, the authors also describe mutations, genes and proteins expression pattern that are involved in tumour development in target organ.
I.F.: 3,698
N. citazioni = 53

236. Iacovelli R, Sternberg CN, **Porta C**, Verzoni E, De Braud F, Escudier B, Procopio G. Inhibition of the VEGF/VEGFR Pathway Improves Survival in Advanced Kidney Cancer: A Systematic Review and Meta-Analysis. *Curr Drug Targets* 2015;16:164-70.

ABSTRACT - Despite the improvement in progression-free survival and response rates, none of the five anti- VEGF/VEGFR agents used for treatment of metastatic renal cell carcinoma (mRCC) reported a significant increase in patients' survival. This analysis aims to investigate their effect on overall survival (OS), performing a meta-analysis of the available studies. MEDLINE/PubMed and the Cochrane Library were searched for randomised phase III trials that compared anti-VEGF/VEGFR agents with controls as upfront treatment for mRCC. The search was restricted to phase III trials, and data extraction was conducted according to the PRISMA statement. Five randomised phase III trials were included for a total of 3,469 patients; among these, 1,801 received anti-VEGF/VEGFR agents and 1,668 were treated with a placebo or interferon-α. In the overall population, the reduction in the risk of death was 13% (HR: 0.87; 95%CI, 0.80 - 0.95; p=0.002). When patients were divided based on use of VEGFR agents or an anti-VEGF monoclonal antibody, the reduction in the risk of death was 13% and 12%, respectively. If only treatmentnaïve patients are considered, we can confirm a significant reduction of 12% (HR=0.88; 95%CI, 0.79 - 0.97; p=0.010) in the risk of death. Our analysis reports a positive improvement of OS with the inhibition of the VEGF/VEGFR pathway in mRCC.
I.F. = 3,597
N. citazioni = 32

237. Santoni M, Buti S, Conti A, **Porta C**, Procopio G, Sternberg CN, Bracarda S, Basso U, De Giorgi U, Rizzo M, Derosa L, Ortega C, Massari F, Milella M, Bersanelli M, Cerbone L, Muzzonigro G, Burattini L, Montironi R, Santini D, Cascinu S. Prognostic significance of host immune status in patients with late relapsing renal cell carcinoma treated with targeted therapy. *Target Oncol* 2015;10:517-22.

ABSTRACT - We aimed to assess the prognostic role of pretreatment neutrophilia, lymphocytopenia, and neutrophil to lymphocyte ratio (NLR) in patients treated with vascular endothelial growth factor-tyrosine kinase inhibitors (VEGFR-TKIs) for late relapsing (>5 years) metastatic renal cell carcinoma (mRCC). Data were collected from 13 Italian centers involved in the treatment of metastatic RCC. Late relapse was defined as >5 years after initial radical nephrectomy. One hundred fifty-one patients were included in this analysis. Among them, MSKCC risk score was favorable in 68 %, intermediate in 29 %, and poor in 3 %. Fifty-six patients (37 %) had NLR ≥3 at the start of VEGFR-TKI therapy (group A), while 95 had lower NLR (63 %, group B). The median overall survival (OS) was 28.8 months in group A and 68.7 months (95 % confidence interval (CI) 45.3-NA) in group B (p < 0.001). The median progression-free survival (PFS) was 15.8 months in group A and 25.1 months in group B (p = 0.03). At multivariate analysis, MSKCC risk group and NLR were independent prognostic factors for both OS and PFS. Pretreatment NLR is an independent prognostic factor for patients with late relapsing mRCC treated with first-line VEGFR-TKIs. A better characterization of baseline immunological impairment may optimize the management of this RCC subpopulation.
I.F. = 3,458
N. citazioni = 37

238. Negri FV, Dal Bello B, **Porta C**, Campanini N, Rossi S, Tinelli C, Poggi G, Missale G, Fanello S, Salvagni S, Ardizzoni A, Silini EM. Expression of pERK and VEGFR-2 in advanced hepatocellular carcinoma and resistance to Sorafenib treatment. *Liver Int* 2015;35:2001-8.

ABSTRACT - Background & Aims - The study aimed to evaluate the tissue expression of molecules involved in intracellular signalling pathways as predictors of response to sorafenib in advanced hepatocellular carcinoma (HCC). Methods - We considered 77 patients enrolled into three prospective trials of sorafenib treatment for whom pretreatment tumour tissue was available. The tissue expression of β-catenin, glutamine synthetase (GS), phosphorylated extracellular signal regulated kinase (pERK), phosphorylated v-akt murine thymoma viral oncogene homolog (pAKT) and vascular endothelial growth factor receptor-2 (VEGFR-2) was analysed by immunostaining. Stains were scored semiquantitatively and compared with a reference group of 56 untreated HCCs. Results - Overall, the expression of antigens was comparable between treated and untreated patients. Shorter progression-free survival (PFS) and overall survival (OS) were associated with increased pERK staining (≥ 2+ sco-

res) (PFS: 75th percentile 4.4 vs 8.4 months; P = 0.01; OS: 75th percentile 7.0 vs 15.0 months; P = 0.005) and VEGFR-2 staining (≥ 2+ scores) (PFS: 75th percentile 3.8 vs 7.0 months; P = 0.039; OS: 75th percentile 6.3 vs 15.0 months; P = 0.004). At multivariate analysis, both pERK and VEGFR-2 staining maintained an independent effect on OS (HR 2.09; 95% CI, 1.13-3.86, P = 0.019 and HR 2.28; 95% CI, 1.13-4.61, P = 0.021 respectively). No effect was observed for the other tested biomarkers. Conclusions - Elevated tissue expression of pERK and VEGFR-2 was predictive of poor outcome in advanced HCC treated with sorafenib.

I.F. = 4,447

N. citazioni = 39

239. Massari F, Santoni M, Ciccarese C, Santini D, Alfieri S, Martignoni G, Brunelli M, Piva F, Berardi R, Montironi R, **Porta C**, Cascinu S, Tortora G. PD-1 blockade therapy in renal cell carcinoma: current studies and future promises. *Cancer Treat Rev* 2015;41:114-121.

ABSTRACT - RCC is considered an immunogenic tumor with a prominent dysfunctional immune cell infiltrate, unable to control tumor growth. Evasion of immune surveillance, a process defined immune-editing, leads to malignant progression. The striking improvement of knowledge in immunology has led to the identification of immune checkpoints (such as CTLA-4 and PD-1), whose blockage enhances the antitumor immunity. The interaction between PD-1, an inducible inhibitory receptor expressed on lymphocytes and DCs, and PD-L1 ligand, expressed by tumor cells, results in a down-regulation of the T-cell response. Therefore, the PD-1/PD-L1 axis inhibition by targeted-antibodies, increasing the T-cell proliferation and cytotoxicity, represents a promising mechanism to stimulate the anti-tumor activity of the immune system, improving the outcomes of cancer patients. Several PD-1 and PD-L1 inhibitors have been evaluated in different tumor types, showing promising results. The interesting correlation between lymphocytes PD-1 expression and RCC advanced stage, grade and prognosis, as well as the selective PD-L1 expression by RCC tumor cells and its potential association with worse clinical outcomes, have led to the development of new anti PD-1/PD-L1 agents, alone or in combination with anti-angiogenic drugs or other immunotherapeutic approaches, for the treatment of RCC. In this review we discuss the role of PD-1/PD-L1 in RCC, focusing on the biological rationale, current clinical studies and promising therapeutic perspectives to target the PD-1 pathway.

I.F. = 6,466

N. citazioni = 136

240. Santoni M, Conti A, Procopio G, **Porta C**, Ibrahim T, Barni S, Guida F, Fontana A, Berruti A, Berardi R, Massari F, Vincenzi B, Ortega C, Ottaviani D, Carteni G, Lanzetta G, De Lisi D, Silvestris N, Satolli M, Collovà E, Russo A, Badalamenti G, Luzi Fedeli S, Tanca F, Adamo V, Maiello E, Sabbatini R, Felici A, Cinieri S, Montironi R, Bracarda S, Tonini G, Cascinu S, Santini D. Bone metastases in patients with metastatic renal cell carcinoma: are they always associated with poor prognosis? *J Exp Clin Cancer Res* 2015;34:10.

ABSTRACT - Purpose - Aim of this study was to investigate for the presence of existing prognostic factors in patients with bone metastases (BMs) from RCC since bone represents an unfavorable site of metastasis for renal cell carcinoma (mRCC). Materials and methods - Data of patients with BMs from RCC were retrospectively collected. Age, sex, ECOG-Performance Status (PS), MSKCC group, tumor histology, presence of concomitant metastases to other sites, time from nephrectomy to bone metastases (TTBM, classified into three groups: <1 year, between 1 and 5 years and >5 years) and time from BMs to skeletal-related event (SRE) were included in the Cox analysis to investigate their prognostic relevance. Results - 470 patients were enrolled in this analysis. In 19 patients (4%),bone was the only metastatic site; 277 patients had concomitant metastases in other sites. Median time to BMs was 16 months (range 0−44y) with Median OS of 17 months. Number of metastatic sites (including bone, p=0.01), concomitant metastases, high Fuhrman grade (p<0.001) and non-clear cell histology (p=0.013) were significantly associated with poor prognosis. Patients with TTBM >5 years had longer OS (22 months) compared to patients with TTBM <1 year (13 months) or between 1 and 5 years (19 months) from nephrectomy (p<0.001), no difference was found between these two last groups (p=0.18). At multivariate analysis, ECOG-PS, MSKCC group and concomitant lung or lymph node metastases were independent predictors of OS in patients with BMs. Conclusions - Our study suggest that age, ECOG-PS, histology, MSKCC score, TTBM and the presence of concomitant metastases should be considered in order to optimize the management of RCC patients with BMs.

I.F. = 3,27

N. citazioni = 55

241. **Porta C**, Cosmai L, Gallieni M, Pedrazzoli P, Malberti F, Renal effects of targeted therapies. *Nature Rev Nephrol* 2015;11:354-70.

ABSTRACT - The use of novel targeted anticancer agents has led to overall improvement in the prognosis of many patients affected by various malignancies, but has also been associated with an increased risk of poorly characterized toxic effects to different organs, including the kidneys. The high prevalence of kidney impairment in the general population complicates the issue further. Nephrologists most frequently work with patients with cancer when they are asked to investigate kidney function to assess the need for dose adjustments in anticancer therapy. A thorough knowledge of the renal safety profile of novel life-prolonging anticancer therapies, specific features of their metabolism, and pharmacokinetic and pharmacodynamic properties (under normal circumstances as well as in the setting of renal replacement therapy) is, therefore, necessary to preserve kidney function as far as possible and to ensure optimum treatment. In this Review we summarize the present knowledge of renal toxic effects from novel targeted anticancer agents and discuss whether the management of patients' treatment needs to be modified. We also advocate the development of a new onconephrology subspeciality.

I.F.: 8,368

N. citazioni = 60

242. Rimassa L, Santoro A, Daniele B, Germano D, Gasbarrini A, Salvagni S, Masi G, Abbadessa G, Lamar M, Goldberg T, **Porta C**. Tivantinib, a new option for second-line treatment of advanced hepatocellular carcinoma? The experience of the Italian centers. *Tumori* 2015;101:139-43.

ABSTRACT - In the last decades the management of hepatocellular car-

cinoma (HCC) has undergone significant changes following the introduction of novel therapies such as sorafenib, which have improved patient survival. Nevertheless, HCC is still the third most common cause of cancer-related death worldwide. The evidence-based therapy for advanced HCC that is unsuitable for locoregional treatment is limited to sorafenib, with no second-line option available. This article focuses on the development of the MET inhibitor tivantinib in HCC as a promising treatment option for patients who failed sorafenib. A randomized, placebo-controlled phase II study showed activity of tivantinib in patients with high MET expression. Based on these results, the METIV-HCC phase III study in second-line treatment for MET-high patients was initiated to demonstrate the survival advantage of tivantinib compared to placebo.

I.F.: 1,090

N. citazioni = 5

243. Pantano F, Santoni M, Procopio G, Rizzo M, Iacovelli R, **Porta C**, Conti A, Lugini A, Milella M, Galli L, Ortega C, Guida FM, Silletta M, Schinzari G, Verzoni E, Modica D, Crucitti P, Rauco A, Felici A, Ballatore V, Cascinu S, Tonini G, Carteni G, Russo A, Santini D. The changes of lipid metabolism in advanced renal cell carcinoma patients treated with everolimus: a new pharmacodynamic marker? *PLoS One* 2015;10:e0120427.

ABSTRACT - Background: Everolimus is a mammalian target of rapamycin (mTOR) inhibitor approved for the treatment of metastatic renal cell carcinoma (mRCC). We aimed to assess the association between the baseline values and treatmentrelated modifications of total serum cholesterol (C), triglycerides (T), body mass index (BMI), fasting blood glucose level (FBG) and blood pressure (BP) levels and the outcome of patients treated with everolimus for mRCC. Methods: 177 patients were included in this retrospective analysis. Time to progression (TTP), clinical benefit (CB) and overall survival (OS) were evaluated. Results: Basal BMI was significantly higher in patients who experienced a CB (p=0,0145). C,T and C+T raises were significantly associated with baseline BMI (p=0.0412, 0.0283 and 0.0001). Median TTP was significantly longer in patients with T raise compared to patients without T (10 vs 6, p=0.030), C (8 vs 5, p=0.042) and C+T raise (10.9 vs 5.0, p=0.003). At the multivariate analysis, only C+T increase was associated with improved TTP (p=0.005). T raise (21.0 vs 14.0, p=0.002) and C+T increase (21.0 vs 14.0, p=0.006) were correlated with improved OS but were not significant at multivariate analysis.
Conclusion: C+T raise is an early predictor for everolimus efficacy for patients with mRCC.

I.F. = 3,534

N. citazioni = 9

244. **Porta C**, Giglione P, Ferrari A, Reversi F, Liguigli W, Imarisio I, Ganini C. Tivantinib (ARQ197) in hepatocellular carcinoma. *Expert Rev Anticancer Ther* 2015;15:615-22.

ABSTRACT - Here we review the development of tivantinib, a selective oral inhibitor of c-MET. The initially identified dose and schedule for clinical use was 360 mg twice daily. Biological considerations and early results suggested its activity against hepatocellular carcinoma after progression on sorafenib. The results of randomized Phase II study in this setting have already been reported; while in the overall population, the risk of progression was reduced by 36% (HR: 0.64; 90% CI: 0.43–0.94; p = 0.04), in the pre-defined MET-high population median overall survival (7.2 vs 3.8 months; p = 0.01), median time to progression (2.7 vs 1.4 months; p = 0.03) as well as disease control rate (50 vs 20%), were increased by tivantinib. During study conduction, tivantinib dose was amended to 240 mg twice daily, due to a high incidence of neutropenia, without losing clinical efficacy. Presently, a global phase III trial is being conducted.

I.F. = 2,279

N. citazioni = 12

245. Negri F, **Porta C**. Urea-based cream to prevent sorafenib-induced hand and foot skin reaction: which evidence? *J Clin Oncol* 2015;33:3219-20.

SUMMARY - Sorafenib tosylate is one of oldest commercially available multikinase inhibitors. It was first approved for the treatment of advanced kidney cancer in 2005 and then hepatocellular carcinoma (HCC) in 2007. More recently, in 2013, it was also approved for use in the treatment of metastatic differentiated thyroid cancer. From the beginning, it was clear that, among the peculiar adverse events (AEs) induced by this agent, hand-and-foot skin reaction (HFSR) and diarrhea were the most troublesome for our patients. These frequently affected our ability to administer a correct dosage intensity of oncologic treatment. It was also clear then that any attempt to prevent HFSR was key to guaranteeing the best treatment possible and to maintaining the highest quality of life. Therefore, practical use of urea-based creams (UBCs) to prevent and/or treat HFSR was implemented from almost the first time sorafenib and other similar multikinase inhibitors were clinically used.This practical approach was recently validated by the results of a large, randomized controlled trial performed in the People's Republic of China involving more than 850 patients with HCC and reported in the article by Ren et al. Although results of this study provide the highest level of evidence and the highest grade of recommendation regarding the prophylactic use of UBC for sorafenib-induced HFSR, potentially useful information is still missing, and relevant doubts remain unsolved. First, because UBCs are commonly used, given the advice of many authors starting in 2009, what practical relevance should we give to this trial? That is, UBC was compared with nothing. Beyond the lack of a placebo, the most important issue with this trial is: what was the true control arm? It was not best supportive care (BSC). Careful reading of the article by Ren et al. reveals that BSC was scheduled, per protocol, just to manage AEs other than HFSR. This suggests that no other preventive measures were applied to prevent HFSR beyond the application of the UBC itself. If so, this is a huge bias because it is well established that a number of preventive measures—which should be regarded as part of an adequate BSC—should be applied in patients who are treated with drugs that can potentially induce HFSR, such as sorafenib. A few other questions remain. Are there possible differences between patients with HCC and patients who have other solid tumors, such as kidney and thyroid cancer, for which sorafenib is used? What is the ideal concentration of urea? Finally, should we regard UBC as the present standard of care for the prevention of HFSR? The first question is all but trivial because cirrhosis, irrespective of its cause, is often associated with skin manifestations. This, once again, makes the typical patient with HCC quite different from any other patient with cancer. The most appropriate concentration of urea is still unknown; 10% and 12.5%3 have been empirically suggested. Finally, last year, data from a phase II randomized trial of a limited number of patients with renal cancer suggested that a hydrocolloid dressing containing ceramide could prevent sorafenib-induced HFSR more effectively than a 10% UBC. Ren et al. should be applauded for their effort as well as for providing us with a high level of evidence for the use of UBC to prevent HFSR.

Still, many unanswered questions remain regarding how to deal with this distressing and difficult to manage AE.

I.F. = 17,960

N. citazioni = 4

246. **Porta C**, Giglione P, Liguigli W, Paglino C. Dovitinib (CHIR258, TKI258): structure, development and preclinical and clinical activity. *Future Oncol* 2015;11:39-50.

ABSTRACT - Dovitinib is an oral multikinase inhibitor targeting FGF receptors, PDGF receptors and VEGF receptors. Its activity against FGF receptors suggests its usefulness in treating cancers after the failure of VEGF/VEGF receptor-targeting agents. The identified dose and schedule to be used in further studies was 500 mg orally for 5 days on and 2 days off. Biological considerations and the results achieved in a Phase I/II trial suggested its activity in advanced renal cell carcinoma patients pretreated with a tyrosine kinase inhibitor and an mTOR inhibitor. Surprisingly, in a randomized controlled Phase III trial versus sorafenib in the same setting, dovitinib failed to demonstrate any superiority. At present, dovitinib is being tested in different tumor types. However, molecular-based patient selection seems to be key to fully exploit the activity of this drug.

I.F. = 2,477

N. citazioni = 43

247. Gore ME, Szczylik C, **Porta C**, Bracarda S, Bjarnason GA, Oudard S, Lee SH, Haanen J, Castellano D, Vrdoljak E, Schöffski P, Mainwaring P, Hawkins RE, Crinò L, Kim TM, Carteni G, Eberhardt WE, Zhang K, Fly K, Matczak E, Lechuga MJ, Hariharan S, Bukowski R. Final results from the large Sunitinib global expanded-access trial in metastatic renal cell carcinoma. *Br J Cancer* 2015;113:12-9.

ABSTRACT - Background: We report final results with extended follow-up from a global, expanded-access trial that pre-regulatory approval provided sunitinib to metastatic renal cell carcinoma (mRCC) patients, ineligible for registration-directed trials. Methods: Patients ? 18 years received oral sunitinib 50 mg per day on a 4-weeks-on-2-weeks-off schedule. Safety was assessed regularly. Tumour measurements were scheduled per local practice. Results: A total of 4543 patients received sunitinib. Median treatment duration and follow-up were 7.5 and 13.6 months. Objective response rate was 16% (95% confidence interval (CI): 15-17). Median progression-free survival (PFS) and overall survival (OS) were 9.4 months (95% CI: 8.8-10.0) and 18.7 months (95% CI: 17.5-19.5). Median PFS in subgroups of interest: aged ? 65 years (33%), 10.1 months; Eastern Cooperative Oncology Group performance status ? 2 (14%), 3.5 months; non-clear cell histology (12%), 6.0 months; and brain metastases (7%), 5.3 months. OS was strongly associated with the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model (n=4065). The most common grade 3/4 treatment-related adverse events were thrombocytopenia (10%), fatigue (9%), and asthenia, neutropenia, and hand-foot syndrome (each 7%). Conclusion: Final analysis of the sunitinib expanded-access trial provided a good opportunity to evaluate the long-term side effects of a tyrosine kinase inhibitor used worldwide in mRCC. Efficacy and safety findings were consistent with previous results.

I.F. = 4,836

N. citazioni = 135

248. Frascà GM, Sandrini S, Cosmai L, **Porta C**, Asch W, Santoni M, Salviani C, D'Errico A, Malvi D, Balestra E, Gallieni M. Renal cancer in kidney transplanted patients. *J Nephrol* 2015;28:659-68.

ABSTRACT - Renal cancer occurs more frequently in renal transplanted patients than in the general population, affecting native kidneys in 90 % of cases and the graft in 10 %. In addition to general risk factors, malignancy susceptibility may be influenced by immunosuppressive therapy, the use of calcineurin inhibitors (CNI) as compared with mammalian target of rapamycin inhibitors, and the length of dialysis treatment. Acquired cystic kidney disease may increase the risk for renal cancer after transplantation, while autosomal dominant polycystic kidney disease does not seem to predispose to cancer development. Annual ultrasound evaluation seems appropriate in patients with congenital or acquired cystic disease or even a single cyst in native kidneys, and every 2 years in patients older than 60 years if they were on dialysis for more than 5 years before transplantation. Immunosuppression should be lowered in patients who develop renal cancer, by reduction or withdrawal of CNI. Although more evidence is still needed, it seems reasonable to shift patients from CNI to everolimus or sirolimus if not already treated with one of these drugs, with due caution in subjects with chronic allograft nephropathy.

I.F. = 1,454

N. citazioni = 23

249. Bracarda S, Iacovelli R, Boni L, Rizzo M, Derosa L, Rossi M, Galli L, Procopio G, Sisani M, Longo F, Santoni M, Morelli F, Di Lorenzo G, Altavilla A, **Porta C**, Camerini A, Escudier B for the RAINBOW Group. Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis. *Ann Oncol* 2015;26:2107-13.

ABSTRACT - Background: First-line sunitinib is recommended in metastatic renal cell carcinoma (mRCC), but it is frequently associated with relevant toxicities and subsequent dose reductions. Alternative schedules, such as 2-week-on treatment and 1-week-off (2/1 schedule), might improve tolerability. We evaluated the safety and outcomes of this schedule in a large multicenter analysis. Patients and methods: Retrospective, multicenter analysis of mRCC patients treated with first-line sunitinib on a 2/1 schedule. Data of 249 patients were reviewed: 208 cases who started sunitinib on the 4/2 schedule (full dosage: 188/208, 90.4%) and thereafter switched to the 2/1 schedule for toxicity (group 4/2→2/1) and 41 patients who started first-line sunitinib with the 2/1 schedule because of suboptimal clinical conditions (group 2/1). A total of 211 consecutive patients treated with the 4/2 schedule in another institution served as external controls. Safety was the primary end point. Treatment duration (TD), progression-free survival (PFS) and overall survival (OS) were also analyzed. Results: In group 4/2→2/1, the overall incidence of grade ≥3 toxicities was significantly reduced (from 45.7% to 8.2%, P < 0.001) after the switch to 2/1 schedule. This advantage was maintained also in the 106/188 cases (56.4%) who maintained the full dosage. Fatigue, hypertension, hand-foot syndrome and thrombocytopenia were less frequent. The incidence of grade ≥3 adverse events in the negatively selected group 2/1 (only 73.2% starting at full dose) was 26.8%, similar to what observed in the external control group (29.4%). Median TD was 28.2 months in the 4/2→2/1 group (total time spent with both schedules), 7.8 months in the 2/1 group and 9.7 months in external controls. Median PFS was 30.2, 10.4 and 9.7 months, respectively.

Median OS was not reached, 23.2 and 27.8 months, respectively. Conclusions: mRCC patients who moved to a modified 2/1 schedule of sunitinib experience an improved safety profile compared with that observed during the initial 4/2 schedule.

I.F. = 7,040

N. citazioni = 67 + 14 (da: Corrigendum)

250. Giglione P, Lombardo F, Toscani I, Paglino C, **Porta C**. Approccio al trattamento di prima linea del carcinoma renale a cellule chiare metastatico. *Rec Prog Med* 2015;106:370-9.

ABSTRACT - The medical treatment of renal cell carcinoma has been revolutionized in recent years, thanks to translation of our increasingly accurate knowledge on the molecular pathogenesis of this tumor, and of its clear cell histology in particular, into an accelerated drug development, and then into everyday's clinical practice. In this review, starting with the pathogenesis of clear cell renal cell carcinoma, we shall address the results of the clinical trials that led to the registration of seven targeted agents for this disease once orphan of active treatments, taking into account the different prognostic groups in which the patients suffering from it can be divided. Finally, we shall discuss the complex and controversial issue of the ideal timing to start a systemic treatment, a critical and still highly debated topic. All major international guidelines agree on the standard first line therapeutic options, which are represented by sunitinib, bevacizumab (associated with interferon-α) and pazopanib for patients with good or intermediate risk features, and temsirolimus for poor-risk patients. All these agents proved able to prolong progression-free survival within randomized phase III trials. The use of an observation period, before starting a systemic treatment, seems also reasonable, at least in the more indolent tumors and in patients with a better prognosis, even if the topic is still controversial. Finally, the individualization of therapy and the proper conduct of the same is essential for a successful outcome of the treatment.

I.F. = n.r.

N. citazioni = 1

251. Rothermundt C, Bailey A, Cerbone L, Eisen T, Escudier B, Gillessen S, Grünwald V, Larkin J, McDermott D, Oldenburg J, **Porta C**, Rini B, Schmidinger M, Sternberg CN, Putora PM. Algorithms in the first-line treatment of metastatic clear cell renal cell carcinoma-Analysis using diagnostic nodes. *Oncologist* 2015;20:1028-35.

ABSTRACT - Background: With the advent of targeted therapies, many treatment options in the first-line setting of metastatic clear cell renal cell carcinoma (mccRCC) have emerged. Guidelines and randomized trial reports usually do not elucidate the decision criteria for the different treatment options. In order to extract the decision criteria for the optimal therapy for patients, we performed an analysis of treatment algorithms from experts in the field. Materials and methods: Treatment algorithms for the treatment of mccRCC from experts of 11 institutions were obtained, and decision trees were deduced. Treatment options were identified and a list of unified decision criteria determined. The final decision trees were analyzed with a methodology based on diagnostic nodes, which allows for an automated cross-comparison of decision trees. The most common treatment recommendations were determined, and areas of discordance were identified. Results: The analysis revealed heterogeneity in most clinical scenarios. The recommendations selected for first-line treatment of mccRCC included sunitinib, pazopanib, temsirolimus, interferon-α combined with bevacizumab, high-dose interleukin-2, sorafenib, axitinib, everolimus, and best supportive care. The criteria relevant for treatment decisions were performance status, Memorial Sloan Kettering Cancer Center risk group, only or mainly lung metastases, cardiac insufficiency, hepatic insufficiency, age, and "zugzwang" (composite of multiple, related criteria). Conclusion: In the present study, we used diagnostic nodes to compare treatment algorithms in the first-line treatment of mccRCC. The results illustrate the heterogeneity of the decision criteria and treatment strategies for mccRCC and how available data are interpreted and implemented differently among experts. Implications fro practice: The data provided in the present report should not be considered to serve as treatment recommendations for the management of treatment-naïve patients with multiple metastases from metastatic clear cell renal cell carcinoma outside a clinical trial; however, the data highlight the different treatment options and the criteria used to select them. The diversity in decision making and how results from phase III trials can be interpreted and implemented differently in daily practice are demonstrated.

I.F. = 4,54

N. citazioni = 21

252. Cosmai L, Gallieni M, **Porta C**. Renal toxicity of anticancer agents targeting HER2 and EGFR. *J Nephrol* 2015;28:647-57.

ABSTRACT - EGFR and HER2 are found overexpressed and/or activated in many different human malignancies (e.g. breast and colon cancer), and a number of drugs specifically targeting these two tyrosine kinases have been developed over the years as anticancer agents. In the present review, the renal safety profile of presently available agents targeting either HER2 or EGFR will be discussed, together with the peculiarities related to their clinical use in patients with impaired renal function, or even in dialysis. Indeed, even though renal toxicity is not so common with these agents, it may nevertheless happen, especially when these agents are combined with traditional chemotherapeutic agents. As a whole, kidney impairment or dialysis should not be regarded per se as reasons not to administer or to stop an active anti-HER or anti-EGFR anticancer treatment, especially given the possibility of significantly improving the life expectancy of many cancer patients with the use of these agents.

I.F. = 1,454

N. citazioni = 25

253. Kramar A, Negrier S, Sylvester R, Joniau S, Mulders P, Powles T, Bex A, Bonnetain F, Bossi A, Bracarda S, Bukowski R, Catto J, Choueiri TK, Crabb S, Eisen T, El Demery M, Fitzpatrick J, Flamand V, Goebell PJ, Gravis G, Houédé N, Jacqmin D, Kaplan R, Malavaud B, Massard C, Melichar B, Mourey L, Nathan P, Pasquier D, **Porta C**, Pouessel D, Quinn D, Ravaud A, Rolland F, Schmidinger M, Tombal B, Tosi D, Vauleon E, Volpe A, Wolter P, Escudier B, Filleron T for the DATECAN Renal Cancer group. Guidelines for the definition of time-to-event end points in renal cell cancer clinical trials: results of the DATECAN project. *Ann Oncol* 2015;26:2392-8.

ABSTRACT - Background: In clinical trials, the use of intermediate time-to-event end points (TEEs) is increasingly common, yet their choice and definitions are not standardized. This limits the usefulness for comparing treatment effects between studies. The aim of the DATECAN Kidney pro-

ject is to clarify and recommend definitions of TEE in renal cell cancer (RCC) through a formal consensus method for end point definitions. Materials and methods: A formal modified Delphi method was used for establishing consensus. From a 2006-2009 literature review, the Steering Committee (SC) selected 9 TEE and 15 events in the nonmetastatic (NM) and metastatic/advanced (MA) RCC disease settings. Events were scored on the range of 1 (totally disagree to include) to 9 (totally agree to include) in the definition of each end point. Rating Committee (RC) experts were contacted for the scoring rounds. From these results, final recommendations were established for selecting pertinent end points and the associated events. Results: Thirty-four experts scored 121 events for 9 end points. Consensus was reached for 31%, 43% and 85% events during the first, second and third rounds, respectively. The expert recommend the use of three and two endpoints in NM and MA setting, respectively. In the NM setting: disease-free survival (contralateral RCC, appearance of metastases, local or regional recurrence, death from RCC or protocol treatment), metastasis-free survival (appearance of metastases, regional recurrence, death from RCC); and local-regional-free survival (local or regional recurrence, death from RCC). In the MA setting: kidney cancer-specific survival (death from RCC or protocol treatment) and progression-free survival (death from RCC, local, regional, or metastatic progression). Conclusions: The consensus method revealed that intermediate end points have not been well defined, because all of the selected end points had at least one event definition for which no consensus was obtained. These clarified definitions of TEE should become standard practice in all RCC clinical trials, thus facilitating reporting and increasing precision in between trial comparisons.

I.F. = 7,040

N. citazioni = 23

254. Guida A, Masini C, Milella M, Di Lorenzo G, Santoni M, Prati V, **Porta C**, Cosmai L, Donati D, Del Giovane C, Mighali P, Sabbatini R. Retrospective analysis on safety and efficacy of everolimus in treatment of metastatic renal cancer patients receiving dialysis. *Future Oncol* 2015;11:3159-66.

ABSTRACT - Aims: This retrospective study aimed to investigate safety and efficacy of everolimus in patients with metastatic renal cell carcinoma (mRCC) and end-stage renal disease requiring dialysis. Patients and methods: From November 2009 to December 2012, 11 mRCC patients undergoing dialysis were treated with everolimus after failure of anti-VEGF therapy at six Italian institutions. Patient characteristics, safety and outcomes were collected. Results: Progression-free survival and overall survival were determined using the Kaplan-Meier method. Median progression-free survival and overall survival were 9.01 and 15.7 months, respectively. No unexpected adverse events were reported. Conclusion: Everolimus appears to be safe in mRCC patients with renal impairment or end-stage renal disease requiring dialysis. Larger prospective studies are required to confirm these findings.

I.F. = 2,477

N. citazioni = 8

255. **Porta C**, Gore ME, Rini BI, Escudier B, Hariharan S, Charles LP, Yang L, DeAnnuntis L, Motzer RJ. Long-term Safety of Sunitinib in Metastatic Renal Cell Carcinoma. *Eur Urol* 2016;69:345-51.

ABSTRACT - Background: Metastatic renal cell carcinoma (mRCC) patients receiving first-line sunitinib typically survive >2 yr, with chronic treatment sometimes extending to ≥6 yr. Objective: To analyze long-term safety with sunitinib in mRCC patients. Design, setting, and participants: Data were pooled from 5739 patients in nine trials, comprising seven phase II studies, a phase III study, and an expanded-access trial in various treatment settings (e.g. cytokine refractory or treatment-naïve). Outcome measurements and statistical analysis: Interval and cumulative time-period analyses evaluated the incidence of treatment-related adverse events (TRAEs) for up to 6 yr, in the overall population and in those with long-term (≥2 yr) sunitinib treatment. Results and limitations: Among long-term patients (n=807), most TRAEs occurred initially in the first year and then decreased in frequency; TRAEs following this pattern included decreased appetite, diarrhea, dysgeusia, dyspepsia, fatigue, hypertension, mucosal inflammation, nausea, and stomatitis. However, hypothyroidism increased by interval analysis from 6% at 0-<6 mo to 42% at 5-<6 yr and by cumulative analysis from 14% at 0-<1 yr to 36% over 6 yr. Grade 3/4 TRAEs in long-term patients peaked during the first year and then steadily decreased. The overall population displayed only minor differences from long-term patients, with no clinically significant differences between grade ≥3 TRAE profiles (<5% difference in incidence rates at all intervals). Limitations included retrospective design, assessment variability, lack of pharmacokinetic data, and absence of baseline characteristics for long-term patients. Conclusions: Prolonged sunitinib was not associated with new types or increased severity of TRAEs. Except hypothyroidism, toxicity was not cumulative. Patient summary: More than 800 mRCC patients received sunitinib for between 2 and 6 yr without experiencing new or more severe treatment-related toxicity. Clinicians may be able to prescribe chronic sunitinib treatment for as long as patients continue to derive clinical benefit, without untoward additional risk.

I.F. = 13,938

N. citazioni = 45

256. Cosmai L, **Porta C**, Gallieni M, Perazella MA. Onco-nephrology: a decalogue. *Nephrol Dial Transplant* 2016;31:515-9.

ABSTRACT - Onco-nephrology is an evolving subspecialty that focuses on the complex relationships existing between kidney and cancer. In this opinion piece, we propose a 'decalogue of onco-nephrology', in order to highlight the areas where the nephrologist and oncologist should work closely over the ensuing years to provide cutting-edge care for patients afflicted with cancer and kidney disease. The 10 points we have highlighted include (1) acute kidney injury and chronic kidney disease in cancer patients; (2) nephrotoxic effects of anticancer therapy, either traditional chemotherapeutics or novel molecularly targeted agents; (3) paraneoplastic renal manifestations; (4) management of patients nephrectomized for a kidney cancer; (5) renal replacement therapy and active oncological treatments; (6) kidney transplantation in cancer survivors and cancer risk in ESRD patients; (7) oncological treatment in kidney transplant patients; (8) pain management in patients with cancer and kidney disease, (9) development of integrated guidelines for onco-nephrology patients and (10) clinical trials designed specifically for onco-nephrology. Following these points, a multidisciplinary onco-nephrology team will be key to providing outstanding, cutting-edge care in both the acute and chronic setting to these patients.

I.F. = 3,577

N. citazioni = 39

257. Iacovelli R, Nolè F, Verri E, Renne G, Paglino C, Santoni M, Cossu Rocca M, Giglione P, Aurilio G, Cullurà D,

Cascinu S, **Porta C**. Prognostic role of PD-L1 expression in Renal Cell Carcinoma. A systematic review and meta-Analysis. *Target Oncol* 2016;11:143-8.

ABSTRACT - Background: Several clinical trials have reported that therapies targeting programmed death-1 (PD1) and its ligand (PD-L1) improve patient outcomes, while tumor response has been related to PD-L1 expression. Objective: To investigate the prognostic role of PD-L1 expression in patients affected by renal cell carcinoma (RCC). Methods: MEDLINE/PubMed, the Cochrane Library, and ASCO University were searched for studies investigating the prognostic role of PD-L1 expression in RCC. Data extraction was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Results: Six studies and 1323 cases were included in the final analysis. PD-L1 was expressed in 24.2 % of clear cell tumors compared to 10.9 % of non-clear cell tumors (p = 0.002). In the overall population, a higher level of PD-L1 expression increased the risk of death by 81 % (HR; 1.81, 95 % CI 1.31-2.49; p < 0.001). When the analysis was restricted to cases evaluated by immunohistochemistry alone, the higher expression of PD-L1 more than doubled the risk of death (HR; 2.05, 95 % CI 1.38-3.05; p < 0.001). In clear cell histology, higher PD-L1 expression increased the risk of death by 53 % (HR; 1.53, 95 % CI 1.27-1.84; p < 0.001), while in metastatic patients, the evaluation of PD-L1 expression on primary tumors revealed that it retains its prognostic role (HR; 1.45, 95 % CI 1.08-1.93; p = 0.01). Limitations: Significant heterogeneity has been identified among the included studies. As a consequence, cautious interpretation of the results is recommended. Conclusion: This meta-analysis indicates that a higher level of PD-L1 expression is a negative prognostic factor in RCC. Its validation as an independent prognostic factor compared to other traditionally used clinical parameters in localized or advanced disease is recommended.

I.F. = 4,0

N. citazioni = 111

258. Pani A, **Porta C**, Cosmai L, Melis P, Floris M, Piras D, Gallieni M, Rosner M, Ponticelli C. Glomerular diseases and cancer: evaluation of underlying malignancy. *J Nephrol* 2016;29:143-52.

ABSTRACT - Onconephrology is an emerging medical subspecialty focused on the numerous interconnections between cancer and kidney diseases. Patient with malignancies commonly experience kidney problems including acute kidney injury, tumor lysis syndrome, fluid and electrolyte disorders and chronic kidney disease, often as a consequence of the anti-cancer treatment. Conversely, a number of glomerulopathies, tubulopathies and vascular renal diseases can early signal the presence of an underlying cancer. Furthermore, the administration of immunosuppressive drugs, especially cytotoxic drugs and calcineurin inhibitors, may strongly impair the immune response increasing the risk of cancer. The objective of this review article is to: (i) discuss paraneoplastic glomerular disease, (ii) review cancer as an adverse effect of immunosuppressive agents used to treat glomerulopathies, and (iii) in the absence of international approved guidelines, propose a screening program based on expert opinion aimed at guiding nephrologists to early detect malignancies during their clinical practice.

I.F. = 1,454

N. citazioni = 34

259. Massari F, Ciccarese C, Caliò A, Munari E, Cima L, Porcaro AB, Novella G, Artibani W, Sava T, Eccher A, Ghimenton C, Bertoldo F, Scarpa A, Sperandio N, **Porta C**, Bronte V, Chilosi M, Bogina G, Zamboni G, Tortora G, Samaratunga H, Martignoni G, Brunelli M. Magnitude of PD-1, PD-L1 and T lymphocyte expression on tissue from castration-resistant prostate adenocarcinoma: an exploratory analysis. *Target Oncol* 2016;11:345-51.

ABSTRACT - Background and aim: Recent therapeutic strategies for castration-resistant prostate cancer have focused on immunomodulation, especially the PD-1/PD-L1 pathway related to tumor-infiltrating lymphocytes. Few cases of castration-resistant prostate adenocarcinoma have been tested simultaneously for PD-1, PD-L1 and T lymphocytes in cancerous tissue. We quantified the PD-1/PD-L1 immune pathway and T lymphocyte infiltrates in a series of patients with castrate-resistant prostate adenocarcinoma. Patients and methods: Expression of PD-1, PD-L1, CD3 and FOXP3 was identified in tissue microarrays, with five tissue spots per patient from 16 patients over at least 5 years of follow-up. Two scores were defined. The first described the percentage of PD-1-positive T lymphocytes (CD3+): negative (0), <5 %; low (1+), 5-30 %; high (2+), >30 %. The second described PD-L1 staining intensity: 0 (no signal), 1+ (light signal), 2+ (high signal) in >50 % of neoplastic cells. Results: Tumor-infiltrating T lymphocytes (CD3+) were seen in 11/16 cases (69 %). Nine of 16 cases expressed PD-1 (56 %), among which 19 % were scored 2+. Eight of 16 cases expressed PD-L1 (50 %), with 19 % scored as strong 2+. The subgroup with high PD1/PD-L1 also exhibited FOXP3 expression. Conclusions: Approximately 19 % of patients in our series showed simultaneous high PD-1/PD-L1 immunoscores, and were the best candidates for receiving targeted anti-PD-1/PD-L1 immunotherapy, as determined using a tissue based rationale.

I.F. = 4,0

N. citazioni = 48

260. Kwiatkowski DJ, Choueiri TK, Fay AP, Rini BI, Thorner AR, De Velasco G, Tyburczy M, Hamieh L, Albiges L, Agarwal N, Ho TH, Song J, Pignon JC, Barrios PM, Michaelson MD, Van Allen EM, Krajewski KM, **Porta C**, Pal SK, Bellmunt J, McDermott DF, Heng DY, Gray KP, Signoretti S. Mutations in TSC1, TSC2, and MTOR are associated with response to rapalogs in patients with metastatic Renal Cell Carcinoma. *Clin Cancer Res* 2016;22:2445-52.

ABSTRACT - Purpose: We examined the hypothesis that mutations in mTOR pathway genes are associated with response to rapalogs in metastatic renal cell carcinoma (mRCC). Experimental design: We studied a cohort of mRCC patients who were treated with mTOR inhibitors with distinct clinical outcomes. Tumor DNA from 79 subjects was successfully analyzed for mutations using targeted next generation sequencing of 560 cancer genes. Responders were defined as those with partial response (PR) by RECIST v1.0 or stable disease with any tumor shrinkage for six months or longer. Non-responders were defined as those with disease progression during the first three months of therapy. Fisher's exact test assessed the association between mutation status in mTOR pathway genes and treatment response. Results: Mutations in MTOR, TSC1 or TSC2 were more common in responders, 12 (28%) of 43, than non-responders, 4 (11%) of 36 (p=0.06). Mutations in TSC1 or TSC2 alone were also more common in responders, 9 (21%), than non-responders, 2(6%), (p=0.05). Furthermore, 5 (42%) of 12 subjects with PR had mutations in MTOR, TSC1 or TSC2 compared to 4 (11%) of 36 non-respon-

ders (p=0.03). Eight additional genes were found to be mutated in at least 4 of 79 tumors (5%); none were associated positively with response. Conclusion: In this cohort of mRCC patients, mutations in MTOR, TSC1 or TSC2 were more common in patients who experienced clinical benefit from rapalogs than in those who progressed. However, a substantial fraction of responders (31 of 43, 72%) had no mTOR pathway mutation identified.

I.F. = 8,722

N. citazioni = 152

261. Massari F, Modena A, Ciccarese C, Pilotto S, Maines F, Bracarda S, Sperduti I, Giannarelli D, Carlini P, Santini D, Tortora G, **Porta C**, Bria E. Addressing the expected survival benefit for clinical trial design in metastatic castration-resistant prostate cancer: sensitivity analysis of randomized trials. *Crit Rev Oncol Hematol* 2016;98:254-63.

ABSTRACT - We performed a sensitivity analysis, cumulating all randomized clinical trials (RCTs) in which patients with metastatic castration-resistant prostate cancer (mCRPC) received systemic therapy, to evaluate if the comparison of RCTs may drive to biased survival estimations. An overall survival (OS) significant difference according to therapeutic strategy was more likely be determined in RCTs evaluating hormonal drugs versus those studies testing immunotherapy, chemotherapy or other strategies. With regard to control arm, an OS significant effect was found for placebo-controlled trials versus studies comparing experimental treatment with active therapies. Finally, regarding to docetaxel (DOC) timing, the OS benefit was more likely to be proved in Post-DOC setting in comparison with DOC and Pre-DOC. These data suggest that clinical trial design should take into account new benchmarks such as the type of treatment strategy, the choice of the comparator and the phase of the disease in relation to the administration of standard chemotherapy.

I.F. = 5,039

262. **Porta C**, Giglione P, Paglino C. Targeted therapy for renal cell carcinoma: focus on 2nd and 3rd line. *Expert Opin Pharmacother* 2016;17:643-55.

ABSTRACT - Second- and third-line treatments are more and more frequently administered to metastatic renal cell carcinoma (mRCC) patients. Areas Covered: Here we discuss the various levels of evidence supporting presently available recommendations, trying to address a number of as yet unanswered issues, and also to take a glowing glance at the future. To do this, we interrogated the Medline database, as well as the proceedings of the main Oncological and Urological conferences for relevant studies. Expert Opinion: Until recently, with regard to choosing the second line treatment after the failure of therapy with vascular endothelial growth factor receptors-tyrosine kinase inhibitors (VEGFR-TKIs), the continued inhibition of the VEGF/VEGR pathway, or else the switch to an mTOR inhibitor, is recommended. These two options are characterized by partly different targets, completely different toxicity profiles, but a comparable efficacy. This scenario will change soon, after the publication of two randomized, controlled, phase III trials in which cabozantinib and nivolumab proved to be superior as compared to everolimus. As regards third line treatment, where a sequence of two VEGFR-TKIs has been used beforehand, the choice is represented by the mTOR inhibitor everolimus, whilst if a VEGFR-TKI followed by everolimus has been chosen, a return to VEGF pathway inhibition is suggested.

I.F. = 3,543

N. citazioni = 9

263. Poletto V, Dragoni S, Lim D, Biggiogera M, Aronica A, Cinelli M, De Luca A, Rosti V, **Porta C**, Guerra G, Moccia F. Endoplasmic reticulum Ca^{2+} handling and apoptotic resistance in tumor-derived endothelial colony forming cells. *J Cell Biochem* 2016;117:2260-71.

ABSTRACT - Truly endothelial progenitor cells (EPCs) can be mobilized from bone marrow to support the vascular network of growing tumors, thereby sustaining the metastatic switch. Endothelial colony forming cells (ECFCs) are the only EPC subtype belonging to the endothelial phenotype and capable of incorporating within neovessels. The intracellular Ca2+ machinery plays a key role in ECFC activation and is remodeled in renal cellular carcinoma-derived ECFCs (RCC-ECFCs). Particularly, RCC-ECFCs seems to undergo a drop in endoplasmic reticulum (ER) Ca2+ concentration ([Ca2+]ER). This feature is remarkable when considering that inositol-1,4,5-trisphosphate (InsP3)-dependent ER-to-mitochondria Ca2+ transfer regulates the intrinsic apoptosis pathway. Herein, we sought to assess whether: 1) the [Ca2+]ER and the InsP3 -induced ER-mitochondria Ca2+ shuttle are reduced in RCC-ECFCs; and 2) the dysregulation of ER Ca2+ handling leads to apoptosis resistance in tumor-derived cells. RCC-ECFCs displayed a reduction both in [Ca2+]ER and in the InsP3 -dependent mitochondrial Ca2+ uptake, while they expressed normal levels of Bcl-2 and Bak. The decrease in [Ca2+]ER was associated to a remarkable ER expansion in RCC-ECFCs, which is a hallmark of ER stress, and did not depend on the remodeling of the Ca2+ -transporting and the ER Ca2+ -storing systems. As expected, RCC-ECFCs were less sensitive to rapamycin- and thapsigargin-induced apoptosis; however, buffering intracellular Ca2+ levels with BAPTA dampened apoptosis in both cell types. Finally, store-operated Ca2+ entry was seemingly uncoupled from the apoptotic machinery in RCC-ECFCs. Thus, the chronic underfilling of the ER Ca2+ pool could confer a survival advantage to RCC-ECFCs and underpin RCC resistance to pharmacological treatment.

I.F. = 3,446

N. citazioni = 24

264. Santini D, Santoni M, Conti A, Procopio G, Verzoni E, Galli L, di Lorenzo G, De Giorgi U, De Lisi D, Nicodemo M, Maruzzo M, Massari F, Buti S, Altobelli E, Biasco E, Ricotta R, **Porta C**, Vincenzi B, Papalia R, Marchetti P, Burattini L, Berardi R, Muto G, Montironi R, Cascinu S, Tonini G. Risk of recurrence and conditional survival in complete responders treated with TKIs plus or less locoregional therapies for metastatic renal cell carcinoma. *Oncotarget* 2016;7:33381-90.

ABSTRACT - Purpose: We retrospectively analyzed the risk of recurrence and conditional Disease-Free Survival (cDFS) in 63 patients with complete remission during treatment with tirosin kinase inhibitor (TKI), alone or with local treatment in metastatic renal cell carcinoma. Results: 37% patients achieve CR with TKI alone, while 63% with additional loco-regional treatments. 49% patients recurred after CR, with a median Disease free survival of 28.2 months. Patients treated with multimodal approaches present lower rate of recurrence (40% vs 61%) and longer Disease free survival compared to patient treated with TKI alone (16.5 vs 41.9 months, p=0.039).Furthermore the rate of recurrence was higher in

patients with brain (88%), pancreatic (71%) and bone metastasis (50%). Patients who continued TKI therapy after complete response had a longer disease free survival than patients who stopped therapy, although the difference was not significant (42.1 vs 25.1 months, p=0.254). 2y-cDFS was better in patients treated with multimodal treatment and who continued TKIs than the other patient arms. Conclusions: The prognostic value of CR depends on the site where was obtained and how was obtained (with or without locoregional treatment). Cessation of TKI should be carefully considered in complete responder patients.

I.F. = 6,359

N. citazioni = 12

265. Czarnecka AM, Niedzwiedzka M, **Porta C**, Szczylik C. Hormone signaling pathways as treatment targets in renal cell cancer. *Int J Oncol* 2016;48:2221-35.

ABSTRACT - Epidemiological, clinical, biochemical and genetic research has revealed that renal cell cancer (RCC) etiology is hormone-related. It was shown that hormone receptors are abnormally expressed in RCC cells. Abnormal endocrine stimulation also plays a significant role in RCC pathophysiology. Cellular proliferation, migration, angiogenesis, and drug resistance in RCC is modulated by para- and autocrine hormonal stimulation. In particular, RCC overexpression of gonadotropin-releasing hormone and its receptor was reported. On the contrary, corticotropin releasing hormone was reported to inhibit RCC cell proliferation and regulate angiogenesis. Overexpression of luteinizing hormone also promotes RCC tumor angiogenesis. Estrogen receptor α overexpression increases the transcriptional factor activity of hypoxia inducible factor HIF-1α, but estrogen receptor β has a cancer suppressive role. Glucocorticoid receptors and androgen receptor are markers of indolent RCC and assigned tumor suppressive activity. Proopiomelanocortin is upregulated in VHL-mutated renal cell carcinoma via Nur77 transcription factor signaling. In RCC, follicle-stimulating hormone receptor promotes angiogenesis and metastatic formation via VEGF release. Mineralocorticoid receptor overexpression promotes cell survival and increases RCC cell proliferation. Vitamin D receptor expression is downregulated or absent in RCC and differentiate subtypes of renal cell tumors. RAR-β promotes tumorigenesis but retinoic acid receptor γ expression correlates negatively with the TNM stage at diagnosis. Finally, progesterone receptor expression is negatively correlated with the cancer stage. Molecular data analysis revealed the possibility of renal cancer cell proliferation induction via hormone activated pathways. Inhibition of hormonal signaling may thus play a putative role in supportive therapies against this cancer type.

I.F. = 3,018

N. citazioni = 18

266. Grassi P, Doucet L, Giglione P, Grünwald V, Melichar B, Galli L, De Giorgi U, Sabbatini R, Ortega C, Santoni M, Bamias A, Verzoni E, Derosa L, Studentova H, Pacifici M, Coppa J, Mazzaferro V, de Braud F, **Porta C**, Escudier B, Procopio G. Clinical impact of pancreatic metastases from Renal Cell Carcinoma: a multicenter retrospective analysis. *PLoS One* 2016;11:e0151662.

ABSTRACT - Pancreatic metastases from renal cell carcinoma are uncommon and their prognostic significance is not well defined. In this analysis we evaluated the outcome of patients with pancreatic metastases treated with either targeted therapies or local treatment to the pancreas. Patients with pancreatic metastases from renal cell carcinoma treated between 1993 and 2014 were identified from 11 European centers. Clinical records were retrospectively reviewed. Kaplan-Meier method and log-rank test were used to evaluate progression-free survival and overall survival. Cox's proportional hazard models were used for survival analysis. In total, 276 PM patients were evaluated, including 77 (28%) patients treated by either surgery or radiotherapy to the pancreas, and 256 (93%) who received systemic therapy. Median time from nephrectomy to diagnosis of pancreatic metastases was 91 months (IQR 54-142). Disease control rate after first-line TTs was 84%, with a median progression-free survival of 12 months (95% CI 10-14). Median overall survival was 73 months (95% CI 61-86) with a 5-year OS of 58%. Median OS of patients treated with local treatment was 106 months (95% CI 78-204) with a 5-year overall survival of 75%. On multivariable analysis, nephrectomy (HR 5.31; 95%CI 2.36-11.92; p<0.0001), Memorial Sloan Kettering/International Metastatic RCC Database Consortium prognostic score (HR 1.45, 95% CI 0.94-2.23 for intermediate vs good vs risk; HR 2.76 95%, CI 1.43-5.35 for poor vs good risk p = 0.0099) and pancreatic local treatment (HR 0.48; 95%CI 0.30-0.78 p = 0.0029) were associated with overall survival. Difference in median OS between patients with PM and that reported in a matched-control group of mRCC patients with extrapancreatic metastases was statistically significant (p < .0001). Pancreatic metastases from renal cell carcinoma usually occur years after nephrectomy, are associated with an indolent behavior and a prolonged survival. Targeted therapies and locoregional approaches are active and achieve high disease control rate.

I.F. = 3,54

N. citazioni = 40

267. **Porta C**, Cosmai L, Gallieni M, Perazella MA. Harmonization of Renal Function Assessment Is Needed Throughout the Whole Process of Anticancer Drug Development. *J Clin Oncol* 2016;34:2429-30 [Letter].

SUMMARY - The article by Beumer et al. addressed the effect of renal impairment on the toxicity of anticancer compounds tested in phase I trials over three decades, and the accompanying editorial by Rudek et al. called for harmonization of kidney function assessment during early clinical development of anticancer agents. Although the authors should be congratulated for their interesting and clinically relevant work, we strongly believe that, with this work, Beumer et al have opened a Pandora's box. Indeed, despite the fact that the Renal Insufficiency and Cancer Medications study demonstrated that more than half of patients affected with an active cancer concomitantly show an estimated glomerular filtration rate < 90 mL/min/1.73 m2 and that the prevalence of stage 3 to 5 chronic kidney disease (CKD) accounts for approximately 12% of patients with cancer, patients affected with CKD are often denied entry not only into early-phase studies, but also into registrative, randomized, controlled, phase III trials, which introduces a significant selection bias. It appears that many phase III trial designs are all too often written using a cut-and-paste function, without adequate knowledge of the pharmacokinetic properties of a given drug. For example, because large molecular weight monoclonal antibodies are not metabolized or excreted by the kidneys, it is not sensible to limit their clinical use to patients with normal or near-normal kidney function. Furthermore, it is often difficult, if not impossible, to evaluate the true nature and incidence of adverse renal events from phase III trials. Indeed, it is common to find definitions such as creatinine increase in tables summarizing adverse events. This vague descriptor has little meaning for the clinician and has no clinical value. This approach leads to a dramatic lack of uniformity in the definition of CKD between oncologic trials, drug summaries of product characteristics, and nephrologic classifications of adverse renal events. Although it

is clear that pharmacokinetic studies in patients with impaired renal function are sorely needed, as suggested by a recent European Medicine Agency guideline, it is also clear that harmonization of kidney function assessment is mandatory, not only in early clinical trials, but also—because of a larger practical impact—within registrative trials of novel anticancer agents. Excluding patients with CKD and end-stage renal disease from these trials, especially from those that generate specific pharmacokinetic data, makes the results obtained in these studies highly biased and not transferrable to a significant number of patients with cancer with underlying kidney disease. For these reasons, nephrologists should be involved in the design of the next generation of oncologic trials, especially (but not exclusively) when renal toxicity is expected to be an issue. Furthermore, the respective scientific societies should work together to accomplish this goal. Indeed, the development of onconephrology as a new subspecialty is badly needed because a number of key questions in the field remain not only unaswered, but also never asked.

I.F. = 20,982

N. citazioni = 4

268. Moccia F, Zuccolo E, Poletto V, Turin I, Guerra G, Pedrazzoli P, Rosti V, **Porta C**, Montagna D. Targeting Stim and Ora1 proteins as an alternative approach in anticancer therapy. *Curr Med Chem* 2016;23:3450-80.

ABSTRACT - An increase in intracellular Ca2+ concentration plays a key role in the establishment of many cancer hallmarks, including aberrant proliferation, migration, invasion, resistance to apoptosis and angiogenesis. The dysregulation of Ca2+ entry is one of the most subtle mechanisms by which cancer cells overwhelm their normal counterparts and gain the adaptive advantages that result in tumour growth, vascularisation and dissemination throughout the organism. Both constitutive and agonist-induced Ca2+ influx may be mediated by store-dependent as well as store-independent Ca2+ entry routes. A growing body of evidences has shown that different isoforms of Stromal Interaction Molecules (Stim1) and Orai proteins, i.e. Stim1, Stim2, Orai1 and Orai3, underlie both pathways in cancer cells. The alteration in either the expression or the activity of Stim and Orai proteins has been linked to the onset and maintenance of tumour phenotype in many solid malignancies, including prostate, breast, kidney, esophageal, skin, brain, colorectal, lung and liver cancers. Herein, we will survey the existing data in support of Stim and Orai involvement in tumourigenesis and provide the rationale to target them in cancer patients. Besides, we will summarize the most recent advances in the identification of novel pharmacological tools that could be successfully used in clinical therapy.

I.F. = 3,455

N. citazioni = 44

269. Bono P, Oudard S, Bodrogi I, Hutson TE, Escudier B, Machiels JP, Thompson JA, Figlin RA, Ravaud A, Basaran M, **Porta C**, Bracarda S, Brechenmacher T, Lin C, Voi M, Grunwald V, Motzer RJ. Outcomes in patients with metastatic Renal Cell Carcinoma who develop Everolimus-related hyperglycemia and hypercholesterolemia: combined subgroup analyses of the RECORD-1 and REACT trials. *Clin Genitourin Cancer* 2016;14:406-14.

ABSTRACT - Background: Hyperglycemia and hypercholesterolemia are class effects of mammalian target of rapamycin inhibitors. The purpose of this study was to characterize safety and efficacy of patients with metastatic renal cell carcinoma (mRCC) treated with everolimus in RECORD-1 (REnal Cell cancer treatment with Oral RAD001 given Daily) and REACT (RAD001 Expanded Access Clinical Trial in RCC) who developed these events. Patients and Methods: Adults with vascular endothelial growth factor-refractory mRCC received everolimus 10 mg/d in the randomized RECORD-1 (n = 277) and open-label REACT (n = 1367) studies. Outcomes included safety, treatment duration, overall response, and progression-free survival for patients who developed hypercholesterolemia or hyperglycemia. Results: In RECORD-1, 12% (33 of 277) and 20% (55 of 277) of patients developed any grade hyperglycemia or hypercholesterolemia, respectively, with only 6% (78 of 1367) and 1% (14 of 1367) of the same events, respectively, in REACT. Median everolimus treatment duration was similar for patients with hyperglycemia or hypercholesterolemia (RECORD-1, 6.2 and 6.2 months, respectively; REACT, 4.4 and 4.5 months, respectively), but longer than the overall populations (RECORD-1, 4.6 months; REACT, 3.2 months). In RECORD-1/REACT, 82%/68% of patients with hyperglycemia and 75%/71% of patients with hypercholesterolemia achieved partial response or stable disease. The incidence of clinically notable Grade 3 or 4 adverse events, other than anemia and lymphopenia, appeared to be similar across trials and subgroups. Although there was a trend for improved progression-free survival with development of hyperglycemia or hypercholesterolemia, the association was not statistically significant. Conclusion: Hyperglycemia and hypercholesterolemia were observed in low numbers of patients, and although these events might be associated with improved response to everolimus, the differences were not significant. These findings should be validated with prospective biomarker studies.

I.F. = 2,599

N. citazioni = 7

270. Tracz AF, Szczylik C, **Porta C**, Czarnecka AM. Insulin-like growth factor-1 signaling in renal cell carcinoma. *BMC Cancer* 2016;16:453.

ABSTRACT - Renal cell carcinoma (RCC) incidence is highest in highly developed countries and it is the seventh most common neoplasm diagnosed. RCC management include nephrectomy and targeted therapies. Type 1 insulin-like growth factor (IGF-1) pathway plays an important role in cell proliferation and apoptosis resistance. IGF-1 and insulin share overlapping downstream signaling pathways in normal and cancer cells. IGF-1 receptor (IGF1R) stimulation may promote malignant transformation promoting cell proliferation, dedifferentiation and inhibiting apoptosis. Clear cell renal cell carcinoma (ccRCC) patients with IGF1R overexpression have 70 % increased risk of death compared to patients who had tumors without IGF1R expression. IGF1R signaling deregulation may results in p53, WT, BRCA1, VHL loss of function. RCC cells with high expression of IGF1R are more resistant to chemotherapy than cells with low expression. Silencing of IGF1R increase the chemosensitivity of ccRCC cells and the effect is greater in VHL mutated cells. Understanding the role of IGF-1 signaling pathway in RCC may result in development of new targeted therapeutic interventions. First preclinical attempts with anti-IGF-1R monoclonal antibodies or fragment antigen-binding (Fab) fragments alone or in combination with an mTOR inhibitor were shown to inhibit in vitro growth and reduced the number of colonies formed by of RCC cells.

I.F. = 3,265

N. citazioni = 33

271. **Porta C**, Tortora G, Larkin JM, Hutson TE. Management of poor-risk metastatic renal cell carcinoma: current approaches, the role of temsirolimus and future directions. *Future Oncol* 2016;12:533-49.

ABSTRACT - Targeted therapies have substantially improved outcomes in metastatic renal cell carcinoma (mRCC). As expected, poor-risk patients have the worst outcomes. Temsirolimus is currently the only agent licensed for treatment of poor-risk mRCC patients. It is associated with meaningful improvements in survival and quality of life, highlighting the importance of correctly stratifying risk in mRCC patients so they receive optimal treatment. Currently, data for other targeted therapies in poor-risk patients are relatively sparse. Optimizing outcomes in these patients is the subject of ongoing research, including studies of biomarkers and studies to elucidate the role of nephrectomy and neoadjuvant targeted therapy in poor-risk mRCC patients. The impacts of novel combinations including temsirolimus have also been explored to further improve outcomes.

I.F. = 2,129

N. citazioni = 6

272. **Porta C**, Chiellino S. ASSURE vs. S-TRAC: conflicting results of adjuvant treatments for kidney cancer in the era of targeted agents and genomics. *Ann Transl Med* 2016 Oct;4(Suppl 1):S14.

On March 8, the final results of the ASSURE trial of adjuvant therapy for high-risk resected kidney cancer were published online on Lancet. ASSURE was a double-blind, placebo-controlled, randomised, phase 3 trial in which 1943 patients from 226 study centers in the United States and Canada were randomized to receive 54 weeks of sunitinib 50 mg per day orally throughout the first 4 weeks of each 6 week cycle, sorafenib 400 mg twice per day orally throughout each cycle, or placebo. Unfortunately, no significant differences in disease-free survival (DFS), the primary endpoint of the study, were evidenced between the three treatment arms. Indeed, median DFS was 5.8 years for sunitinib [hazard ratio (HR): 1.02; 97.5% CI: 0.85–1.23; P=0.8038], 6.1 years for sorafenib (HR: 0.97; 97.5% CI: 0.80–1.17; P=0.7184), and 6.6 years for placebo; furthermore, substantial treatment discontinuations occurred because of treatment-related adverse events, despite dose reductions. Authors concluded that their results "… provide a strong rationale against the use of these drugs …"—i.e., vascular endothelial growth factor receptors (VEGFRs)-targeting agents—"… for high-risk kidney cancer in the adjuvant setting and suggest that the biology of cancer recurrence might be independent of angiogenesis". Thus, ASSURE joined a long list of adjuvant trials which yielded not simply negative, but often detrimental results, as demonstrated by a recent meta-analysis. As it appears from the above conclusive sentence of the abstract of the ASSURE trial publication, what afflicted most the researchers was the failure of this study to confirm the VEGF/VEGFRs pathway as a rational target for adjuvant treatment in patients radically resected for a localized kidney cancer, despite the well known high dependancy of the majority of kidney cancers (at least those of clear cell histology) from VEGF/VEGFRs-driven angiogenesis. Is this the only and most correct way to read the results of this study? Probably not, in our opinion. First, the rational of using a relatively short antiangiogenic treatment in the adjuvant setting could be considered not so strong. Indeed, from the first pioneeristic studies conducted by Judah Folkman in Boston, to more recent preclinical data with modern antiangiogenic agents, it appears clear that the inhibition of VEGF-induced angiogenesis is quickly reversible at treatment discontinuation. For example, an elegant paper by Mancuso et al. showed that empty sleeves of basement membrane and accompanying pericytes provide a scaffold for rapid revascularization of tumors after removal of anti-VEGFRs therapy, even when a potent third generation tyrosine kinase inhibitor (TKI) such as axitinib is used; and this revascularization takes just days, not months or years. Given these considerations, it is hard to believe that a temporally limited treatment with an antiangiogenic agent (like in the case of ASSURE) could positively impact on the risk of relapse of a tumor such as kidney cancer, which quite often relapse years, if not decades, after the resection of its primary site. If so, should we disregard VEGFR-TKIs as a possible adjuvant treatment for kidney cancer, and thus expect negative results also from all the other adjuvant studies presently ongoing? Despite all the above considerations, this seems not to be the case, since very recently positive results of the S-TRAC study, in which sunitinib was tested as an adjuvant treatment, were published. Someway surprisingly, the study yielded positive results; indeed, the median duration of DFS (the primary endpoint of the study) was 6.8 years (95% CI: 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI: 3.8−6.6) in the placebo group (HR: 0.76; 95% CI: 0.59−0.98; P=0.03). It is thus clear that the above figure will give new hope for those who will suffer from this disease in the future. However, why sunitinib in one study (i.e., ASSURE) failed, and in another (i.e., S-TRAC) succeeded? A possible answer could be patient selection; and indeed, from a staging viewpoint inclusion criteria of the adjuvant studies using VEGFR-TKIs differed in several key characteristics. In particular, in ASSURE, patients with pT1b tumors were allowed (provided a Fuhrman's grade of 3 or 4), while in the S-TRAC study, pT1 patients without nodal involvement weren't allowed; furthermore, the histological presence of at least a component of clear cell was mandatory in S-TRAC, but not in ASSURE. Furthermore, a significant heterogeneity exists amongst presently available nomograms aimed at estimating the risk of recurrence in localized kidney cancer. As highlighted by Pal and Haas in a recent provocative review paper, using different nomograms or scoring systems, the risk of recurrence varies widely. The Authors made the examples of a patient with a pT2, N0 disease (Fuhrman grade 2) who would have a 5-year DFS estimate of 85.4% by the Leibovich nomogram, as compared to 66% by the Kattan nomogram; similarly, for a patient with pT3, N0 disease (Fuhrman grade 3), the 5-year DFS estimate would be 50% by the Leibovich nomogram, vs. 74% by the Kattan nomogram. Moreover, we should acknowledge that the vast majority of the characteristics included in the main nomograms or prognostication scores used to stratify patients in adjuvant trials are definitely not objective, with the unique exception of tumor stage (and size). Indeed, tumor grading is operator-dependant [not to take into account the fact that Fuhrman's grading has been presently substituted by the novel International Society of Urological Pathology (ISUP) nucleolar grading system], Eastern Cooperative Oncology Group (ECOG) Performance Status is not objective too, and even nodal status isn't; indeed, lymphadenectomy is presently performed almost uniquely when enlarged or suspiciuos lymphnodes are evident, either at pre-operative work-up, or at the sight of the operating Urologist. Furthermore, among all the criteria included in the risk scoring systems we do use, just the presence of necrosis, included in the Leibovich nomogram—used in the SORCE adjuvant trial, quite superficially reflects the biology of the tumor, or of the relationships between the tumor and the host. Thus, selection of patients with different degrees of risk of relapse due to the use of different, and not univocal, risk stratification criteria, may account for the different results of different trials. How to try to solve all these issues, better interpret the results of completed or presently ongoing studies, and design more appropriately the next generation of adjuvant trials for kidney cancer? The answer probably is to head to genetics. Indeed, a genetic recurrence score (RS) to predict the risk of recurrence in radically resected kidney cancer patients has been recently developed and validated. Initially, the association bet-

ween expression of 732 genes, measured by reverse-transcription Polymerase Chain Reaction, and clinical outcome in a large cohort of patients with stage I–III clear cell kidney cancer who had undergone nephrectomy at the Cleveland Clinic was studied; 516 genes were then associated with recurrence-free interval and 11 of these genes were selected by further statistical analyses. These 11 genes were combined with five reference genes, from which a RS algorithm was developed. The RS was then validated in an independent cohort of stage I to III radically resected patients from France. The association between the RS and the risk of recurrence as well as cancer-specific survival in the first 5 years after surgery was then assessed, stratified by tumour stage (stage I vs. stage II vs. III). Thus, RS proved able to identify a clinically relevant proportion of patients with both stage I and II-III kidney cancers with a very low risk of recurrence and, more importantly, also a significant number of stage I patients with more than 20% risk of recurrence at 5 years. However, beyond those genes considered in the RS, other genes have been proposed to play a prognostic role in kidney cancer; in another elegant paper, the University of Texas Southwestern (UTSW) group showed that the expression of PBRM1 and BAP1 genes were correlated with a different survival, worst for BAP1-expressing tumors, a finding that was externally validated using the The Cancer Genome Atlas (TCGA) network cohort; furthermore, the co-expression of the two genes, although a rare event, contributed to confer a particularly poor prognosis to patients. Notably, 80% of patients from both the development, as well as the validation, cohort had localized, or loco-regional, disease making this series of kidney cancer patients similar, although not identical, to that used to develop the RS. Despite all the above novelties, unfortunately none of the recently completed or ongoing adjuvant trials with targeted agents has been already prospectively implemented with genetic analyses such as the RS. Thus, one could speculate if this score could help us to understand why Sunitinib, as an adjuvant treatment, failed in the ECOG ASSURE trial, while succeeded in the S-TRAC one. However, relative to these genomic analyses, other issues remain open. First of all, although 'good' and 'bad' genes have been identified so far, we still do not have clearcut mechanistical explanation of their biological role. Furthermore, and more importantly, why BAP-1 and PBRM1, which in the UTSW/TCGA cohorts proved to be of prognostic value in a similar (although not identical) setting of patients, didn't make the final set of genes within the RS? Unfortunately enough, we cannot but conclude that, despite all the efforts made to date, and despite the huge amount of money put into the development of precision medicine by many countries, it still appears to be more a political claim than a reality for all patients worldwide … especially in the field of the adjuvant treatment of kidney cancer.

I.F. = n.r.

N. citazioni = 9

273. Rimassa L, Abbadessa G, Personeni N, **Porta C**, Borbath I, Daniele B, Salvagni S, Van Laethem JL, Van Vlierberghe H, Trojan J, De Toni EN, Weiss A, Miles S, Gasbarrini A, Lencioni M, Lamar ME, Wang Y, Shuster D, Schwartz BE, Santoro A. Tumor and circulating biomarkers in patients with second-line hepatocellular carcinoma from the randomized phase II study with tivantinib. *Oncotarget* 2016;7:72622-33.

ABSTRACT - ARQ 197-215 was a randomized placebo-controlled phase II study testing the MET inhibitor tivantinib in second-line hepatocellular carcinoma (HCC) patients. It identified tumor MET as a key biomarker in HCC. Aim of this research was to study the prognostic and predictive value of tumor (MET, the receptor tyrosine kinase encoded by the homonymous MNNG-HOS transforming gene) and circulating (MET, hepatocyte growth factor [HGF], alpha-fetoprotein [AFP], vascular endothelial growth factor [VEGF]) biomarkers in second-line HCC. Tumor MET-High status was centrally assessed by immunohistochemistry. Circulating biomarkers were centrally analyzed on serum samples collected at baseline and every 4-8 weeks, using medians as cut-off to determine High/Low status. Tumor MET, tested in 77 patients, was more frequently High after (82%) versus before (40%) sorafenib. A significant interaction (p = 0.04) between tivantinib and baseline tumor MET in terms of survival was observed. Baseline circulating MET and HGF (102 patients) High status correlated with shorter survival (HR 0.61, p = 0.03, and HR 0.60, p = 0.02, respectively), while the association between AFP (104 patients) or VEGF (103 patients) status and survival was non-significant. Conclusions: Tumor MET levels were higher in patients treated with sorafenib. Circulating biomarkers such as MET and HGF may be prognostic in second-line HCC. These results need to be confirmed in larger randomized clinical trials.

I.F. = 5,008

N. citazioni = 47

274. Escudier B, **Porta C**, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, Gruenvald V, Horwich A, ESMO Guidelines Committee. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27(suppl 5):v58-v68.

I.F. = 9,269

N. citazioni = 370

275. Escudier B, Molinie V, Bracarda S, Maroto P, Szczylik C, Nathan P, Negrier S, Weiss C, **Porta C**, Grünwald V, Albiges L. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *Eur J Cancer* 2016;69:226-35.

ABSTRACT - Background: Papillary histology accounts for 10-15% of renal cell carcinoma (RCC), and treatment options for patients with this subtype are limited. The RAPTOR (RAD001 in Advanced Papillary Tumor Program in Europe; ClinicalTrials.gov, NCT00688753) study evaluated first-line everolimus in patients with papillary metastatic RCC (mRCC). Methods: This phase 2 trial enrolled previously untreated patients with type 1 or type 2 papillary mRCC. Papillary histology was confirmed by central review and was performed for every patient. Patients received oral everolimus 10 mg once daily until disease progression or unacceptable toxicity. The primary end-point was progression-free survival (PFS) rate at 6 months among the first 44 patients of the per protocol (PP) population. Secondary end-points included PFS, tumour response, overall survival (OS), and safety. Findings: Analysis sets included safety (N = 92; 100%), intent-to-treat (ITT) (n = 88), and PP populations (n = 46). In the safety population, most patients were men (78%) and the mean age was 60 years (range 23-84). Papillary histology was confirmed in 78% of patients (type 1, 32%; type 2, 64%; missing information, 4%). PFS rate at 6 months was 34% (80% confidence interval [CI] 25-45). In the ITT population, median PFS was 4.1 months (95% CI 3.6-5.5), 65% of patients achieved stable disease, and median OS was 21.4 months (95% CI 15.4-28.4). Among patients with type 1 or type 2 histology, median PFS was 7.9 months (95% CI 2.1-11.0) and 5.1 months (95% CI 3.3-5.5), respectively, and median OS was 28.0 months (95% CI 7.6-not estimable) and 24.2 months (95% CI 15.8-32.8), respectively. Common

grade >2 adverse events were asthenia (13%), anaemia (7%), and fatigue (5%). Interpretation: Results of this large prospective study in papillary mRCC demonstrated that everolimus provides some clinical benefit to this patient population and highlight the need for central pathological review of this rare tumour.

I.F. = 7,191

N. citazioni = 45

276. Brodaczewska KK, Szczylik C, Fiedorowicz M, **Porta C**, Czarnecka AM. Choosing the right cell line for renal cell cancer research. *Mol Cancer* 2016;15:83.

ABSTRACT - Cell lines are still a tool of choice for many fields of biomedical research, including oncology. Although cancer is a very complex disease, many discoveries have been made using monocultures of established cell lines. Therefore, the proper use of in vitro models is crucial to enhance our understanding of cancer. Therapeutics against renal cell cancer (RCC) are also screened with the use of cell lines. Multiple RCC in vitro cultures are available, allowing in vivo heterogeneity in the laboratory, but at the same time, these can be a source of errors. In this review, we tried to sum up the data on the RCC cell lines used currently. An increasing amount of data on RCC shed new light on the molecular background of the disease; however, it revealed how much still needs to be done. As new types of RCC are being distinguished, novel cell lines and the re-exploration of old ones seems to be indispensable to create effective in vitro tools for drug screening and more.

I.F. = 2,278

N. citazioni = 123

277. Frascà GM, D'Errico A, Malvi D, **Porta C**, Cosmai L, Santoni M, Sandrini S, Salviani C, Gallieni M, Balestra E. Transplantation of kidneys with tumors. *J Nephrol* 2016;29:163-8.

ABSTRACT - The shortage of donors in the face of the increasing number of patients wait-listed for renal transplantation has prompted several strategies including the use of kidneys with a tumor, whether found by chance on harvesting from a deceased donor or intentionally removed from a living donor and transplanted after excision of the lesion. Current evidence suggests that a solitary well-differentiated renal cell carcinoma, Fuhrman nuclear grade I-II, less than 1 cm in diameter and resected before grafting may be considered at minimal risk of recurrence in the recipient who, however, should be informed of the possible risk and consent to receive such a graft.

I.F. = 2,153

N. citazioni = 7

278. Rothermundt C, von Rappard J, Eisen T, Escudier B, Grünwald V, Larkin J, McDermott D, Oldenburg J, **Porta C**, Rini B, Schmidinger M, Sternberg CN, Putora PM. Second-line treatment for metastatic clear cell renal cell cancer: experts' consensus algorithms. *World J Urol* 2017;35:641-8.

ABSTRACT - Second-line systemic treatment options for metastatic clear cell renal cell cancer (mccRCC) are diverse and treatment strategies are variable among experts. Our aim was to investigate the approach for the second-line treatment after first-line therapy with a tyrosine kinase inhibitor (TKI). Recently two phase III trials have demonstrated a potential role for nivolumab (NIV) and cabozantinib (CAB) in this setting. We aimed to estimate the impact of these trials on clinical decision making. Materials and methods: Eleven international experts were asked to provide their treatment strategies for second-line systemic therapy for mccRCC in the current setting and once NIV and CAB will be approved and available. The treatment strategies were analyzed with the objective consensus approach. Results: The analysis of the decision trees revealed everolimus (EVE), axitinib (AXI), NIV and TKI switch (sTKI) as therapeutic options after first-line TKI therapy in the current situation and mostly NIV and CAB in the future setting. The most commonly used criteria for treatment decisions were duration of response, TKI tolerance and zugzwang a composite of several related criteria. Conclusion: In contrast to the first-line setting, recommendations for second-line systemic treatment of mccRCC among experts were not as heterogeneous. The agents mostly used after disease progression on a first-line TKI included: EVE, AXI, NIV and sTKI. In the future setting of NIV and CAB availability, NIV was the most commonly chosen drug, whereas several experts identified situations where CAB would be preferred.

I.F. = 2,397

N. citazioni = 8

279. Fiorentino M, Gruppioni E, Massari F, Giunchi F, Altimari A, Ciccarese C, Bimbatti D, Scarpa A, Iacovelli R, **Porta C**, Virinder S, Tortora G, Artibani W, Schiavina R, Ardizzoni A, Brunelli M, Knuutila S, Martignoni G. Wide spetcrum mutational analysis of metastatic renal cell cancer: a retrospective next generation sequencing approach. *Oncotarget* 2017;8:7328-35.

ABSTRACT - Renal cell cancer (RCC) is characterized by histological and molecular heterogeneity that may account for variable response to targeted therapies. We evaluated retrospectively with a next generation sequencing (NGS) approach using a pre-designed cancer panel the mutation burden of 32 lesions from 22 metastatic RCC patients treated with at least one tyrosine kinase or mTOR inhibitor. We identified mutations in the VHL, PTEN, JAK3, MET, ERBB4, APC, CDKN2A, FGFR3, EGFR, RB1, TP53 genes. Somatic alterations were correlated with response to therapy. Most mutations hit VHL1 (31,8%) followed by PTEN (13,6%), JAK3, FGFR and TP53 (9% each). Eight (36%) patients were wild-type at least for the genes included in the panel. A genotype concordance between primary RCC and its secondary lesion was found in 3/6 cases. Patients were treated with Sorafenib, Sunitinib and Temsirolimus with partial responses in 4 (18,2%) and disease stabilization in 7 (31,8%). Among the 4 partial responders, 1 (25%) was wild-type and 3 (75%) harbored different VHL1 variants. Among the 7 patients with disease stabilization 2 (29%) were wild-type, 2 (29%) PTEN mutated, and single patients (14% each) displayed mutations in VHL1, JAK3 and APC/CDKN2A. Among the 11 non-responders 7 (64%) were wild-type, 2 (18%) were p53 mutated and 2 (18%) VHL1 mutated. No significant associations were found among RCC histotype, mutation variants and response to therapies. In the absence of predictive biomarkers for metastatic RCC treatment, a NGS approach may address single patients to basket clinical trials according to actionable molecular specific alterations.

I.F. = 5,168

N. citazioni = 15

280. **Porta C**, Toscani I, Czarnecka AM, Szczylik CA.

Immuno-oncology for renal cell carcinoma treatment: future perspectives for combinations and sequences with molecularly targeted agents. *Expert Opin Biol Ther* 2017;17:151-162.

ABSTRACT - From a theoretical viewpoint, combining molecularly targeted agents endowed with antiangiogenic properties with immunotherapy makes sense in treatment of metastatic renal cell carcinoma (RCC); this neoplasm is highly angiogenesis-dependent, as well as potentially immunogenic. Areas covered: The authors performed a literature search looking for clinical trials aimed at evaluating efficacy and tolerability of combinations (or sequences) of molecularly targeted agents and different immunotherapeutic approaches in metastatic RCC. Expert opinion: Combinations of molecularly targeted agents with old immunotherapeutics (i.e., cytokines) seem to add little to the presently available treatment standards (mainly monotherapy with targeted agents). Newer combinations with immune checkpoint inhibitors are promising but cumulative toxicity is an important issue, although highly dependent on the different companion drugs. Combinations with vaccines are ongoing, but first available data are not encouraging. A more thorough comprehension of the complex effects of these combinations on the immune system is mandatory to develop less empiric treatments.

I.F. = 3,974

N. citazioni = 3

281. Cosmai L, Gallieni M, Liguigli W, **Porta C**. Renal toxicity of anticancer agents targeting vascular endothelial growth factor (VEGF) and its receptors (VEGFRs). *J Nephrol* 2017;30:171-180.

ABSTRACT - Since angiogenesis plays a key role in tumor growth, progression and metastasization, anti-vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) agents have been developed over the years as anticancer agents, and have changed, for the better, the natural history of a number of cancer types. In the present review, the renal safety profile of presently available agents targeting either VEGF or VEGFRs will be discussed, together with the peculiarities related to their clinical use in patients with impaired renal function, or even in dialysis. Indeed, renal toxicity (especially, but not exclusively, hypertension and proteinuria) are quite commonly observed with these agents, and may be increased by the concomitant use of cytoxic chemotherapeutics. Despite all the above, kidney impairment or dialysis must not be regarded di per se as reasons not to administer or to stop an active anticancer treatment, especially considering the possibility of a significant survival improvement in many cancer patients treated with these agents.

I.F. = 1,352

N. citazioni = 26

282. Bracarda S, Negrier S, Casper J, **Porta C**, Schmidinger M, Larkin J, Gross Goupil M, Escudier B. How clinical practice is changing the rules: the sunitinib 2/1 schedule in metastatic renal cell carcinoma. *Expert Rev Anticancer Ther* 2017;17:227-33.

ABSTRACT – Currently, sunitinib is a standard of care in first-line treatment for metastatic renal cell carcinoma (mRCC). However, with the standard 4/2 schedule (sunitinib 50 mg/day; 4 consecutive weeks on treatment; 2 weeks' rest), 50% of patients require dose reductions to mitigate toxicity, highlighting the need to investigate alternative dosing schedules that improve tolerability without compromising efficacy. Areas covered: We present a concise critical review of published studies comparing the efficacy and safety of the 4/2 and 2/1 schedule (2 weeks on treatment; 1 week rest) for sunitinib. While all studies evaluating the 2/1 schedule have a low level of evidence, the results indicate that the 2/1 schedule improves tolerability compared with the 4/2 schedule, including significant reductions in the incidence of specific adverse events. It was not possible to make any definitive conclusions regarding efficacy due to methodologic limitations of these studies. Expert commentary: In the absence of strong evidence supporting the safety and efficacy of the 2/1 schedule, we recommend that patients should be initiated on sunitinib therapy with the standard 4/2 schedule and only be switched to the 2/1 schedule after the development of dose-limiting toxicities from weeks 3-4 (cycle 1) of the 4/2 schedule cycle.

I.F.: 2,347

N. citazioni = 10

283. **Porta C**, Chiellino S, Ferrari A, Mariucci S, Liguigli W. Pharmacotherapy for treating metastatic clear cell renal cell carcinoma. *Expert Opin Pharmacother* 2017;18:205-216.

ABSTRACT - Over the past decade metastatic renal cell carcinoma (RCC) treatment landscape has dramatically evolved from the era of cytokines-based immunotherapy (which benefited very few patients, at the expenses of high toxicities) to the present era of targeted agents and novel immunotherapeutics, greatly improving the prognosis of our patients. Areas covered: Here we have reviewed the present status of the medical treatment of metastatic RCC. To do this, we interrogated the Medline database, as well as the proceedings of the main Oncological and Urological conferences for the relevant trials coducted so far. Expert opinion: Despite all the advances made in these relatively few years, further improvements are needed, since none of the available agents proved able to cure even a sigle metastatic RCC patient. In particular, advances are awaited from the results of ongoing trial of combinations of different immune checkpoint inhibitors and of immune checkpoint inhibitors with anti-VEGF/VEGFRs agents. Furthermore, a better understanding of the molecular escape pathways used by the tumor to overcome VEGFR blockade or immune activation will hopefully bring soon to the clinic more active, tailored treatments, to be used in second line and beyond.

I.F. = 3,475

N. citazioni = 3

284. Personeni N, Giordano L, Abbadessa G, **Porta C**, Borbath I, Daniele B, Van Laethem JL, Van Vlierberghe H, Trojan J, De Toni EN, Gasbarrini A, Lencioni M, Lamar ME, Wang Y, Shuster D, Schwartz B, Santoro A, Rimassa L. Prognostic value of the neutrophil-to-lymphocyte ratio in the ARQ 197-215 second-line study for advanced hepatocellular carcinoma. *Oncotarget* 2017;8:14408-15.

ABSTRACT - The ARQ 197-215 study randomized patients to tivantinib or placebo and pre-specified efficacy analyses indicated the predictive value of MET expression as a marker of benefit from tivantinib in hepatocellular carcinoma (HCC). We aimed to explore the neutrophil-to-lymphocyte ratio (NLR) in 98 ARQ 197-215 patients with available absolute neutrophil count and absolute lymphocyte count at baseline. The cut-off value used to define high versus low NLR was 3.0. In univariate analy-

sis, high NLR was associated with hazard ratio (HR) for overall survival (OS) of 1.58 [95% confidence interval (CI) 1.01; 2.47; P <0.046], corresponding to median OS of 5.1 months versus 7.8 months in patients with low NLR (P = 0.044). In contrast, time to progression was not significantly affected by NLR (P = 0.20). Multivariable model confirmed that both NLR >3 (P = 0.03) and presence of vascular invasion (P = 0.017) were negatively associated with OS. After adjustment for vascular invasion, NLR independently predicted survival in both the placebo and the tivantinib cohort. For OS, no interaction was detected between NLR status and treatment (Pinteraction = 0.40). Baseline NLR is an independent prognostic biomarker in patients with HCC and compensated liver function who are candidate for second-line treatments.

I.F. = 5,168

N. citazioni = 18

285. Capri S, **Porta C**, Delea TE. Cost-effectiveness of Pazopanib versus Sunitinib as first-line treatment for locally advanced or metastatic Renal Cell Carcinoma from an Italian National Health Service perspective. *Clin Ther* 2017;39:567-80.

ABSTRACT - Purpose: A prior randomized controlled trial (COMPARZ [Comparing the Efficacy, Safety and Tolerability of Pazopanib versus Sunitinib]) found non-inferior progression-free survival for pazopanib versus sunitinib as first-line therapy in patients with advanced or metastatic renal cell carcinoma. The present study evaluated the cost-effectiveness of pazopanib versus sunitinib as first-line treatment for patients with metastatic renal cell carcinoma from an Italian National Health Service perspective. Methods: A partitioned-survival analysis model with 3 health states (progression-free survival, post-progression survival, and dead) was employed. The model time horizon was 5 years. For each treatment strategy, the model generated expected progression-free life years, post-progression life years, overall life years, quality-adjusted life years (QALYs), and costs. Results were reported as incremental costs per QALY gained and the net monetary benefit of pazopanib versus sunitinib. Probabilistic and deterministic sensitivity analyses were conducted to assess the impact on results of methodological and parameter uncertainty. Findings: In the base case, pazopanib was associated with higher QALYs and lower costs and dominated sunitinib. Using willingness-to-pay thresholds of €30,000 and €50,000 per QALY, the net monetary benefits with pazopanib were €6508 and €7702 per patient, respectively, versus sunitinib. The probability that pazopanib is cost-effective versus sunitinib was estimated to be 85% at a cost-effectiveness threshold of €20,000, 86% at a threshold of €30,000, and 81% at a threshold of €50,000 per QALY. Results were robust to changes in key parameter values and assumptions. Implications: These results suggest that pazopanib is likely to represent a cost-effective treatment option compared with sunitinib as first-line treatment for patients with metastatic renal cell carcinoma in Italy.

I.F. = 2,947

N. citazioni = 18

286. Rimassa L, Reig M, Abbadessa G, Peck-Radosavljevic M, Harris W, Zagonel V, Pastorelli D, Rota Caremoli E, **Porta C**, Damjanov N, Patel H, Daniele B, Lamar M, Schwartz B, Goldberg T, Santoro A, Bruix J. Tumor biopsy and patient enrollment in clinical trials for advanced hepatocellular carcinoma. *World J Gastroenterol* 2017;23:2448-52.

ABSTRACT - Tumor biopsies may help to reliably distinguish hepatocellular carcinoma (HCC) from other tumors, mostly cholangiocarcinoma as well as to identify the patient populations who most benefit from target-driven HCC treatments, in order to improve the success rate of experimental therapies. Clarifying tumor biology may also lead to identify biomarkers with prognostic role and/or enabling to predict response or resistance to therapies. Recently, clinical trials have more efficiently included biomarker endpoints and increasingly collected tumor tissue from enrolled patients. Due to their frail status and sometimes fast-progressing disease, the performance status of patients with HCC progressing on first-line therapy can deteriorate quickly, preventing their enrollment in clinical trials. However, the challenge of identifying the proper patient at the proper time can be overcome by periodic inter-department meetings involving the key specialists taking care of HCC patients, and solid networks between research centers and referring institutions. An early planned biopsy would also facilitate timely inclusion of patients in biology-driven clinical trials. Ultimately, institution of multidisciplinary teams can optimize treatment choice, biopsy timing, and quick enrollment of patients in clinical trials, before their performance status deteriorates.

I.F. = 3,300

N. citazioni = 10

287. Grassi P, Doucet L, Giglione P, Grünwald V, Melichar B, Galli L, De Giorgi U, Sabbatini R, Ortega C, Santoni M, Bamias A, Verzoni E, Derosa L, Studentova H, Porcu L, De Braud F, **Porta C**, Procopio G. Outcome of patients with Renal Cell Carcinoma and multiple glandular metastases treated with targeted agents. *Oncology* 2017;92:269-75.

ABSTRACT - Purpose: Pancreatic metastases (PM) from renal cell carcinoma (RCC) have been associated with long-term survival. The aim of this study was to evaluate the outcome of RCC patients with multiple glandular metastases (MGM) treated with targeted therapies (TTs). Methods: Sixty-four MGM patients treated between 1993 and 2014 were retrospectively identified from a database of 274 RCC patients with PM from 11 European centers. The survival of MGM patients was compared with that of both patients with PM only and a cohort of 325 RCC patients with non-GM (control group) treated with TTs. Survival was estimated using the Kaplan-Meier method and was statistically compared using the log-rank test. Results: Fifty-six patients (88%) had at least 2 MGM, 7 patients (11%) had 3 MGM and 1 patient had 4 MGM, while non-GM were present in the remaining patients. The median overall survival (OS) was 54.2 months for MGM and 73.4 months for patients with PM only. The median OS in the control group was 22.7 months and statistically inferior to both MGM (p < 0.001) and PM patients (p < 0.001). Conclusion: MGM from RCC are associated with a remarkable survival. Despite some limitations, these findings suggest that GM might be considered a predictor of a favorable prognosis.

I.F. = 2,262

N. citazioni = 5

288. Moccia F, Fotia V, Tancredi R, Della Porta MG, Rosti V, Bonetti E, Poletto V, Marchini S, Beltrame L, Gallizzi G, Da Prada GA, Pedrazzoli P, Riccardi A, **Porta C**, Zambelli A, D'Incalci M. Breast and renal cancer-derived endothelial colony forming cells share a common gene signature. *Eur J Cancer* 2017;77:155-64.

ABSTRACT - Background: Neovascularisation supports the metastatic switch in many aggressive solid cancers. Tumour neovessels are mostly lined by endothelial cells sprouting from nearby capillaries, but they could also be contributed by circulating endothelial progenitor cells (EPCs). However, scant information is available about tumour-derived EPCs. Methods: We carried out the first thorough, unbiased comparison of phenotype, function and genotype of normal versus tumour-derived endothelial colony forming cells (ECFCs), a truly endothelial EPC subtype. We used healthy donors-derived ECFCs (N-ECFCs) as control for breast cancer (BC)- and renal cell carcinoma (RCC)-derived ECFCs. Results: We found that both BC- and RCC-ECFCs belong to the endothelial lineage. Normal and tumour-derived ECFCs did not differ in terms of proliferative and tubulogenic rates. However, RCC-ECFCs were more resistant to rapamycin-induced apoptosis, whereas BC-ECFCs were more sensitive as compared with N-ECFCs. Gene expression profiling revealed 382 differentially expressed genes (DEGs; 192 upregulated and 150 downregulated) and 71 DEGs (33 upregulated, 38 downregulated) when comparing, respectively, BC- and RCC-ECFCs with N-ECFCs. Nonetheless, BC- and RCC-derived ECFCs shared 35 DEGs, 10 of which were validated by qRT-PCR; such 35 DEGs are organised in a gene network centred on FOS. Conclusion: These results provide the first clear-cut evidence that BC- and RCC-derived ECFCs exhibit an altered gene expression profile as compared with N-ECFCs; yet, they share a common gene signature that could highlight novel and more specific targets to suppress tumour vascularisation.

I.F. = 7,191

N. citazioni = 14

289. **Porta C**, Cosmai L, Previtali P. Editorial Comment from Dr. Porta et al. to Patterns of care among patients receiving sequential targeted therapies for advanced renal cell carcinoma: A retrospective chart review in the USA. *Int J Urol* 2017;24:279-80.

In this issue of the journal, Pal et al. reported on patterns of care among metastatic renal cell carcinoma in the USA. At present, the metastatic renal cell carcinoma therapeutic landscape in industrialized countries resembles, to a certain extent, the one shown therein: a growing number of metastatic renal cell carcinoma patients are receiving several lines of treatments sequentially, and this abundance of options has undoubtedly improved their survival. However, this situation also encompasses some risks, irrespective of the fact that unexpected disparities between countries in the (once) rich and industrialized Western world are emerging. First, the availability of so many active agents could also contribute to non-virtuous behaviors. Indeed, if one can easily move from one agent to another in the event of toxicities, even only a few days after commencing the treatment, why try to adapt the treatment dosage and schedule, and/or aggressively apply supportive measures in order to keep the treatment going? An unusual scenario, one might say. Not really; this is quite often observable in everyday clinical practice, although almost no scientific papers have ever dealt with this issue. If so, it is clear that all the knowledge we have gathered over the years might simply vanish at the first difficulty, or in the presence of a complaint (although often justified) from the patient. On the whole, is this possibility an opportunity, or a pitfall? Both, but with a disturbing trend towards the latter case. Indeed, managing toxicities by just shifting from one agent to the other, just because the latter is perceived as (or even is) less toxic, not only deprives a given patient of an option (which, in many countries, cannot be resumed later), but also potentially has a detrimental impact on the treatment outcome. Despite a fast approval system empowered by the European Medicines Agency, a second emerging issue is the disparity among European countries in the real availability of novel anticancer agents. Several years ago, Tim Eisen strongly criticized the British system for denying the reimbursability of several kidney cancer drugs due to economic considerations.4 Although difficult to accept from a patient's perspective, such a decision was based on serious pharmacoeconomical and macroeconomical considerations. What in recent years has happened in Italy is definitely more difficult to understand; denying highly active treatments to cancer patients just because the Italian Agency for Drugs "fights" pharmaceutical companies over drug prices is really hard to accept. This is just an ultimately useless way to save money, without any serious attempt to prioritize expenses by evaluating how much expense is worthwhile for a given clinical benefit. That's why the magnitude of clinical benefit scale recently empowered by the European Society of Oncology should be applauded, offering governments sound instruments to decide if, how and where to allocate resources in a tough global economic situation. However, the subsequent necessary step would (and should) be the real application of such an instrument. The choice of not taking any responsibility, but rather to pass these responsibilities on to those who produce and sell the drugs, thus denying patients (i.e. those whom a government regulatory body should serve) therapeutic opportunities and probably months of life, is not the

answer. Fortunately enough, a medical oncologist now chairs the Italian Agency for Drugs, hopefully bringing patients (and not drugs) back to center stage.

I.F. = 1,941

290. Gore ME, Jones RJ, Ravaud A, Kuczyk M, Demkow T, Bearz A, Shapiro J, Strauss UP, **Porta C**. Sorafenib dose escalation in treatment-naïve patients with metastatic renal cell carcinoma: a non-randomised, open-label, Phase 2b study. *BJU Int* 2017;119:846-53.

ABSTRACT – Objective: To assess the efficacy and safety of sorafenib dose escalation in metastatic renal cell carcinoma (mRCC). Patients and methods: Intra-patient dose escalation may enhance the clinical benefit of targeted anticancer agents in metastatic disease. In this non-randomised, open-label, Phase 2b study, treatment-naïve patients with mRCC were initially treated with the standard oral sorafenib dose [400 mg twice daily (BID)]. Two dose escalations were planned, each 200 mg BID after 28 days at the prior level. Dose reductions, interruptions, or delayed escalations were used to manage adverse events (AEs). The primary endpoint was objective response rate (ORR) in the modified intent-to-treat (mITT) population, which comprised patients with ≥6 months of treatment including ≥4 months of therapy at their highest tolerated dose. Secondary endpoints included progression-free survival (PFS) and safety. Results: In all, 83 patients received sorafenib. The dose received for the longest duration was 400, 600, and 800 mg BID in 48.2%, 15.7%, and 24.1% of patients, respectively. The ORR was 44.4% [n = 8/18; 95% confidence interval (CI) 21.5-69.2] and 17.9% (n = 12/67; 95% CI 9.6-29.2) in the mITT and ITT populations, respectively. The median (95% CI) PFS was 7.4 (6.0-11.7) months (ITT). The most common AEs of any grade were hand-foot skin reaction (66.3%) and diarrhoea (63.9%). Conclusion: Sorafenib demonstrated clinical benefit in treatment-naïve patients with mRCC. However, relatively few patients could sustain doses of >400 mg BID. There was evidence that, where tolerated, escalation from the standard sorafenib dose may have enhanced clinical benefit. However, this study does not support dose escalation for most patients with treatment-naïve mRCC. Alternative protocols for sorafenib dose escalation could be explored.

I.F.: 4,688

N. citazioni = 3

291. **Porta C**, Ferrari A, Czarnecka AM, Szczylik CA. Pazopanib in patients with clear-cell Renal Cell Carcinoma: seeking the right patient. *Front Pharmacol* 2017;8:329.

SUMMARY - Current guidelines suggest pazopanib as one of the standards of care for first-line treatment of mRCC; in the presence of just one head-to-head comparison, which demonstrated the noninferiority of pazopanib as compared to sunitinib, it is crucial to figure out the ideal patients to treat with one or the other agent. Although, its favorable safety profile makes pazopanib appealing for treatment of frail patients, elderly, and those with poor risk prognostic features, available data promote its use in young and fit patients, with good performance status and good prognostic features. Furthermore, its ability to induce significant tumor shrinkage is emerging in recent years, thus supporting its potential in patients who need tumor shrinkage.

I.F. = 3,831
N. citazioni = 6

292. Tannir NM, Figlin RA, Gore ME, Michaelson MD, Motzer RJ, **Porta C**, Rini BI, Hoang C, Lin X, Escudier B. Long-term response to Sunitinib treatment in metastatic Renal Cell Carcinoma: a pooled analysis of clinical trials. *Clin Genitourin Cancer* 2017;16:6-12.

ABSTRACT - Background – We characterized clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib who were long-term responders (LTRs), defined as patients having progression-free survival (PFS) > 18 months. Patients and Methods – A retrospective analysis of data from 5714 patients with mRCC treated with sunitinib in 8 phase II/III clinical trials and the expanded access program. Duration on-study and objective response rate (ORR) were compared between LTRs and patients with PFS ≤ 18 months ("others"). PFS and overall survival (OS) were summarized using Kaplan-Meier methodology. Results – Overall, 898 (15.7%) patients achieved a long-term response and 4816 (84.3%) patients did not achieve long-term response. The median (range) duration on-study was 28.6 (16.8-70.7) months in LTRs and 5.5 (0-68.8) months in others. ORR was 51% in LTRs versus 14% in others (P < .0001). Median PFS in LTRs was 32.11 months and median OS was not reached. LTRs had higher percentage of early tumor shrinkage ≥ 10% at the first scan (67.1% vs. 51.2%; P = .0018) and greater median maximum on-study tumor shrinkage from baseline (-56.9 vs. -27.1; P < .0001) versus others. White race, Eastern Cooperative Oncology Group performance status 0, time from diagnosis to treatment ≥ 1 year, clear cell histology, no liver metastasis, lactate dehydrogenase ≤ 1.5 upper limit of normal (ULN), corrected calcium ≤ 10 mg/dL, hemoglobin greater than the lower limit of normal, platelets less than or equal to ULN, body mass index ≥ 25 kg/m2, and low neutrophil-to-lymphocyte ratio were associated with LTR. Conclusion – A subset of patients with mRCC treated with sunitinib achieved long-term response. LTRs had improved ORR, PFS, and OS.

I.F. = 2.539
N. citazioni = 9

293. Sobczuk P, Szczylik C, **Porta C**, Czarnecka AM. Renin angiotensin system deregulation as renal cancer risk factor. *Oncol Lett* 2017;14:5059-68.

ABSTRACT – For numerous years, the non-cardiovascular role of the renin-angiotensin system (RAS) was underestimated, but recent studies have advanced the understanding of its function in various processes, including carcinogenesis. Numerous evidence comes from preclinical and clinical studies on the use of antihypertensive agents targeting the RAS, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers. It has been demonstrated that the use of ACEIs can alter the incidence of renal cell carcinoma (RCC) and may have a positive effect by prolonging patient survival. It has an effect on the complex action of ACEI, resulting in decreased angiotensin II (Ang-II) production and altered levels of bradykinin or Ang 1-7. The present review discusses the existing knowledge on the effects of ACE and its inhibitors on RCC cell lines, xenograft models, and patient survival in clinical studies. A brief introduction to molecular pathways aids in understanding the non-cardiovascular effects of RAS inhibitors and enables the conduction of studies on combined cancer treatment with the application of ACEIs. Recent evidence regarding the treatment of hypertension associated with tyrosine kinase inhibitors, one of the most pronounced and common side effects in modern RCC treatment, are also outlined. Captopril, an ACEI, may be used to lower blood pressure in patients, particularly due to its additional renoprotective actions.

I.F.: 1,664
N. citazioni = 25

294. Massari F, Ciccarese C, Bria E, **Porta C**, La Russa F, Knuutila S, Artibani W, Porcaro AB, Bimbatti D, Modena A, Sava T, Tortora G, Cheng L, Eccher A, Cima L, Pedron S, Ghimenton C, Martignoni G, Brunelli M. Reprofiling metastatic samples for chromosome 9p and 14q aberrations as a strategy to overcome tumor heterogeneity in clear-cell Renal Cell Carcinoma. *Appl Immunohistochem Mol Morphol* 2017;25:39-43.

ABSTRACT - Losses of chromosomes 9p and 14q are associated with worse outcomes in patients affected by clear-cell renal cell carcinoma (RCC) and are helpful for prognostic risk stratification. Both chromosomal loci harbor several hot-spot molecular pathways suitable for targeted therapeutic interventions. Intratumor heterogeneity may foster tumor adaptation and therapeutic failure. We sought to investigate the presence of losses of the hot spots of chromosomal loci 9p and 14q in primary clear-cell RCC and matched metastatic tissues. CD10 and CD13 were performed on 7 cases of clear-cell RCC with hematogenous tissue metastases. Cytogenetic fluorescence in situ hybridization analysis was performed on primary and matched metastatic tissues using specific probes mapping the 9p and the 14q loci. The loss of chromosome 9p was observed in 85% of both primary clear-cell RCCs and in matched metastases; 14% showed discordance between primary and matched metastases showing gains. The loss of chromosome 14q was observed in 58% of both primary and matched metastases. Only 3/7 (42%) did show an equal status of loss of chromosome 14q. Heterogeneity of the cytogenetic status between metastatic and primary clear-cell RCCs is observed for the loss of chromosome 14q rather than chromosome 9p. The impact of chromosome 14q cytogenetic status, harboring the HIF1 gene, a major driver for the angiogenenic switch, may drive the efficacy of targeted inhibitors, whereas the loss of chromosome 9p, harboring other hot-spot genes, seems to be related to the metastatic behavior per se, without cytogenetic modulation. Reprofiling the metastatic tissue, as compared with the primary tumor, in patients affected by metastatic RCC could be a novel approach to overcome resistance to VEGF(Rs)-targeting agents.

I.F. = 2,012
N. citazioni = 6

295. Dufies M, Giuliano S, Viotti J, Borchiellini D, Cooley LS, Ambrosetti D, Guyot M, Ndiaye PD, Parola J, Claren A, Schiappa R, Gal J, Frangeul A, Jacquel A, Cassuto O, Grépin R, Auberger P, Bikfalvi A, Milano G, Escudier B, Rioux-Leclercq N, **Porta C**, Negrier S, Chamorey E, Ferrero JM, Pagès G. CXCL7 is a predictive marker of sunitinib efficacy in clear cell renal cell carcinomas. *Br J Cancer* 2017;117:947-53.

ABSTRACT – Background: Sunitinib is one of the first-line standard treatments for metastatic clear cell renal cell carcinoma (ccRCC) with a median time to progression shorter than 1 year. The objective is to discover predictive markers of response to adapt the treatment at diagnosis. Methods: Prospective phase 2 multi-centre trials were conducted in ccRCC patients initiating sunitinib (54 patients) or bevacizumab (45 patients) in the first-line metastatic setting (SUVEGIL and TORAVA trials). The plasmatic level of CXCL7 at baseline was correlated with progression-free survival (PFS). Results: The cut-off value of CXCL7 for PFS was 250 ng ml-1. Patients with CXCL7 plasmatic levels above the cut-off at baseline (250 ng ml-1) had a significantly longer PFS (hazard ratio 0.323 (95% confidence interval 0.147-0.707), P=0.001). These results were confirmed in a retrospective validation cohort. The levels of CXCL7 did not influence PFS of the bevacizumab-treated patients. Conclusions: CXCL7 may be considered as a predictive marker of sunitinib efficacy for ccRCC patients.
I.F.: 5,922
N. citazioni = 14

296. Massari F, Di Nunno V, Ciccarese C, Graham J, **Porta C**, Comito F, Cubelli M, Iacovelli R, Heng DYC. Adjuvant therapy in renal cell carcinoma. *Cancer Treat Rev* 2017;60:152-7.

ABSTRACT – Several drugs have demonstrated clinical activity in metastatic renal cell carcinoma (mRCC). The identification of key metabolic pathways has led to the development of novel targeted therapies which have drastically changed the treatment paradigm of mRCC. Moreover, immune-checkpoint inhibitors have recently shown significant activity in advanced disease. Despite these advancements, the role of adjuvant therapy in localized, non-metastatic RCC remains unclear. The utility of many of these agents in the adjuvant setting is currently being actively explored. In this review, we will summarize the main clinical trials investigating adjuvant therapy in renal cell carcinoma, focusing primarily on immunotherapy and targeted agents.
I.F.: 8,122
N. citazioni = 26

297. Rizzo M, **Porta C**. Sunitinib in the treatment of renal cell carcinoma: an update on recent evidence. *Ther Adv Urol* 2017;9:195-207.

ABSTRACT – Sunitinib is a multitarget tyrosine kinase inhibitor endowed mainly by antiangiogenic effects, although an indirect inhibitory effect on tumor growth and, more recently, a complex activity on antitumor immune response has been described. From approval by the US Food and Drug Administration (FDA) in January 2006, sunitinib represents a key molecule in the treatment of metastatic renal cell carcinoma (mRCC) due to the peculiar molecular pathogenesis of this neoplasm. Over the past 10 years, clinical trials and real-world experiences helped clinicians to understand how, when and for how long to use sunitinib. Although a huge amount of data evidenced the relationship existing between sunitinib dose intensity and improved clinical outcome, the management of sunitinib-induced adverse events is often complex; thus, alternative schedules have been proposed over time which allow increased tolerability, without decreased daily sunitinib exposure, leading to improved clinical outcomes. To date, combinations of sunitinib with other approved targeted agents did not demonstrate any significant benefit over its single-agent use, mainly due to tolerability issues. Sunitinib has also been tested in the adjuvant setting, within the ASSURE and S-TRAC trials, with opposite results; indeed, equivocal risk-stratification criteria, as well as immature overall survival (OS) data prevent any definitive conclusion on this important issue. Despite being on the market for a long time, sunitinib still plays a role as the 'comparator arm' of a number of trials in the field of mRCC. Combinations with immune checkpoint inhibitors and vaccines look promising; once again, sunitinib can help us to optimize mRCC management.
I.F.: n.r.
N. citazioni = 22

298. Massari F, Ciccarese C, Hes O, Michal M, Caliò A, Fiorentino M, Giunchi F, D'Amuri A, Sanguedolce F, Sabbatini R, Guida A, Ardizzoni A, **Porta C**, Iacovelli R, Tortora G, Cima L, Ortega C, Lapini A, Martignoni G, Brunelli M. The tumor entity denominated "clear cell-papillary renal cell carcinoma" according to the WHO 2016 new classification, have the clinical characters of a renal cell adenoma as does harbor a benign outcome. *Pathol Oncol Res* 2018;24:447-56.

ABSTRACT - The new WHO 2016 classification of renal neoplasia encounters the new entity called "clear cell papillary renal cell carcinoma" (ccpRCC). The ccpRCC has been long included as a subtype of clear cell RCC histotype and it actually ranges from 2 to 9% in different routinely available cohort of renal carcinomas. Of important note, ccpRCC does not show any recurrences or metastases or lymph-node invasion and the outcome is always good. We reviewed twenty-four publications with available follow-up for patients (no. 362) affected by clear cell papillary RCCs/renal adenomatoid tumours and notably ccpRCC harbors an indolent clinical behavior after a mean of 38 months (3.5 years) of follow-up. This paper reviews the histological, molecular and clinical features characterizing ccpRCC, with the goal of focusing the knowledge of the benign fashion of this new tumour entity, supporting the idea of a new renal cell adenoma recruited morphologically from ex conventional clear cell RCC tumours.
I.F. = 1.736
N. citazioni = 10

299. Vitelli V, Falvo P, G Nergadze S, Santagostino M, Khoriauli L, Pellanda P, Bertino G, Occhini A, Benazzo M, Morbini P, Paulli M, **Porta C**, Giulotto E. Telomeric Repeat-Containing RNAs (TERRA) decrease in squamous cell carcinoma of the head and neck is associated with worsened

clinical outcome. *Int J Mol Sci* 2018;19:274

ABSTRACT – Telomeres are transcribed into noncoding telomeric repeat-containing RNAs (TERRA), which are essential for telomere maintenance. Deregulation of TERRA transcription impairs telomere metabolism and a role in tumorigenesis has been proposed. Head and neck cancer (HNC) is one of the most frequent cancers worldwide, with head and neck squamous cell carcinoma (HNSCC) being the predominant type. Since HNSCC patients are characterized by altered telomere maintenance, a dysfunction in telomere transcription can be hypothesized. In this prospective study, we compared TERRA levels in the tumor and matched normal tissue from 23 HNSCC patients. We then classified patients in two categories according to the level of TERRA expression in the tumor compared to the normal tissue: (1) lower expression in the tumor, (2) higher or similar expression in tumor. A significant proportion of patients in the first group died of the disease within less than 34 months postsurgery, while the majority of patients in the second group were alive and disease-free. Our results highlight a striking correlation between TERRA expression and tumor aggressiveness in HNSCC suggesting that TERRA levels may be proposed as a novel molecular prognostic marker for HNSCC.

I.F.: 3,687

N. citazioni = 7

300. Krawczyk KM, Matak D, Szymanski L, Szczylik C, **Porta C**, Czarnecka AM. Culture in embryonic kidney serum and xeno-free media as renal cell carcinoma and renal cell carcinoma cancer stem cells research model. *Cytotechnology* 2018;70:761-82.

ABSTRACT – The use of fetal bovine serum hinders obtaining reproducible experimental results and should also be removed in hormone and growth factor studies. In particular hormones found in FBS act globally on cancer cell physiology and influence transcriptome and metabolome. The aim of our study was to develop a renal carcinoma serum free culture model optimized for (embryonal) renal cells in order to select the best study model for downstream auto-, para- or endocrine research. Secondary aim was to verify renal carcinoma stem cell culture for this application. In the study, we have cultured renal cell carcinoma primary tumour cell line (786-0) as well as human kidney cancer stem cells in standard 2D monolayer cultures in Roswell Park Memorial Institute Medium or Dulbecco's Modified Eagle's Medium and Complete Human Kidney Cancer Stem Cell Medium, respectively. Serum-free, animal-component free Human Embryonic Kidney 293 media were tested. Our results revealed that xeno-free embryonal renal cells optimized culture media provide a useful tool in RCC cancer biology research and at the same time enable effective growth of RCC. We propose bio-mimic RCC cell culture model with specific serum-free and xeno-free medium that promote RCC cell viability.

I.F.: 1,461

N. citazioni = 3

301. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, **Porta C**, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B; CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in advanced Renal-Cell Carcinoma. *N Engl J Med* 2018;378:1277-90.

ABSTRACT – Background: Nivolumab plus ipilimumab produced objective responses in patients with advanced renal-cell carcinoma in a pilot study. This phase 3 trial compared nivolumab plus ipilimumab with sunitinib for previously untreated clear-cell advanced renal-cell carcinoma. Methods: We randomly assigned adults in a 1:1 ratio to receive either nivolumab (3 mg per kilogram of body weight) plus ipilimumab (1 mg per kilogram) intravenously every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram) every 2 weeks, or sunitinib (50 mg) orally once daily for 4 weeks (6-week cycle). The coprimary end points were overall survival (alpha level,0.04), objective response rate (alpha level, 0.001), and progression-free survival (alpha level, 0.009) among patients with intermediate or poor prognostic risk. Results: A total of 1096 patients were assigned to receive nivolumab plus ipilimumab (550 patients) or sunitinib (546 patients); 425 and 422, respectively, had intermediate or poor risk. At a median follow-up of 25.2 months in intermediate- and poor-risk patients, the 18-month overall survival rate was 75% (95% confidence interval [CI], 70 to 78) with nivolumab plus ipilimumab and 60% (95% CI, 55 to 65) with sunitinib; the median overall survival was not reached with nivolumab plus ipilimumab versus 26.0 months with sunitinib (hazard ratio for death, 0.63; P<0.001). The objective response rate was 42% versus 27% (P<0.001), and the complete response rate was 9% versus 1%. The median progression-free survival was 11.6 months and 8.4 months, respectively (hazard ratio for disease progression or death, 0.82; P=0.03, not significant per the prespecified 0.009 threshold). Treatment-related adverse events occurred in 509 of 547 patients (93%) in the nivolumab-plus-ipilimumab group and 521 of 535 patients (97%) in the sunitinib group; grade 3 or 4 events occurred in 250 patients (46%) and 335 patients (63%), respectively. Treatment-related adverse events leading to discontinuation occurred in 22% and 12% of the patients in the respective groups. Conclusions: Overall survival and objective response rates were significantly higher with nivolumab plus ipilimumab than with sunitinib among intermediate- and poor-risk patients with previously untreated advanced renal-cell carcinoma (ClinicalTrials.gov number, NCT02231749).

I.F.: 79,258

N. citazioni = 2040

302. Rimassa L, Assenat E, Peck-Radosavljevic M, Pracht M, Zagonel V, Mathurin P, Rota Caremoli E, **Porta C**, Daniele B, Bolondi L, Mazzaferro V, Harris W, Damjanov N, Pastorelli D, Reig M, Knox J, Negri F, Trojan J, López López C, Personeni N, Decaens T, Dupuy M, Sieghart W, Abbadessa G, Schwartz B, Lamar M, Goldberg T, Shuster D, Santoro A, Bruix J. Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study. *Lancet Oncol* 2018;19:682-93.

SUMMARY – Background: Tivantinib (ARQ 197), a selective, oral MET inhibitor, improved overall survival and progression-free survival compared with placebo in a randomised phase 2 study in patients with high MET expression (MET-high) hepatocellular carcinoma previously treated with sorafenib. The aim of this phase 3 study was to confirm the results of the phase 2 trial. Methods: We did a phase 3, randomised, double-

blind, placebo-controlled study in 90 centres in Australia, the Americas, Europe, and New Zealand. Eligible patients were 18 years or older and had unresectable, histologically confirmed, hepatocellular carcinoma, an Eastern Cooperative Oncology Group performance status of 0–1, high MET expression (MET-high; staining intensity score ≥2 in ≥50% of tumour cells), Child-Pugh A cirrhosis, and radiographically-confirmed disease progression after receiving sorafenib-containing systemic therapy. We randomly assigned patients (2:1) in block sizes of three using a computer-generated randomisation sequence to receive oral tivantinib (120 mg twice daily) or placebo (twice daily); patients were stratified by vascular invasion, extrahepatic spread, and α-fetoprotein concentrations (≤ 200 ng/mL or > 200 ng/mL). The primary endpoint was overall survival in the intention-to-treat population. Efficacy analyses were by intention to treat and safety analyses were done in all patients who received any amount of study drug. This study is registered with ClinicalTrials.gov, number NCT01755767. Findings: Between Dec 27, 2012, and Dec 10, 2015, 340 patients were randomly assigned to receive tivantinib (n=226) or placebo (n=114). At a median follow-up of 18.1 months (IQR 14.1-23.1), median overall survival was 8.4 months (95% CI 6.8-10.0) in the tivantinib group and 9.1 months (7.3-10.4) in the placebo group (hazard ratio 0.97; 95% CI 0.75-1.25; p=0.81). Grade 3 or worse treatment-emergent adverse events occurred in 125 (56%) of 225 patients in the tivantinib group and in 63 (55%) of 114 patients in the placebo group, with the most common being ascites (16 [7%] patients]), anaemia (11 [5%] patients), abdominal pain (nine [4%] patients), and neutropenia (nine [4%] patients) in the tivantinib group. 50 (22%) of 226 patients in the tivantinib group and 18 (16%) of 114 patients in the placebo group died within 30 days of the last dose of study medication, and general deterioration (eight [4%] patients) and hepatic failure (four [2%] patients) were the most common causes of death in the tivantinib group. Three (1%) of 225 patients in the tivantinib group died from a treatment-related adverse event (one sepsis, one anaemia and acute renal failure, and one acute coronary syndrome). Interpretation: Tivantinib did not improve overall survival compared with placebo in patients with MET-high advanced hepatocellular carcinoma previously treated with sorafenib. Although this METIV-HCC trial was negative, the study shows the feasibility of doing integral tissue biomarker studies in patients with advanced hepatocellular carcinoma. Additional randomised studies are needed to establish whether MET inhibition could be a potential therapy for some subsets of patients with advanced hepatocellular carcinoma.

I.F.: 33,9

N. citazioni = 212

303. Gallieni M, Cosmai L, **Porta C**. Acute kidney injury in cancer patients. *Contrib Nephrol* 2018;193:137-48.

ABSTRACT – Background: Renal complications are a relevant clinical issue in patients with cancer; conversely, cancer in patients affected by kidney diseases is a growing problem mainly due to the aging of the general population. Onco-Nephrology is a novel subspecialty addressing these issues. Summary: Acute kidney injury (AKI) is an important cause of morbidity and mortality in cancer patients, and recognizes a number of different causes, which can impact, directly and indirectly, on kidney function. Furthermore, the appearance of AKI may have a tremendously negative impact on oncological treatments, often denying cancer patients active and life-prolonging treatments. Overall, patients with cancer are at risk of AKI, which could be caused by antineoplastic treatments, sepsis, metabolic disturbances, hematopoietic stem cell transplantation, primary thrombotic micro-angiopathies, and direct involvement of the kidney by hematological malignancies and also by solid cancer, in particular kidney and urothelial malignancies. Key Messages: (1) AKI is a frequent and increasing complication of cancer. (2) There is a bidirectional relationship between cancer and kidney disease, and in both cases, AKI is more likely to happen. (3) AKI in patients with cancer is associated with increased morbidity and mortality. (4) In cancer patients, a multidisciplinary approach and early intervention may reduce the incidence of AKI and its life-threatening consequences. (5) Onco-Nephrology is a growing area of nephrology that requires clinicians to have a better understanding of the renal complications of cancer including AKI.

I.F.: 0,388

N. citazioni = 12

304. Bracarda S, Galli L, Maruzzo M, Lo Re G, Buti S, Favaretto A, Di Costanzo F, Sacco C, Merlano M, Mucciarini C, Zafarana E, Romito S, Maestri A, Giorgio CG, Ionta MT, Turci D, De Giorgi U, Procopio G, Cortesi E, Giannarelli D, **Porta C**. Negative prognostic factors and resulting clinical outcome in patients with metastatic renal cell carcinoma included in the Italian nivolumab-expanded access program. *Future Oncol* 2018;14:1347-54.

ABSTRACT – Aim: We report the outcomes observed with nivolumab in metastatic renal cell carcinoma patients with poor prognostic features enrolled in the Italian expanded access program. Patients & Methods: Nivolumab was available for patients who relapsed after at least one prior systemic treatment in the advanced or metastatic setting. Results: Of 389 patients, 32 (8%) had brain metastasis, 129 (33%) had liver and 193 (50%) had bone metastasis. These subpopulations achieved a disease control rate of 53, 45 and 47%, respectively. Fifty-one patients had G4 tumor, and they showed 23% objective response rate. The safety profile of the subgroups was in line with the expanded access program population. No new safety signals were reported. Conclusion: Patients with poor prognostic features may derive relevant benefits from nivolumab.

I.F.: 2,369

N. citazioni = 7

305. Iacovelli R, De Giorgi U, Galli L, Zucali P, Nolè F, Sabbatini R, Fraccon AP, Basso U, Mosca A, Atzori F, Santini D, Facchini G, Fornarini G, Pasini F, Masini C, Massari F, Buti S, Sava T, Sacco C, Ricotta R, Sperduti I, Tortora G, **Porta C**. Is It possible to improve prognostic classification in patients affected by metastatic Renal Cell Carcinoma with an intermediate or poor prognosis? *Clin Genitourin Cancer* 2018;16:355-9.e1.

ABSTRACT – Background: The International mRCC (metastatic renal cell carcinoma) Database Consortium (IMDC) is the standard classification for mRCC. We aimed to evaluate the outcomes of a large cohort of patients with an intermediate or a poor prognosis treated with sunitinib using a different cutoff point for IMDC to improve the classification. Patients and methods: Patients with an intermediate or a poor prognosis according to the IMDC criteria and treated with sunitinib were included in the present study. A new cutoff point was used to categorize the patients. The new score was validated in an independent cohort of patients. Results: A total of 457 patients were included in the present study. Significant differences in overall survival (OS) were highlighted regarding the number of prognostic factors. Three categories were identified according to the presence of 1 (ie, favorable-intermediate group), 2 (ie, real-

intermediate group), and > 2 (ie, poor group) factors. The corresponding median OS periods were 32.9, 20.0, and 8.9 months, with significant differences among the groups. The validation cohort included 389 patients. The median OS period for the favorable-intermediate group, real-intermediate group, and poor group was 34.3, 19.4, and 9.0 months, respectively, with confirmed significant differences among the groups. Conclusion: Our analysis revealed significant differences among patients with an intermediate prognosis using the IMDC prognostic factors. Further investigations to optimize the use of available and upcoming therapies are required.

I.F.: 2,539

N. citazioni = 24

306. Iacovelli R, Cossu Rocca M, Galli L, Sabbatini R, De Giorgi U, Santini D, Facchini G, Mosca A, Atzori F, Zucali P, Fornarini G, Massari F, Buti S, Ricotta R, Masini C, Toscani I, Biasco E, Guida A, Lolli C, De Lisi D, Rossetti S, Terrone C, Scartozzi M, Miggiano C, Pastorino A, Bersanelli M, Carlo-Stella G, Pinto C, Nobili E, Nolè F, Tortora G, **Porta C**. The outcome to axitinib or everolimus after sunitinib in metastatic renal cell carcinoma. *Anticancer Drug* 2018;29:705-9.

ABSTRACT – We aimed to investigate the different outcomes in patients with metastatic renal cell carcinoma treated with second-line axitinib or everolimus after sunitinib. Patients treated in 16 oncological centres in Italy were included, and those receiving axitinib or everolimus from January 2013 onwards were analysed for outcomes. Descriptive statistical tests were used to highlight differences between groups. The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS). Data on 634 patients with metastatic renal cell carcinoma treated with first-line sunitinib have been obtained. A total of 182 patients received a second-line therapy with everolimus (79 patients, 43%) or axitinib (103 patients, 57%), respectively. The median PFS was 4.6 [95% confidence (CI): 2.6-6.5] months for patients treated with everolimus and 5.5 (95% CI: 4.3-6.7) months for patients treated with axitinib (P=0.7). The median OS was 13.9 (95% CI: 10.4-17.4) months for patients treated with everolimus and 12.0 (95% CI: 7.9-16.2) months for patients treated with axitinib (P=0.3). No differences were found based on length of first-line treatment. Major limitations are the retrospective nature of the study and the lack of a prospective evaluation of the progression. This study reports no significantly differences between everolimus and axitinib in terms of both PFS and OS. Furthermore, the length of first-line treatment cannot be used as such a predictive factor and cannot suggest the use of a molecule compared with another.

I.F.: 1,869

N. citazioni = 1

307. Cosmai L, **Porta C**, Perazella MA, Launay-Vacher V, Rosner MH, Jhaveri KD, Floris M, Pani A, Teuma C, Szczylik CA, Gallieni M. Opening an onconephrology clinic: recommendations and basic requirements. *Nephrol Dial Transplant* 2018;33:1503-10.

ABSTRACT – Onconephrology is a rapidly evolving subspeciality that covers all areas of renal involvement in cancer patients. The complexity of the field may benefit from well-defined multidisciplinary management administered by a dedicated team. Since there is an increasing need to address the needs of this population in dedicated outpatient clinics, it is critical to highlight basic characteristics and to suggest areas of development. In this brief perspective article, we analyse the requirements of an onconephrology clinic in terms of logistics, critical mass of patients and building a multidisciplinary team. We will further discuss which patients to refer and which conditions to treat. The last part of the article is dedicated to education and performance indicators and to analysis of the potential advantages of applying the hub-and-spoke model to this field. The ultimate aim of this experience-based article is to initiate debate about what an onconephrology outpatient clinic might look like in order to ensure the highest quality of care for this growing population of patients.

I.F.: 4,600

N. citazioni = 20

308. Escudier B, **Porta C**, Eisen T, Belsey J, Gibson D, Morgan J, Motzer R. The role of tivozanib in advanced renal cell carcinoma therapy. *Expert Rev Anticancer Ther* 2018;18:1113-24.

ABSTRACT – The efficacy of VEGF-targeting therapies in clinical trials led to their recommendation in clinical guidelines for use across the advanced or metastatic renal cell carcinoma (RCC) treatment landscape, however, tolerability (including off-target effects) has remained a challenge. Tivozanib is a selective inhibitor of all three VEGFRs, with limited off-target interaction, which demonstrates efficacy with improved tolerability relative to multikinase VEGFR-TKIs. Areas covered: Covered here is the clinical development of tivozanib in advanced RCC, including the pivotal Phase III, multicenter, open-label, randomized clinical study comparing tivozanib with sorafenib for the treatment of VEGF- and mTOR therapy-naïve advanced RCC patients. Also covered are ongoing trials, exploring the efficacy and safety of tivozanib in the setting of refractory disease and the utility of tivozanib in combination with checkpoint inhibitors for advanced RCC. Combination of a VEGFR-TKI and immunotherapy is promising in advanced RCC, if the treatment regimens have acceptable tolerability. Here the selectivity of tivozanib may contribute to an acceptable tolerability profile when used in combination therapy. Expert commentary: The approval of tivozanib provides an additional option for the first-line treatment of advanced or metastatic RCC patients in Europe and allows use of a VEGFR-TKI with selectivity for VEGFRs in this setting.

I.F.: 2,347

N. citazioni = 8

309. Iacovelli R, Ciccarese C, Bria E, Bimbatti D, Fantinel E, Mosillo C, Bisogno I, Brunelli M, Tortora G, **Porta C**. Immunotherapy versus standard of care in metastatic renal cell carcinoma. A systematic review and meta-analysis. *Cancer Treat Rev* 2018;70:112-7.

ABSTRACT – Background: Recently, immune checkpoint inhibitors against PD-1/PD-L1 or CTLA4 have emerged as new treatments for metastatic renal cell carcinoma (mRCC), despite discrepancy between their effects on OS and PFS. We performed a meta-analysis of randomized trials comparing immunotherapy to standard of care (SOC) in mRCC. Methods: Searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts prospective studies were identified. Data extraction was conducted according to the PRISMA statement. The measured outcomes were OS, PFS, and ORR. Results: A total of 2832 patients were available for evaluation of OS, and 3033 for PFS and ORR. Compared to SOC, immunotherapy improved OS (HR = 0.75; 95%CI 0.66-0.85; p < 0.001), and PFS (HR = 0.88; 95%CI 0.80-0.97;

p = 0.009). The PFS benefit was not confirmed when considering patients treated in first-line only (p = 0.10). Conversely, significant ORR improvement was found in patients treated in first-line only (HR = 1.14; 95%CI 1.02-1.28; p = 0.03) but not in the overall population. Conclusions: Immunotherapy improved OS compared to SOC in mRCC, irrespective of treatment line. In first-line, immunotherapy also increased the ORR compared to sunitinib. A lack of correlation between OS and PFS was confirmed, the latter to be used cautiously for the design and interpretation of trials involving immunotherapy in mRCC.

I.F.: 8,122

N. citazioni = 12

310. Yip SM, Wells C, Moreira R, Wong A, Srinivas S, Beuselinck B, **Porta C**, Sim HW, Ernst DS, Rini BI, Yuasa T, Basappa NS, Kanesvaran R, Wood LA, Canil C, Kapoor A, Fu SYF, Choueiri TK, Heng DYC. Checkpoint inhibitors in patients with metastatic renal cell carcinoma: Results from the international metastatic renal cell carcinoma database consortium. *Cancer* 2018;124:3677-83.

ABSTRACT – Background: To the authors' knowledge, outcomes and prognostic tools have yet to be clearly defined in patients with metastatic renal cell carcinoma (mRCC) who are treated with immuno-oncology (IO) checkpoint inhibitors (programmed death-ligand 1 [PD-L1] inhibitors). In the current study, the authors aimed to establish IO efficacy benchmarks in patients with mRCC and update patient outcomes in each International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic class. Methods: A retrospective analysis was performed using the IMDC database with data from 38 centers. It included patients with mRCC who were treated with ≥1 line of IO. Overall response rates (ORRs), duration of treatment (DOT), and overall survival (OS) were calculated. Patients were stratified using IMDC prognostic factors. Results: A total of 687 patients (90% with clear cell and 10% with non-clear cell) were included. The ORR was 27% in evaluable patients (461 patients). In patients treated with first-line nivolumab and ipilimumab (49 patients), the combination of PD-L1 inhibitor and vascular endothelial growth factor inhibitor (72 patients), and PD-L1 inhibitor (51 patients), the ORR was 31%, 39%, and 40%, respectively, and the median DOT was 8.3 months, 14.7 months, and 8.3 months, respectively. The ORR for second-line, third-line, and fourth-line nivolumab was 22%, 24%, and 26%, respectively. The median DOT was 5.7 months, 6.2 months, and 8.3 months, respectively, in the second-line, third-line, and fourth-line settings. When segregated into IMDC favorable-risk, intermediate-risk, and poor-risk groups, the median OS rates for the first-line, second-line, third-line, and fourth-line treatment settings were not reached (NR), NR, and NR, respectively (P = .163); NR, 26.7 months, and 7.4 months, respectively (P < 0. 0001); 36.1 months, 28.2 months, and 11.1 months, respectively (P = .016); and NR, NR, and 6.7 months, respectively (P = .047). Conclusions: The ORR was not found to deteriorate from the first-line to the fourth-line of IO therapy. In the second line through fourth line, the IMDC criteria appropriately stratified patients into favorable-risk, intermediate-risk, and poor-risk groups for OS.

I.F.: 6,537

N. citazioni = 38

311. Massari F, Di Nunno V, Gatto L, Santoni M, Schiavina R, Cosmai L, Brunocilla E, Ardizzoni A, **Porta C**. Should CARMENA really change our attitude towards cytoreductive nephrectomy in metastatic Renal Cell Carcinoma? A systematic review and meta-analysis evaluating cytoreductive nephrectomy in the era of targeted therapy. *Target Oncol* 2018;13:705-14.

ABSTRACT – Background: Cytoreductive nephrectomy in metastatic renal cell carcinoma (mRCC) patients has been common clinical practice due to evidence that resection of the primary tumor results in a survival benefit regardless of systemic treatment. Recently, the first large phase III randomized, non-inferiority prospective clinical trial evaluating this surgical approach demonstrated that systemic treatment alone was not inferior to primary surgery plus systemic treatment. Objective: Our aim was to evaluate if cytoreductive nephrectomy results in a survival benefit over systemic treatment alone in patients with mRCC and in specific subgroups, including patients with brain metastases, poor performance status, poor prognosis according to IMDC or MSKCC criteria, and clear cell and non-clear cell histologies. Patients and methods: We identified 16 published studies providing complete data for the comparison between cytoreductive nephrectomy + systemic treatment versus systemic treatment alone, and selected 9 for subgroup analysis. The inverse variance technique was applied for the meta-analysis of hazard ratios (HR), and, due to the intrinsic heterogeneity of the data, we adopted a random effects model. Risk of bias among the studies was estimated by the Newcastle-Ottawa Scale (NOS). Results: Our analysis suggested a survival benefit for patients receiving cytoreductive nephrectomy (pooled HR of 0.48, 95% confidence interval of 0.42-0.56) in the overall population. Survival advantages were also observed in patients with clear cell and non-clear renal cell carcinoma, while no benefit was evident in patients with brain metastasis, poor performance status, and poor risk. Conclusion: Cytoreductive nephrectomy seems to result in a survival benefit in both clear cell and non-clear cell histology, while no survival advantage was found in patients with specific clinical features. Despite a high level of heterogeneity, our results highlight the importance of a good selection of patients to whom a primary surgical approach could be proposed.

I.F.: 3,877

N. citazioni = 21

312. Poletto V, Rosti V, Biggiogera M, Guerra G, Moccia F, **Porta C**. The role of endothelial colony forming cells in kidney cancer's pathogenesis, and in resistance to anti-VEGFR agents and mTOR inhibitors: A speculative review. *Crit Rev Oncol Hematol* 2018;132:89-99.

ABSTRACT – Renal cell carcinoma (RCC) is highly dependent on angiogenesis, due to the overactivation of the VHL/HIF/VEGF/VEGFRs axis; this justifies the marked sensitivity of this neoplasm to antiangiogenic agents which, however, ultimately fail to control tumor growth. RCC also frequently shows alterations in the mTOR signaling pathway, and mTOR inhibitors have shown a similar pattern of initial activity/late failure as pure antiangiogenic agents. Understanding mechanisms of resistance to these agents would be key to improve the outcome of our patients. Circulating endothelial cells are a family of mainly bone marrow-derived progenitors, which have been postulated to be responsible of the reactivation of angiogenesis in different tumors. In this review, we shall discuss the complex nature and function of these cells, the evidence pro and contra their contribution to tumor vascularization, especially as far as RCC is concerned, and their possible role in determining resistance to presently available treatments.

I.F.: 4,495

N. citazioni = 14

313. De Giorgi U, Cartenì G, Giannarelli D, Basso U, Galli L, Cortesi E, Caserta C, Pignata S, Sabbatini R, Bearz A, Buti S, Lo Re G, Berruti A, Bracarda S, Cognetti F, Rastelli F, Fornarini G, **Porta C**, Turci D, Sternberg CN, Procopio G, fo the Italian Nivolumab Renal Cell Cancer Early Access Program Group. Safety and efficacy of Nivolumab for metastatic Renal Cell Carcinoma: real-world results from an Expanded Access Program. *BJU Int* 2019;123:98-105.

ABSTRACT – Objective: To report the safety and efficacy results of patients enrolled in the Italian Nivolumab Renal Cell Cancer Early Access Program. Patients and methods: Patients with metastatic renal cell cancer (mRCC) previously treated with agents targeting the vascular endothelial growth factor pathway were eligible to receive nivolumab 3 mg/kg once every 2 weeks. Patients included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AEs) using CTCAE v.4.0. Results: A total of 389 patients were enrolled between July 2015 and April 2016, including 18% aged ≥75 years, 6.7% with non-clear cell RCC, 49.6% with bone and 8.2% with brain metastases, 79% after 2 or more previous lines of therapy. The most common any-grade treatment-related AEs were fatigue (13%) and rash (9%). Twenty-two patients (5.7%) discontinued treatment due to AEs. There were no treatment-related deaths. The objective response rate was 23.1%. At a median follow-up of 12 months, the median progression-free survival was 4.5 months (95% CI: 3.7-6.2), the 12-month overall survival rate was 63%. Comparable survival rates were reported among patients with non-clear cell histology, elderly patients, bone and/or brain metastases, prior first-line sunitinib or pazopanib, prior everolimus. Conclusion: The safety and efficacy observed were consistent with those reported in the pivotal Checkmate 025 trial. Results in non-clear cell mRCC, elderly, pretreated with everolimus and bone and/or brain metastases encourage the use of nivolumab in these categories of patients. This article is protected by copyright. All rights reserved.
I.F.: 4,688
N. citazioni = 43

314. Mantovani S, Oliviero B, Lombardi A, Varchetta S, Mele D, Sangiovanni A, Rossi G, Donadon M, Torzilli G, Soldani C, **Porta C**, Pedrazzoli P, Chiellino S, Santambrogio R, Opocher E, Maestri M, Bernuzzi S, Rossello A, Clément S, De Vito C, Rubbia-Brandt L, Negro F, Mondelli MU. Deficient natural killer cell NKp30-mediated function and altered NCR3 splice variants in hepatocellular carcinoma. *Hepatology* 2019;69:1165-79.

ABSTRACT – The activating natural cytotoxicity receptor NKp30 is critical for natural killer (NK) cell function and tumor immune surveillance. The natural cytotoxicity receptor-3 (NCR3) gene is transcribed into several splice variants whose physiological relevance is still incompletely understood. In this study, we investigated the role of NKp30 and its major ligand B7 homolog 6 (B7-H6) in patients with hepatocellular carcinoma (HCC). Peripheral blood NK cell phenotype was skewed toward a defective/exhausted immune profile with decreased frequencies of cells expressing NKp30 and natural killer group 2 member d (NKG2D) and an increased proportion of cells expressing T-cell immunoglobulin and mucin-domain containing-3 (Tim-3). Moreover, NKp30-positive NK cells had a reduced expression of NCR3 immunostimulatory splice variants, and an increased expression of the inhibitory variant in patients with advanced tumor, resulting in deficient NKp30-mediated functionality. Tumor-infiltrating lymphocytes showed a prevalent inhibitory NKp30 isoform profile, consistent with decreased NKp30-mediated function. Of note, there were significant differences in the cytokine milieu between the neoplastic and the surrounding non-neoplastic tissue which may have further influenced NKp30 function. Exposure of NK cells to B7-H6 expressing HCC cells significantly down-modulated NKp30, that was prevented by siRNA-mediated knockdown, suggesting a role for this ligand in inhibiting NKp30-mediated responses. Interestingly, B7-H6 expression was reduced in HCC tissue and simultaneously augmented as a soluble form in HCC patients', particularly those with advanced staging or larger nodule size. Conclusions: These findings provide evidence in support of a role of NKp30 and its major ligand in HCC development and evolutions
I.F.: 14,079
N. citazioni = 29

315. Bracarda S, **Porta C**, Sabbatini R, Rivoltini L. Angiogenic and immunological pathways in metastatic renal cell carcinoma: A counteracting paradigm or two faces of the same medal? The GIANUS Review. *Crit Rev Oncol Hematol* 2019;139:149-57.

ABSTRACT – In the so-called "antiangiogenic era" of recent years, a number of targeted therapies have been approved for the treatment of metastatic renal cell carcinoma (mRCC). Emerging information about the immunological features of mRCC and the immunomodulating properties of antiangiogenic agents, one of the standard treatments for mRCC, indicates that a more rational design of potentially synergistic combinations should be pursued. Indeed, immunotherapy has undergone a resurgence in clinical practice. In this narrative review, we discuss the immunological features of mRCC and the potential interactions that antiangiogenic agents may also exert on host immunity and tumor immunogenicity, possibly working on both sides of this complex cross-talk. Hence, the recall to Gianus, the ancient two-faced Roman God who was looking both at the future and the past. Treatment strategies will be also critically discussed.
I.F.: 4,495
N. citazioni = 7

316. Calvo E, **Porta C**, Grünwald V, Escudier B. The Current and evolving landscape of first-line treatments for advanced Renal Cell Carcinoma. *Oncologist* 2019;24:338-48.

ABSTRACT – Agents targeting the vascular endothelial growth factor (VEGF) and its receptors (VEGFRs), as well as the mammalian target of rapamycin (mTOR) and immune checkpoint receptor programmed death 1 (PD-1) signaling pathway have improved clinical outcomes for patients with advanced renal cell carcinoma (RCC). The VEGFR tyrosine kinase inhibitors (TKIs) pazopanib and sunitinib are FDA-approved first-line treatment options for advanced RCC; however, other treatment options in this setting are available, including the recently approved combination of nivolumab (anti-PD-1) and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein-4 [CTLA-4]) for patients with intermediate or poor risk. Unfortunately, treatment guideline recommendations provide little guidance to aid first-line treatment choice. In addition, several ongoing randomized phase III trials of investigational first-line regimens may complicate the RCC treatment paradigm if these agents gain approval. This arti-

cle reviews clinical trial and real-world evidence for currently approved and investigational first-line treatment regimens for advanced RCC and provides clinical evidence to aid first-line treatment selection. Implication for practice: Vascular endothelial growth factor receptor tyrosine kinase inhibitors are approved by the U.S. Food and Drug Administration as first-line treatment options for advanced renal cell carcinoma; however, the treatment paradigm is rapidly evolving. The combination of nivolumab plus ipilimumab was recently approved for intermediate- and poor-risk patients, and other combination strategies and novel first-line agents will likely be introduced soon.

I.F.: 5,306

N. citazioni = 19

317. **Porta C**, Szczylik C, Casciano R, Fu S, Amzal B, Lister J, Karcher H, Meng J, Neumann M, Dinet J. Second-line cabozantinib versus nivolumab in advanced renal cell carcinoma: Systematic review and indirect treatment comparison. *Crit Rev Oncol Hematol* 2019;139:143-8.

ABSTRACT – Background: Nivolumab and cabozantinib, two new treatment options for previously-treated advanced/metastatic renal cell carcinoma (aRCC), have recently been approved. Methods: Two independent reviewers performed study selection, data extraction, and risk of bias assessment. Indirect treatment comparisons were carried out by directly assessing HR differences and statistical modeling of Kaplan-Meier curves from these two trials. Results: Publications identified showed that no head-to-head comparisons had been carried out. Two indirect treatment comparisons used agreed that there was no significant difference in OS between cabozantinib and nivolumab and that cabozantinib significantly improved PFS compared to nivolumab. Conclusions: The field of aRCC treatments is evolving rapidly, creating opportunities for individualized treatments and challenges for clinicians to keep up with the evidence. In lieu of availability of direct comparisons of all options, advanced modeling results presented herein can help to inform and improve personalized treatments.

I.F.: 4,495

N. citazioni = 8

318. Frascà GM, Brigante F, Volpe A, Cosmai L, Gallieni M, **Porta C**. Kidney transplantation in patients with previous renal cancer: a critical appraisal of current evidence and guidelines. *J Nephrol* 2019;32:57-64.

ABSTRACT – Due to the increasing occurrence of renal cell carcinoma (RCC) in the general population and the high prevalence of chronic kidney disease among cancer patients, many people with a previous RCC may eventually require renal replacement therapy including kidney transplantation. They should accordingly be evaluated to assess their life expectancy and the risk that the chronic immunosuppressive therapy needed after grafting might impair their long-term outcome. Current guidelines on listing patients for renal transplantation suggest that no delay is required for subjects with small or incidentally discovered RCC, while the recommendations for patients who have been treated for a symptomatic RCC or for those with large or invasive tumours are conflicting. The controversial results reported by even recent studies focusing on the cancer risk in kidney graft recipients with a prior history of malignancy do not help to clarify the doubts arising in everyday clinical practice. Several tools, including integrated scoring systems, are currently available to assess the prognosis of patients with a previous RCC and, although they have not been validated in subjects receiving long-term immunosuppressive drugs, they can be used to identify patients suitable to be listed for grafting. Among these, the Leibovich score is currently the most widely used as it has proved simple and reliable enough and helps categorize renal transplant candidates. According to this system, subjects with a score from 0 to 2 are at low risk and may be listed without delay, while those with a score of 6 or higher should be excluded from grafting. In addition, other factors have an established positive prognostic value, including chromophobe or clear cell papillary tumour, or G1 grade cancer; on the contrary, medullary or Bellini's duct carcinoma or those with sarcomatoid dedifferentiation at histological examination should be excluded. All other patients would be better submitted to careful individual evaluation by an Oncologist before being listed for renal transplantation, pending studies specifically focusing on cancer risk evaluation in people already treated for malignancy receiving long-term immunosuppressive therapy.

I.F.: 2,724

N. citazioni = 7

319. Maliszewska-Olejniczak K, Brodaczewska KK, Bielecka ZF, Solarek W, Kornakiewicz A, Szczylik C, **Porta C**, Czarnecka AM. Development of extracellular matrix supported 3D culture of renal cancer cells and renal cancer stem cells. *Cytotechnology* 2019;71:149-163.

ABSTRACT – Novel experimental conditions of cancer cell line culture have evolved throughout the recent years, with significantly growing interest in xeno-free, serum-free and three-dimensional culture variants. The choice of proper culture media may enable to mimic tumor microenvironment and promotion of cancer stem cells proliferation. To assess whether stem-like phenotype inducing media may be applied in renal cancer stem cell research, we performed a widespread screening of 13 cell culture media dedicated for mesenchymal cells, stem cells as well as mesenchymal stem cells. We have also screened extracellular matrix compounds and selected optimal RCC 3D-ECM supported culture model. Our results revealed that 786-O as well as HKCSCs cell line cultures in xeno-free media (NutriStem/StemXvivo) and laminin coated plates provide a useful tool in RCC cancer biology research and at the same time enable effective drug toxicity screening. We propose bio-mimic 3D RCC cell culture model with specific low-serum and xeno-free media that promote RCC cell viability and stem-like phenotype according to the tested genes encoding stemness factors including E-cadherin, N-cadherin, HIF1, HIF2, VEGF, SOX2, PAX2 and NESTIN.

I.F.: 1,461

N. citazioni = 12

320. Canino C, Perrone L, Bosco E, Saltalamacchia G, Mosca A, Rizzo M, **Porta C**. Targeting angiogenesis in metastatic renal cell carcinoma. *Expert Rev Anticancer Ther* 2019;19:245-57.

ABSTRACT – Renal cell carcinoma (RCC), and particularly its clear cell histological subtype, is commonly characterized by genetic alterations in the Von Hippel Lindau (VHL) tumor suppressor gene, leading to a typically exasperated angiogenesis. However, other biological and genetic peculiarities contribute to differentiate this malignancy from other solid tumors, including its immunogenicity. Areas covered: This review focuses on the present and future role of antiangiogenic drugs, administered either alone (as it has been in the past few years), or in combination with

other agents (e.g. immune checkpoint inhibitors), in the treatment of metastatic RCC. Expert commentary: Due to its peculiar pathogenesis, it is unrealistic to expect to be able to get rid of antiangiogenic agents for the treatment of this disease; however, we do expect that combinations of VEGF/VEGFRs-targeting agents with immune checkpoint inhibitors will gradually replace antiangiogenic monotherapies as the standard of care, at least in the first line setting of metastatic RCC patients. Biomarkers discovery remains the highest priority in order to further improve the percentage of patients benefitting of our treatment.
I.F.: 2,347
N. citazioni = 2

321. **Porta C**, Broglia C, Negri F. Medical treatment of advanced hepatocellular carcinoma patients: the issue is not the right drug, but the right patient. *Hepatology* 2019;70:429-30.

ABSTRACT – On July 5th , 2018, the final results of the CELESTIAL trial were published on the authoritative pages of the New England Journal of Medicine; in this placebo-controlled, phase III trial, previously treated patients with advanced hepatocellular carcinoma (HCC) were randomized in a 2 to 1 fashion to receive either the multikinase inhibitor Cabozantinib (targeting, among the others, Vascular Endothelial Growth Factor Receptors [VEGFRs], MET, and AXL), or placebo. The study succeeded in demonstrating a reduction in the risk of death of 24% in favor of Cabozantinib; indeed, median overall survival (OS) was 10.2 months with Cabozantinib and 8.0 months with placebo (Hazard Ratio [HR] = 0.76, 95% confidence interval [CI] = 0.63 to 0.92, p=0.005).
I.F.: 14,079
N. citazioni = 2

322. Grünwald V, Powles T, Choueiri TK, Hutson TE, **Porta C**, Eto M, Sternberg CN, Rha SY, He CS, Dutcus CE, Smith A, Dutta L, Mody K, Motzer RJ. Lenvatinib plus everolimus or pembrolizumab versus sunitinib in advanced renal cell carcinoma: study design and rationale. *Future Oncol* 2019;15:929-41.

ABSTRACT – Aim: Lenvatinib plus everolimus is approved for the treatment of advanced renal cell carcinoma (RCC) after one prior vascular endothelial growth factor-targeted therapy. Lenvatinib plus pembrolizumab demonstrated promising antitumor activity in a Phase I/II trial of RCC. Methods: We describe the rationale and design of the CLEAR study, a three-arm Phase III trial comparing lenvatinib plus everolimus and lenvatinib plus pembrolizumab versus sunitinib monotherapy for first-line treatment of RCC. Eligible patients must have advanced clear cell RCC and must not have received any prior systemic anticancer therapy. The primary end point is progression-free survival; secondary end points include objective response rate, overall survival, safety, health-related quality of life and pharmacokinetics. Biomarker evaluations are included as exploratory end points.
I.F.: 2,369
N. citazioni = 25

323. Escudier B, **Porta C**, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, Grünwald V, Gillessen S, Horwich A for the ESMO Guidelines Committee. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2019;30:706-20.
I.F.: 13,930
N. citazioni = 361

324. **Porta C**, Cosmai L, Leibovich BC, Powles T, Gallieni M, Bex A. The adjuvant treatment of kidney cancer: a multidisciplinary outlook. *Nat Rev Nephrol* 2019;15:423-33.

ABSTRACT – Approximately 70% of cases of kidney cancer are localized or locally advanced at diagnosis. Among patients who undergo surgery for these cancers, 30-35% will eventually develop potentially fatal metachronous distant metastases. Effective adjuvant treatments are urgently needed to reduce the risk of recurrence of kidney cancer and of dying of metastatic disease. To date, almost all of the tested adjuvant agents have failed to demonstrate any benefit. Only two trials of an autologous renal tumour cell vaccine and of the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor sunitinib have shown positive results, but these have been criticized for methodological reasons and conflicting data, respectively. The results of two additional trials of targeted agents as adjuvant therapies have not yet been published. Novel immune checkpoint inhibitors are promising approaches to adjuvant therapy in kidney cancer, and a number of trials are now underway. An important component of the management of patients with kidney cancer, particularly those who undergo radical resection for localized renal cell carcinoma, is the preservation of kidney function to reduce morbidity and mortality. The optimal management of these patients therefore requires a multidisciplinary approach involving nephrologists, oncologists, urologists and pathologists.
I.F.: 14,101
N. citazioni = 32

325. Iacovelli R, Galli L, De Giorgi U, **Porta C**, Nolè F, Zucali P, Sabbatini R, Mosca A, Atzori F, Santini D, Facchini G, Fornarini G, Buti S, Massari F, Masini C, Ricotta R, Biasco E, Lolli C, Gri N, Verri E, Miggiano C, Vitale MG, Tortora G. The effect of a treatment delay on outcome in metastatic renal cell carcinoma. The effect of a treatment delay on outcome in metastatic renal cell carcinoma. *Urol Oncol* 2019;37:529.e1-529.e7.

ABSTRACT – Objectives: To investigate if a first-line treatment delay (TD) can negatively affect the outcomes of patients affected by metastatic renal cancer. Patients and Methods: Patients with a diagnosis of metastatic renal cancer who were ineligible for active surveillance were included in the sample. A TD was defined as the time from the diagnosis of metastatic disease to the start of first-line therapy with tyrosine kinase inhibitors. Results: A total of 835 patients were assessed and 635 were included in the final analysis. The median TD was 6.3 weeks. No significant differences were found in baseline characteristics between patients experiencing a TD below/equal to or above the median value, with the exceptions being the rate of bone metastases (25.3% vs. 35.9%) and advanced disease at diagnosis (34.7% vs. 54.9%). In patients who had received a previous nephrectomy for localized disease, the TD was 5.3 compared to 8.0 weeks for those with metastatic disease at diagnosis (P = 0.001). Among this latter group, 68.7% had received a cytoreductive nephrectomy. In patients with a TD below/equal to and above the median value, the median progression-free survival was 10.3 and 11.2 months, respectively (hazard ratio = 1.03; 95% confidence intervals, 0.86-1.22; P

= 0.78); the median overall survival was 27.3 and 28.2 months, respectively (hazard ratio = 1.04; 95% confidence intervals, 0.86-1.27; P = 0.68). The lack of differences was confirmed when adjusted for prognostic factors and baseline characteristics. Conclusions: This study reports that patients with bone metastases and advanced disease at diagnosis have a significant probability of experiencing delayed first-line therapy of more than 6 weeks from the time of diagnosis. However, a TD does not significantly affect outcomes and survival.

I.F.: 3,397

N. citazioni = 4

326, Nunno VD, Mollica V, Gatto L, Santoni M, Cosmai L, **Porta C**, Massari F. Prognostic impact of neutrophil-to-lymphocyte ratio in renal cell carcinoma: a systematic review and meta-analysis. *Immunotherapy* 2019;11:631-43.

ABSTRACT – Aim: Estimate prognosis and clinical outcome of patients with localized or metastatic renal cell carcinoma (RCC) is an important issue which drive our medical decisions. Methods: We carried out a meta-analysis of available clinical studies exploring neutrophil-to-lymphocyte ratio (NLR) in RCC in order to evaluate if this ratio could be correlated to overall survival (OS) and progression-free survival (PFS) of patients with localized/metastatic RCC. Results: In overall population higher NLR resulted in worst OS and PFS (OS pooled hazard ratio of 1.80; 95% CI: 1.61-2.00; I2 45%; PFS pooled hazard ratio of 1.69; 95% CI: 1.42-2.01; I2 81%), this negative correlation was also confirmed in both metastatic and nonmetastatic patients. Conclusion: The NLR ratio is a variable correlated to prognosis in RCC patients.

I.F.: 3,461

N. citazioni = 16

327. Verzoni E, Cartenì G, Cortesi E, Giannarelli D, De Giglio A, Sabbatini R, Buti S, Rossetti S, Cognetti F, Rastelli F, Sobrero A, Turci D, Sternberg CN, **Porta C**, Cappuzzo F, Tortora G, Tassinari D, Panni S, Pazzola A, Surico G, Raimondi A, De Giorgi U, Procopio G, for the Italian Nivolumab Renal Cell Cancer Early Access Program group. Real-world efficacy and safety of nivolumab in previously-treated metastatic renal cell carcinoma, and association between immune-related adverse events and survival: the Italian expanded access program. *J Immunother Cancer* 2019;7:99.

ABSTRACT – Background: The Italian Renal Cell Cancer Early Access Program was an expanded access program that allowed access to nivolumab, for patients (pts) with metastatic renal cell carcinoma (mRCC) prior to regulatory approval. Methods: Pts with previously treated advanced or mRCC were eligible to receive nivolumab 3 mg/kg every 2 weeks. Pts included in the analysis had received ≥1 dose of nivolumab and were monitored for drug-related adverse events (drAEs) using CTCAE v.4.0. Immune-related (ir) AEs were defined as AEs displaying a certain, likely or possible correlation with immunotherapy (cutaneous, endocrine, hepatic, gastro-intestinal and pulmonary). The association between overall survival (OS) and irAEs was assessed, and associations between variables were evaluated with a logistic regression model. Results: A total of 389 pts were enrolled between July 2015 and April 2016. Overall, the objective response rate was 23.1%. At a median follow-up of 12 months, the median progression-free survival was 4.5 months (95% CI 3.7-6.2) and the 12-month overall survival rate was 63%. Any grade and grade 3-4 drAEs were reported in 124 (32%) and 27 (7%) of pts, respectively, and there were no treatment-related deaths. Any grade irAEs occurred in 76 (20%) of patients, 8% cutaneous, 4% endocrine, 2% hepatic, 5% gastrointestinal and 1% pulmonary. Of the 22 drAEs inducing treatment discontinuation, 10 (45%) were irAEs. Pts with drAEs had a significantly longer survival than those without drAEs (median OS 22.5 versus 16.4 months, p = 0.01). Pts with irAEs versus without irAEs had a more significant survival benefit (median OS not reached versus 16.8 months, p = 0.002), confirmed at the landmark analysis at 6 weeks. The occurrence of irAEs displayed a strong association with OS in univariable (HR 0.48, p = 0.003) and multivariable (HR 0.57, p = 0.02) analysis. Conclusions: The appearance of irAEs strongly correlates with survival benefit in a real-life population of mRCC pts treated with nivolumab.

I.F.: 10,252

N. citazioni = 77

328. **Porta C**, Rizzo M. Immune-based combination therapy for metastatic kidney cancer. *Nat Rev Nephrol* 2019;15:324-5.

On 16 February 2019, the results of two randomized controlled phase III trials of combinations of immune checkpoint inhibitors and antiangiogenic agents for the first-line treatment of metastatic renal cell carcinoma (mRCC) — the JAVELIN Renal 101 and KEYNOTE-426 trials — were published in the New England Journal of Medicine. The JAVELIN Renal 101 trial1 reported that combination therapy with the anti- programmed cell death 1 ligand 1 (PD- L1) monocolonal antibody avelumab plus axitinib was superior to sunitinib monotherapy for both the independent primary end points of progression-free survival (PFS) and overall survival (OS) among patients with PD- L1-positive tumours, as well as for the key secondary end points of PFS in the overall population (which included patients with PD-L1-negative tumours), objective response rate (ORR) irrespective of PD-L1 expression and safety. Among patients with PD-L1-positive tumours, median PFS was 13.8 months with the combination therapy compared with 7.2 months with sunitinib (HR 0.61, 95% CI 0.47–0.79; P < 0.001). In the overall population, the median PFS was 13.8 months and 8.4 months, respectively (HR 0.69, 95% CI 0.56–0.84; P < 0.001). The KEYNOTE-426 trial compared a combination of the anti-programmed cell death 1 (PD-1) monocolonal antibody pembrolizumab with axitinib versus sunitinib monotherapy. Both the primary end points (OS and PFS in the intention- to-treat population),

as well as the key secondary end point of ORR, significantly favoured the combination therapy. After a median followup of 12.8 months, the estimated patient survival at 12 months was 89.9% in the combination therapy group and 78.3% in the sunitinib group (HR 0.53, 95% CI 0.38–0.74; P < 0.0001). Furthermore, median PFS was 15.1 months in the combination therapy group and 11.1 months in the sunitinib group (HR 0.69, 95% CI 0.57–0.84; P < 0.001). These two studies provide evidence in favour of the use of immune- based combinations as potential novel standards of care in the first- line treatment of mRCC. The CheckMate 214 trial3 already demonstrated a significant OS benefit in favour of the combination of the anti- PD1 agent nivolumab with the anti-cytotoxic T lymphocyte antigen 4 (CTLA4) monoclonal antibody ipilimumab compared with sunitinib for the first- line treatment of mRCC in patients from International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate or poor risk groups (that is, the primary efficacy population). At a median follow- up of 25.2 months, the 18-month OS was 75% (95% CI 70–78) with nivolumab plus ipilimumab versus 60% (95% CI 55–65) with sunitinib. Median OS was not reached with the combination therapy but was 26 months with sunitinib (HR 0.63; P < 0.001). At a

minimum follow-up of 30 months, the hazard ratio for OS with the immune combination versus sunitinib in patients with favourable risk improved in comparison to the hazard ratio obtained in the initial efficacy analysis at a minimum follow- up of 17.5 months (1.22 (95% CI 0.73–2.04) versus 1.45 (99.8% CI 0.51–4.12)). Given the above results, a key emerging question is how to choose between the three combination therapies, each of which proved to be superior to the standard of care. Attempting to make direct comparisons between these studies should be avoided because they differ substantially in terms of patient populations, distribution of patients between prognostic groups and end points. Thus, most importantly, we should look at the shape of the survival curves. The late Professor Pieter De Mulder used to say that oncology is "a matter of tails", highlighting the relevance of the tails of survival curves from randomized controlled trials. This approach was a smart suggestion at the time but has become a 'must do' in the present era of immune checkpoint inhibitors, when relatively few patients may achieve huge survival benefits, which are more adequately reflected by landmark analyses than by median survival times or even hazard ratios. Looking at the tails of the survival curves from these three studies, however, is not particularly useful given the different median follow- up periods. Despite this limitation, the tail of the ipilimumab plus nivolumab curve is truly impressive, similar to that observed in patients with melanoma. More interesting hypotheses can be drawn by taking a look at the heads of the survival curves. In CheckMate 214, PFS curves start separating at about 6 months3, whereas in the KEYNOTE-426 trial, curve separation seems to begin just before 3 months of follow- up. Comparisons cannot be made with the head of the survival curves in JAVELIN Renal 101 because the per protocol timing of first disease assessment in this study was different from that of the other trials. The difference in the shapes of the survival curves in CheckMate 214 and KEYNOTE-426 could be related to the different mechanisms of action of the two immune- based combinations. Overall, it is reasonable to assume that the late (tail) benefit observed with ipilimumab plus nivolumab in Checkmate 214 could be mainly due to the four induction doses of ipilimumab, reflecting the time required for activation and expansion of the effector cells of the immune response, whereas the early PFS benefit observed with pembrolizumab plus axitinib in KEYNOTE-426 could be due to the more rapid antiangiogenic effects of axitinib. A late effect of early ipilimumab administration is supported by a number of immunological studies. The blockade of different checkpoints leads to distinct immunological effects in physically distinct structures (that is, lymphnodes versus the tumour microenvironment). In particular, CTLA4 blockade predominantly induces a proliferative signature in a subset of memory T cells, whereas PD1 blockade leads to changes in genes implicated in cytolysis and natural killer cell function. Furthermore, the frequencies of CD8 effector memory T cells at the end of ipilimumab treatment positively correlated with survival in patients with melanoma7. Given these findings, other key questions arise. Should reinduction doses of ipilimumab during nivolumab maintenance be considered in the case of disease progression, especially in the absence of a massive increase in tumour bulk? In addition, should the use of an antiangiogenic agent such as axitinib for a limited period of time be considered at the beginning of treatment with either pembrolizumab or avelumab, particularly in patients with highly aggressive tumours? Further studies are required to address these questions. Another consideration is the percentage of patients who achieve complete responses with the three combination therapies. Although not yet proven, complete responses might select a small number of potentially cured patients, as has been suggested for high-dose treatment of both melanoma and mRCC with IL-2. In this regard, ipilimumab plus nivolumab seems to outperform the other two combination therapies. Indeed, the rates of complete responses increased from 9% at a median follow- up of 25.2 months to 11% at a median follow- up of 30 months4, indicating that late complete responses can be achieved with this combination. Overall, the only possible, though highly empirical, driver of therapeutic choice for individual patients is the biological aggressiveness of the tumour. In the case of very aggressive disease, the use of an immune checkpoint inhibitor plus antiangiogenic agent (vascular endothelial growth factor–tyrosine kinase inhibitor (VEGFR–TKI)) could be a reasonable choice to try to control disease growth while waiting for the later effects of immunotherapy. On the contrary, in patients with less aggressive disease, one could rely on the ipilimumab plus nivolumab immune combination with the aim of achieving a long- term benefit (including a potential late complete response) and avoiding the additional toxicity derived from the use of a VEGFR–TKI. Additional studies are urgently needed to assess these strategies and answer the remaining questions highlighted above. Physicians and academic researchers must continue to ask such questions and push pharmaceutical companies to design and conduct smart studies with the aim of obtaining the answers.

I.F.: 12,146

N. citazioni = 2

329. **Porta C**, Cosmai L, Rizzo M, Melazzini M. Single nucleotide polymorphisms in angiogenesis-related genes and outcomes from antiangiogenic therapies in renal cell carcinoma: really a step towards personalized oncology, or not at all? *Ann Transl Med* 2019;7(Suppl. 1):S15.

By definition, single nucleotide polymorphisms (SNPs) are loci with alleles that differ at a single base level, with the rarer allele having a frequency of at least 1% in a random set of individuals within a given population. Although the majority of these variations are silent, not altering any cellular function, some SNPs have been proved to contribute to the development of different diseases, including cancer, and to influence physiological responses to drugs, including anticancer agents. Identifying which variations are involved in altering responses to anticancer agents could facilitate the development of a really personalized (or precise) approach to cancer patients; a genetic screening for specific SNPs in a person's genome could indeed be theoretically used to select drugs most appropriate for that individual, amplifying the likelihood of achieving a significant benefit, and reducing the risk of unwanted adverse events (AEs). Recently, an exploratory analysis evaluated the association between SNPs evidenced in several angiogenesisor hypoxia-related genes, and the clinical outcomes of patients radically resected for a localized or locallyadvanced renal cell carcinoma (RCC) who were treated with the anti-VEGFRs tyrosine kinase inhibitor (TKI) sunitinib within the already reported randomized, placebocontrolled, adjuvant phase III S-TRAC trial. In this study, correlations between SNPs in VEGFR1, VEGFR2, and eNOS genes and improved disease-free survival (DFS) in the sunitinib group compared with the placebo group were evidenced. Furthermore, SNPs in VEGFR1, VEGFR2, and CCDC26 showed a potential trend toward prognostic value for either DFS or overall survival (OS) across the two treatment arms. How this paper fills into available evidence? Over the past 8 years, a number of different studies have addressed the potential effect on SNPs on different outcomes, including survival (either progression free survival—PFS, or OS), incidence of AEs, and dose reductions, in metastatic RCC (mRCC) patients treated with TKIs (though mainly sunitinib), overall yielding conflicting results, at best. For example, a large study conducted in Sunitinib-treated mRCC patients, showed that most of the selected SNPs in angiogenesis-related genes were not associated with either survival or AEs (4), differently from what observed in other previous reports; only the VEGFR1 rs9582036 SNP showed a statistically significant association with OS. Notably enough, the same VEGFR1 rs9582036 SNP proved to be related to a shorter DFS with sunitinib within the S-TRAC trial. As a whole, the inconclusiveness of

SNPs research in RCC was highlighted in a 2015 News and Views paper published on Nature Reviews Urology by Beuselinck and Zucman-Rossi, who asked themselves if the time for this kind of research was up. Indeed, commenting a large study in which previously observed associations between 22 SNPs in 10 genes and treatment outcome were investigated in 333 Sunitinib-treated mRCC patients, the Authors clearly evidenced that the vast majority of previously described associations were eventually not considered as validated. However, the same Authors correctly noticed that plasma levels and efficacy or toxicity of TKIs are not entirely dependent on polymorphisms in genes involved in pharmacokinetics and pharmacodynamics, and thus claimed for further studies aimed at studying the influence of SNPs in mRCC (as well as other tumor types) treated with targeted agents. Has something changed since the above News and Views paper? Is this research area really a potential step towards a personalized approach to cancer treatment? And finally, is this area still worth pursuing? Let's start from the latter question. The individual response to TKIs like sunitinib is highly variable; indeed, despite being treated with fixed doses of these agents—irrespective of parameters such as sex, age, and body surface area, a choice which, based on availabledata, could be considered not such a smart strategy—some patients experience severe toxicity needing dose reductions, treatment interruptions or even the permanent discontinuation of treatment, whereas others show neither efficacy, nor toxicity. Thus, the identification of specific SNPs in a patient's genome prior to the start of treatment (or even during its course) could help provide him/her with the most effective and the lowest toxic treatment, a condivisible but hypothetical statement which seems to confirm the need to further pursue the research in this field. However, the level of inconclusiveness evidenced by Beuselinck and Zucman-Rossi has not been improved in the past years; indeed, it is not a case that almost all published studies end with sentences such as "… validation studies are needed …", clearly leading to the conclusion—among the others—that SNPs research is presently not a right way towards personalized or precision Medicine. Why this inconclusiveness? In a recent paper by Ritchie and Van Steen, the Authors highlighted the fact that, as our technology improves, challenges in identifying clinically relevant genetic interactions also increase. The Authors summarized these challenges into three categories: abundance of methods, practical considerations, and biological interpretation. The abundance of methods challenge refers not only to the present issue of which is the best suitable technology for conducting these studies, but also to the issue of the ideal material to study (e.g., formalin-fixed, paraffin-embedded tissue), as well as of the most appropriate statistical analysis needed to organize and interpret them; furthermore, from a very practical viewpoint a huge computational complexity arises when previous studies investigating small genomic regions have been replaced by studies covering the whole genome. Indeed, as highlighted by Ritchie and Van Steen "… the number of combinations of interacting SNPs is reasonable when studies evaluated 100 SNPs from candidate genes. But now that GWAS (genomewide association studies) assays include 1 million SNPs or more, the number of combinations to test has exploded …", with all the expected consequences. Finally, correction for confounding factors and covariates is still an unmet need, as it is the common lack of replication and validation datasets to confirm the results of a previous study. Going back to the RCC field, the above complexity, ultimately hampering our ability to draw conclusions from SNPs studies which could be useful in everyday clinical practice, is well evidenced by a recent paper investigating a model which integrates pharmacokinetics, pharmacodynamics, pharmacogenetics, and clinical outcome in patients with mRCC (and metastatic colo-rectal cancer) treated with sunitinib. Given the above premises, it is not strange—but still remains frustrating—that in mRCC patients only baseline soluble vascular endothelial growth factor receptor (VEGFR)-2 levels (and no other, more sophisticated, parameters) proved to be associated with clinical outcome. As a whole, what is quite clear, in our opinion, is that SNPs have only few of the characteristics of the so-calledì "ideal" biomarker, and definitely not the most important ones. How does it fit into the landscape of the presently highly mentioned personalized/precision medicine? Well, it is our (of course debatable) opinion that although a precision Medicine approach represents for sure the near future—also in the field of Oncology, we still need to undoubtedly demonstrate that a personalized/precision medicine approach could lead to a substantial improvement in some really relevant outcomes. This is also the case for SNPs research in RCC. Should we thus desist to persist to use SNPs? Probably not, but we do badly need to change the way we conduct this kind of researches; we do not longer need small, single-centre studies; a coordinated international effort is warranted in order to standardize methodology (as well as statistical analysis), design adequately powered studies (possibly prospective), analyze resulting data, replicate and validate them, and finally design clinical trials aimed at demonstrating the possibility of improving certain outcomes (of efficacy and/or of tolerability) basing on the use of these biomarkers. What will remain of these researches in the future, is presently not known: either just some publications retrievable on the PubMed site, or a prognostic/predictive tool really able to change everyday management of RCC patients. Presently, the first option seems more likely …

I.F.: n.r.

330. Quaquarini E, D'Ambrosio D, Sottotetti F, Gallivanone F, Hodolic M, Baiardi P, Palumbo R, Vellani C, Canevari C, Bernardo A, Castiglioni I, **Porta C**, Trifirò G. Prognostic value of 18F-Fluorocholine PET parameters in metastatic castrate-resistant prostate cancer patients treated with Docetaxel. *Contrast Media Mol Imaging* 2019;2019:4325946.

ABSTRACT – Background and aim: The availability of new treatments for metastatic castrate-resistant prostate cancer (mCRPC) patients increases the need for reliable biomarkers to help clinicians to choose the better sequence strategy. The aim of the present retrospective and observational work is to investigate the prognostic value of 18F-fluorocholine (18F-FCH) positron emission tomography (PET) parameters in mCRPC. Material and Methods: Between March 2013 and August 2016, 29 patients with mCRPC were included. They all received three-weekly docetaxel after androgen deprivation therapy, and they underwent 18F-FCH PET/computed tomography (CT) before and after the therapy. Semi-quantitative indices such as maximum standardized uptake value (SUVmax), mean standardized uptake value (SUVmean) with partial volume effect (PVC-SUV) correction, metabolically active tumour volume (MATV), and total lesion activity (TLA) with partial volume effect (PVC-TLA) correction were measured both in pre-treatment and post-treatment 18F-FCH PET/CT scans for each lesion. Whole-body indices were calculated as sum of values measured for each lesion (SSUVmax, SPVC-SUV, SMATV, and STLA). Progression-free survival (PFS) and overall survival (OS) were considered as clinical endpoints. Univariate and multivariate hazard ratios for whole-body 18F-FCH PET indices were performed, and $p < 0.05$ was considered as significant. Results: Cox regression analysis showed a statistically significant correlation between PFS, SMATV, and STLA. No correlations between OS and 18F-FCH PET parameters were defined probably due to the small sample size. Conclusions: Semi-quantitative indices such as SMATV and STLA at baseline have a prognostic role in patients treated with docetaxel for mCRPC, suggesting a potential role of 18F-FCH PET/CT imaging in clinical decision-making.

I.F.: 2,934

N. citazioni = 2

331. Del Re M, Crucitta S, Sbrana A, Rofi E, Paolieri F, Gianfilippo G, Galli L, Falcone A, Morganti R, **Porta C**, Efstathiou E, van Schaik R, Jenster G, Danesi R. Androgen receptor (AR) splice variant 7 and full-lenght AR expression is associated with clinical outcome: a translational study in patients with castrate resistant prostate cancer. *BJU Int* 2019;124:693-700.

ABSTRACT – Objectives: To investigate if full-length androgen receptor (AR-FL) is associated with resistance to AR-directed therapy independently and/or combined with AR splice variant 7 (AR-V7). Patients and Methods: Plasma samples were prospectively collected from 73 patients with CRPC before first or second-line AR-directed therapy. mRNA was isolated from exosomes and AR-FL and AR-V7 were analyzed by ddPCR. Results: AR-FL was detected in all patients while 22% were AR-V7+ at baseline. AR-FL expression was significantly higher in AR-V7+ vs AR-V7- patients (p<0.0001). Stratifying patients by tertiles for AR-FL expression, PFS was 22 vs 18 vs 4 months for lower vs intermediate vs higher tertile, respectively (p=0.0003). Median PFS and OS were significantly longer in AR-V7- vs AR-V7+ patients (20 vs 4 months, p<0.0001; not reached vs 9 months, p<0.0001, respectively). Conclusions: Resistance to AR-directed therapy is associated with the presence of AR-V7; however, AR-FL expression may help better refine response and survival of patients to AR-directed therapy. Both biomarkers, if validated in prospective trials, may be used to select the best treatment strategy.
I.F.: 4,688
N. citazioni = 18

332. Rini BI, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, Bracarda S, Stadler WM, Donskov F, Lee JL, Hawkins R, Ravaud A, Alekseev B, Staehler M, Uemura M, De Giorgi U, Mellado B, **Porta C**, Melichar B, Gurney H, Bedke J, Choueiri TK, Parnis F, Khaznadar T, Thobhani A, Li S, Piault-Louis E, Frantz G, Huseni M, Schiff C, Green MC, Motzer RJ, for the IMmotion151 Study Group. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet* 2019;393:2404-15.

ABSTRACT – Background: A phase 2 trial showed improved progression-free survival for atezolizumab plus bevacizumab versus sunitinib in patients with metastatic renal cell carcinoma who express programmed death-ligand 1 (PD-L1). Here, we report results of IMmotion151, a phase 3 trial comparing atezolizumab plus bevacizumab versus sunitinib in first-line metastatic renal cell carcinoma. Methods: In this multicentre, open-label, phase 3, randomised controlled trial, patients with a component of clear cell or sarcomatoid histology and who were previously untreated, were recruited from 152 academic medical centres and community oncology practices in 21 countries, mainly in Europe, North America, and the Asia-Pacific region, and were randomly assigned 1:1 to either atezolizumab 1200 mg plus bevacizumab 15 mg/kg intravenously once every 3 weeks or sunitinib 50 mg orally once daily for 4 weeks on, 2 weeks off. A permuted-block randomisation (block size of 4) was applied to obtain a balanced assignment to each treatment group with respect to the stratification factors. Study investigators and participants were not masked to treatment allocation. Patients, investigators, independent radiology committee members, and the sponsor were masked to PD-L1 expression status. Co-primary endpoints were investigator-assessed progression-free survival in the PD-L1 positive population and overall survival in the intention-to-treat (ITT) population. This trial is registered with ClinicalTrials.gov, number NCT02420821. Findings: Of 915 patients enrolled between May 20, 2015, and Oct 12, 2016, 454 were randomly assigned to the atezolizumab plus bevacizumab group and 461 to the sunitinib group. 362 (40%) of 915 patients had PD-L1 positive disease. Median follow-up was 15 months at the primary progression-free survival analysis and 24 months at the overall survival interim analysis. In the PD-L1 positive population, the median progression-free survival was 11·2 months in the atezolizumab plus bevacizumab group versus 7·7 months in the sunitinib group (hazard ratio [HR] 0·74 [95% CI 0·57-0·96]; p=0·0217). In the ITT population, median overall survival had an HR of 0·93 (0·76-1·14) and the results did not cross the significance boundary at the interim analysis. 182 (40%) of 451 patients in the atezolizumab plus bevacizumab group and 240 (54%) of 446 patients in the sunitinib group had treatment-related grade 3-4 adverse events: 24 (5%) in the atezolizumab plus bevacizumab group and 37 (8%) in the sunitinib group had treatment-related all-grade adverse events, which led to treatment-regimen discontinuation. Interpretation: Atezolizumab plus bevacizumab prolonged progression-free survival versus sunitinib in patients with metastatic renal cell carcinoma and showed a favourable safety profile. Longer-term follow-up is necessary to establish whether a survival benefit will emerge. These study results support atezolizumab plus bevacizumab as a first-line treatment option for selected patients with advanced renal cell carcinoma.
I.F.: 53,254
N. citazioni = 462

333. Silvestris N, Argentiero A, Cosmai L, **Porta C**, Gesualdo L, Brunori G, Brunetti O, Rampino T, Secondino S, Rizzo G, Pedrazzoli P. Management of targeted therapies in cancer patients with chronic kidney disease, or on haemodialysis: An Associazione Italiana di Oncologia Medica (AIOM)/Societa' Italiana di Nefrologia (SIN) multidisciplinary consensus position paper. *Crit Rev Oncol Hematol* 2019;140:39-51.

ABSTRACT – The increasing availability of novel biological anticancer agents has greatly improved the outcome of several cancer patients; unfortunately, data regarding efficacy, safety and pharmacokinetics of many of these agents in patients with chronic renal disease or on hemodialysis are scanty. Furthermore these results are controversial and a treatment strategy has not yet been established. Therefore, the Associazione Italiana di Oncologia Medica and the Società italiana di Nefrologia undertook the present work aiming at providing health professionals with a tool for easier clinical management of target therapies in this setting of patients. A web-based search of MEDLINE/PubMed library data published from 2000 to June 2018 has been performed. More than one hundred papers, including recommendations and expert opinions, were selected and discussed by the authors. A panel of experts provided additional biological and clinical information, helping in clarifying some issues in the absence of clear-cut information from the literature.
I.F.: 4,495
N. citazioni = 5

334. Nesiu A, Cimpean AM, Ceausu RA, Adile A, Ioiart I,

Porta C, Mazzanti M, Camerota TC, Raica M. Intracellular Chloride ion channel protein-1 expression in clear cell renal cell carcinoma. *Cancer Genomics Proteomics* 2019;16:299-307.

ABSTRACT – Background/Aim: Chloride intracellular channel 1 (CLIC1) represents a promising target for personalized therapy. Our aim was to assess CLIC1 expression in clear cell renal cell carcinoma (cc RCC) and identify its possible prognostic role. Materials and methods: Fifty cases of cc RCC were evaluated and selected for immunohistochemistry. CLIC1 expression was correlated with tumor grade, invasion and heterogeneity. Results: A total of 87.5% of the cases were CLIC1 positive, with either a homogeneous (31.42%) or a heterogeneous (68.57%) pattern. Low, mild and strong CLIC1 expressing tumors were defined based on nuclear (N), cytoplasmic (C), membrane (M) or combinations of them (NC, NM, CM, NCM) in terms of CLIC1 distribution. A significant correlation was found between tumor grade and percent of positive tumor cells (p=0.017). For G3 tumors, CLIC1 cytoplasmic expression was strongly correlated with high expression status (p=0.025) and tumor heterogeneity (p=0.004). CLIC1 expression was also correlated with metastasis (p=0.046). Conclusion: We defined four cc RCC groups depending on G, CLIC1 expression and pattern: i) G3/NM/low CLIC1+, ii) G2/CM/mild CLIC1+ iii) G1 or G2/NM or CM /high CLIC1+, and iv) G2/M /high CLIC1.
I.F.: 2,432
N. citazioni = 9

335. Vitale MG, Bracarda S, Cosmai L, Crocetti E, Di Lorenzo G, Lapini A, Mandressi A, Martorana G, Masini C, Montironi R, Ortega C, Passalacqua R, **Porta C**, Procopio G, Sepe P, Romano L, Luigi Pappagallo G, Conti G, Guida M, Martignoni G, Nolè F, Pignata S, Gori S, Cartenì G. Management of kidney cancer patients: 2018 guidelines of the Italian Medical Oncology Association (AIOM). *Tumori* 2019;105(Suppl. 4):3-12.

ABSTRACT – In the past two decades, the treatment landscape for patients with metastatic renal cell carcinoma has significantly changed thanks to the approval of several targeted molecular therapies (VEGF and mTOR inhibitors) and recently immune-checkpoint inhibitors. The Italian Association of Medical Oncology (AIOM) Renal Cell Cancer (RCC) Guidelines Panel has developed clinical guidelines to provide evidence-based information and recommendations to oncologists, urologists and all professionals involved in the management of patients with renal cell cancer.
I.F.: 1,234
N. citazioni = 6

336. Vitale MG, Baldessari C, Milella M, Buti S, Militello AM, Di Girolamo S, Fornarini G, Perri G, Basso U, Maruzzo M, **Porta C**, Cosmai L, Pipitone S, Cerma K, Cascinu S, Sabbatini R. Immunotherapy in dialysis-dependent cancer patients: our experience in patients with metastatic renal cell carcinoma and a review of the Literature. *Clin Genitourin Cancer* 2019;17:e903-8.

ABSTRACT – In the past few years, several new drugs such as targeted therapy and immunotherapy have shown activity for the treatment of metastatic renal cell carcinoma (mRCC). Literature data are very limited in some subgroups of patients such as those with end-stage renal disease who require hemodialysis and were excluded from pivotal clinical trials. We retrospectively reviewed the medical records of 8 hemodialysis-dependent patients with mRCC who were treated with nivolumab to evaluate the treatment-related toxicities and the clinical outcomes. Among these 8 patients, the objective response rate was 12.5%, and the disease control rate was 75%. The estimated median progression-free survival was 16 months and median overall survival was 26 months. There were no Grade 4 adverse events and only 2 patients had Grade 3 adverse events. Despite that the retrospective nature of this survey and the relatively small sample size represent major limitations, these data indicate that treatment with nivolumab is feasible with no unexpected toxicity and good efficacy in this cohort of patients. These results merit further confirmation in a larger prospective trial.
I.F.: 2,450
N. citazioni = 11

337. Massari F, Di Nunno V, Santoni M, Gatto L, Caserta C, Morelli F, Zafarana E, Carrozza F, Mosca A, Mollica V, Iacovelli R, Sabbatini R, **Porta C**, Bracarda S. Toward a genome-based treatment landscape for renal cell carcinoma. *Crit Rev Oncol Hematol* 2019;142:141-52.

ABSTRACT – Knowledge about molecular mechanisms driving development and progression of renal cell carcinoma has been elucidated by different studies. In few years we discovered a large difference between genomic landscapes of clear cell and non-clear cell carcinoma. Moreover, tumor heterogeneity and different acquisition of gene mutations during tumor progression are issues of particular interest. In this review we focalized our attention on principal genomic alterations identified among RCC subtypes. Acquired gene mutations may be an adaptive response to several external pressure including metabolic, treatment, genomic and immune-related external pressure. Thus we correlated and discussed principal genomic alterations adopted by tumor to escape from each external pressures. The aim of the present work is to summarize current knowledge about genomic alterations in RCC with special interest of treatment strategies tailored on the basis of disease mutations assessment.
I.F.: 5,012
N. citazioni = 12

338. Massari F, Di Nunno V, Santoni M, Gatto L, Mollica V, **Porta C**. Re: Bimal Bhindi, E. Jason Abel, Laurence Albiges, et al. Systematic review of the role of cytoreductive nephrectomy in the targeted therapy era and beyond: an individualized approach to metastatic renal cell carcinoma. Eur Urol 2019;75:111-28: Cytoreductive nephrectomy in the targeted therapy era: this is not the end. *Eur Urol Oncol* 2019;2:603-4.

ABSTRACT – Bhindi et al. recently carried out a systematic review of the role of cytoreductive nephrectomy (CN) in the targeted therapy era. Among ten studies examined, CN resulted in better survival (hazard ratio [HR] range 0.39–0.68) in both clear cell carcinoma (HR 0.36–0.64) and non-clear cell carcinoma (HR 0.38–0. 61). Notably, the authors also found that the risk of perioperative mortality and complications did not significantly differ between immediate CN and deferred (after systemic

treatment) CN, and that good performance status and good or intermediate International Metastatic renal cell carcinoma Database Consortium (IMDC)/Memorial Sloan Kettering Cancer Center (MSKCC) risk classification were predictive of better survival after CN. We fully agree with the authors' conclusions that CN may still have a role in selected patients with low tumor burden and stable or responding disease after systemic treatment. We recently published results obtained in a systematic review and meta-analysis investigating the impact of CN in patients with metastatic renal cell carcinoma (RCC, overall population) and in specific subgroups of patients with non-clear cell RCC (nccRCC), clear cell RCC (ccRCC), papillary RCC (pRCC), poor performance status, poor IMDC/MSKCC risk, and brain metastases. Similar to the results of the present study, we identified a significant survival benefit in the overall population as well as in patients with nccRCC and pRCC, while the same benefit did not emerge in the other subgroups. Taken together, these results suggest that CN may have a role in patients with metastatic RCC and that there are several issues that still remain unclear. As reported by Bhindi et al., two studies have revised the value of CN. CARMENA is the first noninferiority randomized trial to explore this issue and provides the highest level of evidence. However, it should be noted that several factors could have influenced the final results, including 1) the long accrual time; 2) the high percentage of patients receiving nephrectomy in the sunitinib-alone group and the non-negligible number of patients who did not receive sunitinib after CN; 3) the possible high number of patients with sites of metastases, known to be associated with worse prognosis; and 4) the high number of patients with poor risk (higher than the proportion usually observed in clinical practice). Furthermore, adoption of the MSKCC criteria in this trial excluded the accrual of patients with good risk. Thus, it may be possible to identify patients who would benefit more from CN. Of course, as suggested by the authors, patients with a low metastatic burden and stable disease or a response after systemic treatment are more likely to benefit from CN. However, we think that the site of metastasis may also play a role, as it is possible that some metastatic sites such liver, brain, and bone or peritoneal metastases could be associated with worse prognosis compared to others. In our study, we failed to collect sufficient data to explore this specific outcome; nonetheless we founded no significant benefit of CN for patients with brain metastases. Moreover, this approach has not been fully investigated in patients with nccRCC and we know that these tumors strongly differ from ccRCC in terms of genomic assessment and clinical outcomes. In conclusion, we think that CN still has a role in patients with metastatic RCC. Clinical and perhaps genomic prognostic factors are strongly needed to help clinicians to identify patients more likely to benefit from this approach.
I.F.: n.r.

339. Graham J, Wells JC, Donskov F, Lee JL, Fraccon A, Pasini F, **Porta C**, Bowman IA, Bjarnason GA, Ernst DS, Rha SY, Beuselinck B, Hansen A, North SA, Kollmannsberger CK, Wood LA, Vaishampayan UN, Pal SK, Choueiri TK, Heng DYC. Cytoreductive nephrectomy in metastatic papillary renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol Oncol* 2019;2:643-8.

ABSTRACT – Background: There is evidence that cytoreductive nephrectomy (CN) may be beneficial in metastatic renal cell carcinoma (mRCC). This has been studied predominantly in clear-cell RCC, with more limited data on the role of CN in patients with papillary histology. Objective: To determine the benefit of CN in synchronous metastatic papillary RCC. Design, setting and participants: Using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) database, a retrospective analysis was performed for patients with papillary mRCC treated with or without CN. Outcome measurements and statistical analysis: Median overall survival (OS) and progression-free survival (PFS) were determined for both patient groups. Cox regression analysis was performed to control for imbalances in individual IMDC risk factors. Results and limitations: In total, 647 patients with papillary mRCC were identified, of whom 353 had synchronous metastatic disease. Of these, 109 patients were treated with CN and 244 were not. The median follow-up was 57.1mo (95% confidence interval [CI] 32.9-77.8) and the OS from the start of first-line targeted therapy for the entire cohort was 13.2mo (95% CI 12.0-16.1). Median OS for patients with CN was 16.3mo, compared to 8.6mo (p<0.0001) in the no-CN group. When adjusted for individual IMDC risk factors, the hazard ratio (HR) of death for CN was 0.62 (95% CI 0.45-0.85; p=0.0031). Limitations include the retrospective nature of the analysis. Conclusions: The use of CN in patients with mRCC and papillary histology appears to be associated with better survival compared to no CN after adjustment for risk criteria. Selection of appropriate candidates for CN is crucial. A clinical trial in this rare population may not be possible. Patient summary: In a population of patients with advanced papillary kidney cancer, we found that surgical removal of the primary kidney tumor was associated with better overall survival.
I.F.: n.r.
N. citazioni = 14

340. Del Re M, Crucitta S, Gianfilippo G, Passaro A, Petrini I, Restante G, Michelucci A, Fogli S, de Marinis F, **Porta C**, Chella A, Danesi R. Understanding the mechanisms of resistance in EGFR-positive NSCLC: from tissue to liquid biopsy to guide treatment strategy. *Int J Mol Sci* 2019;20:3951.

ABSTRACT – Liquid biopsy has emerged as an alternative source of nucleic acids for the management of Epidermal Growth Factor Receptor (EGFR)-mutant non-Small Cell Lung Cancer (NSCLC). The use of circulating cell-free DNA (cfDNA) has been recently introduced in clinical practice, resulting in the improvement of the identification of druggable EGFR mutations for the diagnosis and monitoring of response to targeted therapy. EGFR-dependent (T790M and C797S mutations) and independent (Mesenchymal Epithelial Transition [MET] gene amplification, Kirsten Rat Sarcoma [KRAS], Phosphatidyl-Inositol 4,5-bisphosphate 3-Kinase Catalytic subunit Alpha isoform [PI3KCA], and RAF murine sarcoma viral oncogene homolog B1 [BRAF] gene mutations) mechanisms of resistance to EGFR tyrosine kinase inhibitors (TKIs) have been evaluated in plasma samples from NSCLC patients using highly sensitive methods (i.e., digital droplet PCR, Next Generation Sequencing), allowing for the switch to other therapies. Therefore, liquid biopsy is a non-invasive method able to detect the molecular dynamic changes that occur under the pressure of treatment, and to capture tumor heterogeneity more efficiently than is allowed by tissue biopsy. This review addresses how liquid biopsy may be used to guide the choice of treatment strategy in EGFR-mutant NSCLC.
I.F.: 4.183
N. citazioni = 32

341. **Porta C**, Schmidinger M. Renal cell carcinoma treatment after first-line combinations. *Lancet Oncol* 2019;20:1332-4.

Treatment of metastatic renal cell carcinoma has dramatically changed in the past two decades, moving from cytokine-based immunotherapy, to vascular endothelial growth factor (VEGF) pathway inhibitors, and to

combinations of these inhibitors with novel immune checkpoint inhibitors. What was once defined as an "embarassment of riches" has now reached new, unexpected heights. Improvements in overall survival have been mainly achieved by means of sequential treatment, rather than by a single treatment. However, in the past 2 years, two first-line combinations have been approved on the basis of their superior overall survival compared with sunitinib (ipilimumab plus nivolumab and axitinib plus pembrolizumab). Nonetheless, efficacious strategies for subsequent treatment lines need validation. In The Lancet Oncology, Ornstein and colleagues report on the results of a multicentre, phase 2 trial of individualised axitinib dose titration in patients in whom an immune-checkpoint-inhibitor-based treatment failed, irrespective of the treatment line in which it had been used. Despite recruiting just 40 patients and not meeting the prespecified threshold for progression-free survival to be significant, the strength of this study is its prospective design, which differentiates it from various retrospective case series published earlier. The question arises as to whether this study is supported by a scientific and molecular rationale; one might argue that it is just an attempt to generate prospective data on an established agent in a new therapeutic setting. According to the results of an elegant paper by Pal and colleagues, renal cell carcinoma biology changes with the ongoing course of the disease, with the number of mutations increasing from first-line to later lines. For example, genetic alterations to the VHL tumour suppressor gene, the key genetic hallmark of clear cell renal cell carcinoma, were reported to increase between treatment lines. This finding clearly suggests that angiogenesis, the direct molecular consequence of VHL gene alterations, remains key throughout the natural history of renal cell carcinoma. Therefore, axitinib appears to be a reasonable strategy after failure of immune checkpoint inhibitors. At this point, a second key question arises: why axitinib, and not other VEGF receptor (VEGF-R)-targeting drugs? Axitinib has three theoretical advantages over other anti-angiogenics: its potency and selectivity for the three VEGF-Rs, its safety profile with less offtarget adverse events, and the possibility of using individualised dose-titration to exploit its full potential. From preclinical models6 to randomised controlled, phase 3 studies, the potency of axitinib in suppressing angiogenesis has been well established. Moreover, its selectivity for VEGF-Rs results in a predictable and usually manageable safety profile, meaning it might be better tolerated by patients receiving later lines of therapy, who might be less willing to accept side effects. Dose titration allows for individualisation of treatment, which could lead to increased activity, although not necessarily to increased efficacy. Reasonable treatment options after failure of axitinib plus immune-checkpoint inhibitor combinations remain purely speculative. None of the patients reported by Ornstein and colleagues had received axitinib in combination with either avelumab or pembrolizumab. In patients in whom such combinations fail, resistance to VEGF-inhibitors might have occurred. However, resistance to VEGF-targeting agents and the corresponding epithelial-to-mesenchymal transition were shown to be temporary; thus, a certain responsiveness to axitinib or to other potent and selective VEGF-Rs inhibitor, such as tivozanib, might be expected in patients in whom combination treatments have failed. Nevertheless, targeting drivers of resistance to anti VEGF-R therapies (eg, MET and AXL) appears more promising in this setting, making cabozantinib a sensible drug choice. Similar considerations might also be made for the combination of lenvatinib and everolimus. What are the options after first-line immune checkpoint inhibitor-based combinations have failed? Should we stop thinking in treatment lines at all? One aspect worthy of academic study is the timing and duration of tyrosine kinase inhibitor treatment within such combinations. Upfront VEGF-R-tyrosine kinase inhibitor-immune checkpoint inhibitor combinations might make sense, because tyrosine kinase inhibitors were shown to modify the immune system, increasing the likelihood of an immune response. However, whether continuous tyrosine kinase inhibitor dosing is necessary is unknown. Withholding axitinib or intermittent dosing in the case of progression could spare the patients relevant toxicities, without necessarily hampering treatment activity. More academic — and less marketingdriven — studies are strongly warranted to answer these key questions and to optimise treatment outcomes for patients with metastatic renal cell carcinoma.

I.F.: 35,386

N. citazioni = 5

342. Motzer RJ, Rini BI, McDermott DF, Frontera OA, Hammers HJ, Carducci MA, Salman P, EscudierB, BeuselinckB, Amin A, **Porta C**, George S, Neiman V, Bracarda S, Tykodi SS, Barthélémy P, Leibowitz-Amit R, Plimack ER, Oosting SF, Redman B, Melichar B, Powles T, Nathan P, Oudard S, Pook D, Choueiri TK, Donskov F, Grimm M-O, Gurney H, Heng DYC, Kollmannsberger CK, Harrison MR, Tomita Y, Duran I, Grünwald V, McHenry B, Mekan S, Tannir NM, for the CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised phase 3 trial. *Lancet Oncol* 2019;20:1370-85.

ABSTRACT – Background: In the ongoing phase 3 CheckMate 214 trial, nivolumab plus ipilimumab showed superior efficacy over sunitinib in patients with previously untreated intermediate-risk or poor-risk advanced renal cell carcinoma, with a manageable safety profile. In this study, we aimed to assess efficacy and safety after extended follow-up to inform the long-term clinical benefit of nivolumab plus ipilimumab versus sunitinib in this setting. Methods: In the phase 3, randomised, controlled CheckMate 214 trial, patients aged 18 years and older with previously untreated, advanced, or metastatic histologically confirmed renal cell carcinoma with a clear-cell component were recruited from 175 hospitals and cancer centres in 28 countries. Patients were categorised by International Metastatic Renal Cell Carcinoma Database Consortium risk status into favourable-risk, intermediate-risk, and poor-risk subgroups and randomly assigned (1:1) to open-label nivolumab (3 mg/kg intravenously) plus ipilimumab (1 mg/kg intravenously) every 3 weeks for four doses, followed by nivolumab (3 mg/kg intravenously) every 2 weeks; or sunitinib (50 mg orally) once daily for 4 weeks (6-week cycle). Randomisation was done through an interactive voice response system, with a block size of four and stratified by risk status and geographical region. The co-primary endpoints for the trial were overall survival, progression-free survival per independent radiology review committee (IRRC), and objective responses per IRRC in intermediate-risk or poor-risk patients. Secondary endpoints were overall survival, progression-free survival per IRRC, and objective responses per IRRC in the intention-to-treat population, and adverse events in all treated patients. In this Article, we report overall survival, investigator-assessed progression-free survival, investigator-assessed objective response, characterisation of response, and safety after extended follow-up. Efficacy outcomes were assessed in all randomly assigned patients; safety was assessed in all treated patients. This study is registered with ClinicalTrials.gov, number NCT02231749, and is ongoing but now closed to recruitment. Findings: Between Oct 16, 2014, and Feb 23, 2016, of 1390 patients screened, 1096 (79%) eligible patients were randomly assigned to nivolumab plus ipilimumab or sunitinib (550 vs 546 in the intention-to-treat population; 425 vs 422 intermediate-risk or poor-risk patients, and 125 vs 124 favourable-risk patients). With extended follow-up (median follow-up 32·4 months [IQR 13·4-36·3]), in intermediate-risk or poor-risk patients, results

for the three co-primary efficacy endpoints showed that nivolumab plus ipilimumab continued to be superior to sunitinib in terms of overall survival (median not reached [95% CI 35·6-not estimable] vs 26·6 months [22·1-33·4]; hazard ratio [HR] 0·66 [95% CI 0·54-0·80], p<0·0001), progression-free survival (median 8·2 months [95% CI 6·9-10·0] vs 8·3 months [7·0-8·8]; HR 0·77 [95% CI 0·65-0·90], p=0·0014), and the proportion of patients achieving an objective response (178 [42%] of 425 vs 124 [29%] of 422; p=0·0001). Similarly, in intention-to-treat patients, nivolumab and ipilimumab showed improved efficacy compared with sunitinib in terms of overall survival (median not reached [95% CI not estimable] vs 37·9 months [32·2-not estimable]; HR 0·71 [95% CI 0·59-0·86], p=0·0003), progression-free survival (median 9·7 months [95% CI 8·1-11·1] vs 9·7 months [8·3-11·1]; HR 0·85 [95% CI 0·73-0·98], p=0·027), and the proportion of patients achieving an objective response (227 [41%] of 550 vs 186 [34%] of 546 p=0·015). In all treated patients, the most common grade 3-4 treatment-related adverse events in the nivolumab and ipilimumab group were increased lipase (57 [10%] of 547), increased amylase (31 [6%]), and increased alanine aminotransferase (28 [5%]), whereas in the sunitinib group they were hypertension (90 [17%] of 535), fatigue (51 [10%]), and palmar-plantar erythrodysaesthesia (49 [9%]). Eight deaths in the nivolumab plus ipilimumab group and four deaths in the sunitinib group were reported as treatment-related. Interpretation: The results suggest that the superior efficacy of nivolumab plus ipilimumab over sunitinib was maintained in intermediate-risk or poor-risk and intention-to-treat patients with extended follow-up, and show the long-term benefits of nivolumab plus ipilimumab in patients with previously untreated advanced renal cell carcinoma across all risk categories.

I.F.: 35,386

N. citazioni = 338

343. Dudani S, Graham J, Wells JC, Bakouny Z, Pal SK, Dizman N, Donskov F, **Porta C**, de Velasco G, Hansen A, Iafolla M, Beuselinck B, Vaishampayan UN, Wood LA, Liow E, Yan F, Yuasa T, Bjarnason GA, Choueiri TK, Heng DYC. First-line immuno-oncology combination therapies in metastatic renal-cell carcinoma: results from the International Metastatic Renal-cell Carcinoma Database Consortium. *Eur Urol* 2019;76:861-7.

ABSTRACT – Background: In metastatic renal-cell carcinoma (mRCC), recent data have shown efficacy of first-line ipilimumab and nivolumab (ipi-nivo) as well as immuno-oncology (IO)/vascular endothelial growth factor (VEGF) inhibitor combinations. Comparative data between these strategies are limited. Objective: To compare the efficacy of ipi-nivo versus IO-VEGF (IOVE) combinations in mRCC, and describe practice patterns and effectiveness of second-line therapies. Design, setting and participants: Using the International Metastatic Renal-cell Carcinoma Database Consortium (IMDC) dataset, patients treated with any first-line IOVE combination were compared with those treated with ipi-nivo. Intervention: All patients received first-line IO combination therapies. Outcome measurements and statistical analysis: First- and second-line response rates, time to treatment failure (TTF), time to next treatment (TNT), and overall survival (OS) were analysed. Hazard ratios were adjusted for IMDC risk factors. Results and limitations: In total, 113 patients received IOVE combinations and 75 received ipi-nivo. For IOVE combinations versus ipi-nivo, first-line response rates were 33% versus 40% (between-group difference 7%, 95% confidence interval [CI] -8% to 22%, p = 0.4), TTF was 14.3 versus 10.2 mo (p = 0.2), TNT was 19.7 versus 17.9 mo (p = 0.4), and median OS was immature but not statistically different (p = 0.17). Adjusted hazard ratios for TTF, TNT, and OS were 0.71 (95% CI 0.46-1.12, p = 0.14), 0.65 (95% CI 0.38-1.11, p = 0.11), and 1.74 (95% CI 0.82-3.68, p = 0.14), respectively. Sixty-four (34%) patients received second-line treatment. In patients receiving subsequent VEGF-based therapy, second-line response rates were lower in the IOVE cohort than in the ipi-nivo cohort (15% vs 45%; between-group difference 30%, 95% CI 3-57%, p = 0.04; n = 40), though second-line TTF was not significantly different (3.7 vs 5.4 mo; p = 0.4; n = 55). Limitations include the study's retrospective design and sample size. Conclusions: There were no significant differences in first-line outcomes between IOVE combinations and ipi-nivo. Most patients received VEGF-based therapy in the second line. In this group, second-line response rate was greater in patients who received ipi-nivo initially. Patient summary: There were no significant differences in key first-line outcomes for patients with metastatic renal-cell carcinoma receiving immuno-oncology/vascular endothelial growth factor inhibitor combinations versus ipilimumab and nivolumab.

I.F.: 17,298

N. citazioni = 24

344. Brodaczewska KK, Bielecka ZF, Maliszewska-Olejniczak K, Szczylik C, **Porta C**, Bartnik E, Czarnecka AM. Metastatic renal cell carcinoma cells growing in 3D on poly-D-lysine or laminin present a stem-like phenotype and drug resistance. *Oncol Rep* 2019;42:1878-92.

ABSTRACT – 3D spheroids are built by heterogeneous cell types in different proliferative and metabolic states and are enriched in cancer stem cells. The main aim of the study was to investigate the usefulness of a novel metastatic renal cell carcinoma (RCC) 3D spheroid culture for in vitro cancer stem cell physiology research and drug toxicity screening. RCC cell lines, Caki-1 (skin metastasis derived) and ACHN (pleural effusion derived), were efficiently cultured in growth-factor/serum deprived, defined, StemXvivo and Nutristem medium on laminin-coated or poly-D-lysine-coated plates. In optimal 3D culture conditions, ACHN cells (StemXVivo/poly-D-lysine) formed small spheroids with remaining adherent cells of an epithelial phenotype, while Caki-1 cells (StemXVivo/laminin) formed large dark spheroids with significantly reduced cell viability in the center. In the 3D structures, expression levels of genes encoding stem transcription factors (OCT4, SOX2, NES) and RCC stem cell markers (CD105, CD133) were deregulated in comparison to these expression levels in traditional 2D culture. Sunitinib, epirubicin and doxycycline were more toxic to cells cultured in monolayers than for cells in 3D spheroids. High numbers of cells arrested in the G0/G1 phase of the cell cycle were found in spheroids under sunitinib treatment. We showed that metastatic RCC 3D spheroids supported with ECM are a useful model to determine the cancer cell growth characteristics that are not found in adherent 2D cultures. Due to the more complex architecture, spheroids may mimic in vivo micrometastases and may be more appropriate to investigate novel drug candidate responses, including the direct effects of tyrosine kinase inhibitor activity against RCC cells.

I.F.: 3,041

N. citazioni = 8

345. Sternberg CN, Motzer RJ, Hutson TE, Choueiri TK, Kollmannsberger C, Bjarnason GA, Paul Nathan, **Porta C**, Grünwald V, Dezzani L, Han J, Tannir NM. COMPARZ post hoc analysis: characterizing Pazopanib responders with advanced renal cell carcinoma. *Clin Genitourin Cancer*

2019;17:425-354.

ABSTRACT – Background: The phase III COMPARZ study showed non-inferior efficacy of pazopanib versus sunitinib in advanced renal cell carcinoma. In this COMPARZ post hoc analysis we characterized pazopanib responders, patient subgroups with better outcomes, and the effect of dose modification on efficacy and safety. Patients and methods: Patients were randomized to pazopanib 800 mg/d (n = 557) or sunitinib 50 mg/d, 4 weeks on/2 weeks off (n = 553). Secondary end points included time to complete response (CR)/partial response (PR); the proportion of patients with CR/PR ≥10 months and progression-free survival (PFS) ≥10 months; efficacy in patients with baseline metastasis; and logistic regression analyses of patient characteristics associated with CR/PR ≥10 months. Median PFS, objective response rate (ORR), and safety were evaluated in patients with or without dose reductions or interruptions lasting ≥7 days. Results: Median time to response was numerically shorter for patients treated with pazopanib versus sunitinib (11.9 vs. 17.4 weeks). Similar percentages of pazopanib and sunitinib patients had CR/PR ≥10 months (14% and 13%, respectively), and PFS ≥10 months (31% and 34%, respectively). For patients without versus with adverse event (AE)-related dose reductions, median PFS, median overall survival, and ORR were 7.3 versus 12.5 months, 21.7 versus 36.8 months, and 22% versus 42% (all P < .0001) for pazopanib, and 5.5 versus 13.8 months, 18.1 versus 38.0 months, and 16% versus 34% (all P < .0001) for sunitinib; results were similar for dose interruptions. Conclusion: Dose modifications when required because of AEs were associated with improved efficacy, suggesting that AEs might be used as a surrogate marker of adequate dosing for individual patients.
I.F.: 2,450
N. citazioni = 7

346. Brodziak A, Sobczuk P, Bartnik E, Fiedorowicz M, **Porta C**, Szczylik C, Czarnecka AM. Drug resistance in papillary RCC: from putative mechanisms to clinical practicalities. *Nat Rev Urol* 2019;16:655-73.

ABSTRACT – Papillary renal cell carcinoma (pRCC) is the second most common renal cell carcinoma (RCC) subtype and accounts for 10-15% of all RCCs. Despite clinical need, few pharmacogenomics studies in pRCC have been performed. Moreover, current research fails to adequately include pRCC laboratory models, such as the ACHN or Caki-2 pRCC cell lines. The molecular mechanisms involved in pRCC development and drug resistance are more diverse than in clear-cell RCC, in which inactivation of VHL occurs in the majority of tumours. Drug resistance to multiple therapies in pRCC occurs via genetic alteration (such as mutations resulting in abnormal receptor tyrosine kinase activation or RALBP1 inhibition), dysregulation of signalling pathways (such as GSK3β-EIF4EBP1, PI3K-AKT and the MAPK or interleukin signalling pathways), deregulation of cellular processes (such as resistance to apoptosis or epithelial-to-mesenchymal transition) and interactions between the cell and its environment (for example, through activation of matrix metalloproteinases). Improved understanding of resistance mechanisms will facilitate drug discovery and provide new effective therapies. Further studies on novel resistance biomarkers are needed to improve patient prognosis and stratification as well as drug development.
I.F.: 9,333
N. citazioni = 8

347. Santoni M, Heng DY, Bracarda S, Procopio G, Milella M, **Porta C**, Matrana MR, Cartenì G, Crabb SJ, De Giorgi U, Basso U, Masini C, Calabrò F, Vitale MG, Santini D, Massari F, Galli L, Fornarini G, Ricotta R, Buti S, Zucali P, Caffo O, Morelli F, Carrozza F, Martignetti A, Gelibter A, Iacovelli R, Mosca A, Atzori F, Vau N, Incorvaia L, Ortega C, Scarpelli M, Lopez-Beltran A, Cheng L, Paolucci V, Graham J, Pierce E, Scagliarini S, Sepe P, Verzoni E, Merler S, Rizzo M, Sorgentoni G, Conti A, Piva F, Cimadamore A, Montironi R, Battelli N. Real-world data on Cabozantinib in previously treated patients with metastatic renal cell carcinoma: focus on sequences and prognostic factors. *Cancers (Basel)* 2019;30:12.

ABSTRACT – Cabozantinib is approved for the treatment of renal cell carcinoma (RCC). However, prognostic factors are still lacking in this context. The aim of this study was to evaluate prognostic factors in RCC patients treated with second- or third-line cabozantinib. A multicenter retrospective real-world study was conducted, involving 32 worldwide centers. A total of 237 patients with histologically confirmed clear-cell and non-clear-cell RCC who received cabozantinib as second or third-line therapy for metastatic disease were included. We analyzed overall survival (OS), progression-free survival (PFS) and time-to-strategy failure (TTSF) using Kaplan–Meier curves. Cox proportional models were used at univariate and multivariate analyses.The median PFS and OS of cabozantinib were 7.76 months (95% CI 6.51–10.88) and 11.57 months (95% CI 10.90–not reached (NR)) as second-line and 11.38 months (95% CI 5.79–NR) and NR (95% CI 11.51–NR) as third-line therapy. The median TTSF and OS were 11.57 and 15.52 months with the sequence of cabozantinib–nivolumab and 25.64 months and NR with nivolumab–cabozantinib, respectively. The difference between these two sequences was statistically significant only in good-risk patients. In the second-line setting, hemoglobin (Hb) levels (HR = 2.39; 95% CI 1.24–4.60, p = 0.009) and IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) group (HR = 1.72, 95% CI 1.04–2.87, p = 0.037) were associated with PFS while ECOG-PS (HR = 2.33; 95%CI, 1.16–4.69, p = 0.018) and Hb levels (HR = 3.12; 95%CI 1.18–8.26, p = 0.023) correlated with OS at multivariate analysis, while in the third-line setting, only Hb levels (HR = 2.72; 95%CI 1.04–7.09, p = 0.042) were associated with OS. Results are limited by the retrospective nature of the study.This real-world study provides evidence on the presence of prognostic factors in RCC patients receiving cabozantinib.
I.F.: 6,162
N. citazioni = 8

348. Rofi E, Del Re M, Arrigoni E, Rizzo M, Fontanelli L, Crucitta S, Gianfilippo G, Restante G, Fogli S, **Porta C**, Danesi R, Schmidinger M. Clinical pharmacology of monoclonal antibodies targeting anti-PD-1 axis in urothelial cancers. *Crit Rev Oncol Hematol* 2020;144:102812.

ABSTRACT – Chemotherapy is the reference treatment for patients with advanced urothelial carcinoma, both in the neo-adjuvant and adjuvant settings; however, the overall outcome remains poor in this patient population. In the last few years, the addition of immune checkpoint inhibitors into the therapeutic armamentarium has changed the therapeutic landscape of several tumor types, including urothelial carcinoma. Many different molecules have been introduced on the market and several questions about immunotherapies are currently open and deserve a critical analysis. The current review article is aimed at describing the clinical

pharmacology of monoclonal antibodies targeting PD-1 axis in urothelial malignancies to underline possible pharmacodynamic and pharmacokinetic differences among them.
I.F.: 5,012
N. citazioni = 5 + 2 (da: Erratum)

349. Escudier B, Motzer RJ, Tannir NM, **Porta C**, Tomita Y, Maurer MA, McHenry MB, Rini BI. Efficacy of Nivolumab plus Ipilimumab According to Number of IMDC Risk Factors in CheckMate 214. *Eur Urol* 2020;77:449-53.

ABSTRACT – In the randomized, open-label, phase 3 CheckMate 214 trial, nivolumab plus ipilimumab (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 wk for four doses, then nivolumab 3 mg/kg every 2 wk) had superior efficacy over sunitinib (50 mg once daily, 4 wk on, 2 wk off) in patients with untreated International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate- or poor-risk advanced renal cell carcinoma; the benefits were sustained through extended follow-up. To better characterize the association between outcomes and IMDC risk in CheckMate 214, we completed a post hoc analysis (n = 1051) of efficacy by the number of IMDC risk factors. The investigator-assessed objective response rate (ORR), overall survival (OS), and investigator-assessed progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors v1.1 were evaluated. ORR with nivolumab plus ipilimumab was consistent across zero to six IMDC risk factors, whereas with sunitinib it decreased with increasing number of risk factors. Benefits of nivolumab plus ipilimumab over sunitinib in terms of ORR (40-44% vs 16-38%), OS (hazard ratio [HR] 0.50-0.72), and PFS (HR 0.44-0.86) were consistently observed in subgroups with one, two, three, or four to six IMDC risk factors (p < 0.05 for treatment × no. of risk factors interaction). These results demonstrate the benefit of first-line nivolumab plus ipilimumab over sunitinib across all intermediate-risk and poor-risk groups, regardless of the number of IMDC risk factors. PATIENT SUMMARY: This report from the CheckMate 214 study describes a consistent efficacy benefit with first-line nivolumab plus ipilimumab over first-line sunitinib in all groups of patients with intermediate-risk or poor-risk advanced renal cell carcinoma, regardless of the number of risk factors they had before starting treatment. We conclude that there is a benefit of first-line treatment with nivolumab plus ipilimumab for all intermediate-risk patients, including those with one or two risk factors, and for all poor-risk patients, independent of the number of risk factors.
I.F.: 17,298
N. citazioni = 27

350. Rini BI, Pal SK, Escudier BJ, Atkins MB, Hutson TE, **Porta C**, Verzoni E, Needle MN, McDermott DF. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. *Lancet Oncol* 2020;21:85-104.

ABSTRACT – Background: Treatment for renal cell carcinoma has been revolutionised by inhibitors of VEGF receptor. Previous studies have suggested that treatment with a VEGF receptor (VEGFR) tyrosine kinase inhibitor might be effective in patients who had previous checkpoint inhibitor therapy. Therefore, TIVO-3 was designed to compare the efficacy and safety of tivozanib (a potent and selective VEGFR inhibitor) with those of sorafenib as third-line or fourth-line therapy in patients with metastatic renal cell carcinoma. Methods: In this open-label, randomised, controlled trial done at 120 academic hospitals in 12 countries, we enrolled eligible patients older than 18 years with histologically or cytologically confirmed metastatic renal cell carcinoma and at least two previous systemic treatments (including at least one previous treatment with a VEGFR inhibitor), measurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were excluded if they had received previous treatment with tivozanib or sorafenib. Patients were stratified by International Metastatic Renal Cell Carcinoma Database Consortium risk category and type of previous therapy and randomised (1:1) with a complete permuted block design (block size of four) to either tivozanib 1·5 mg orally once daily in 4-week cycles or sorafenib 400 mg orally twice daily continuously. Investigators and patients were not masked to treatment. The primary endpoint was progression-free survival by independent review in the intention-to-treat population. Safety analyses were done in all patients who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, NCT02627963. Findings: Between May 24, 2016, and Aug 14, 2017, 350 patients were randomly assigned to receive tivozanib (175 patients) or sorafenib (175 patients). Median follow-up was 19·0 months (IQR 15·0-23·4). Median progression-free survival was significantly longer with tivozanib (5·6 months, 95% CI 5·29-7·33) than with sorafenib (3·9 months, 3·71-5·55; hazard ratio 0·73, 95% CI 0·56-0·94; p=0·016). The most common grade 3 or 4 treatment-related adverse event was hypertension (35 [20%] of 173 patients treated with tivozanib and 23 [14%] of 170 patients treated with sorafenib). Serious treatment-related adverse events occurred in 19 (11%) patients with tivozanib and in 17 (10%) patients with sorafenib. No treatment-related deaths were reported. Interpretation: Our study showed that tivozanib as third-line or fourth-line therapy improved progression-free survival and was better tolerated compared with sorafenib in patients with metastatic renal cell carcinoma.
I.F.: 35,386
N. citazioni = 30

351. Fogli S, **Porta C**, Del Re M, Crucitta S, Gianfilippo G, Danesi R, Rini BI, Schmidinger M. Optimizing treatment of renal cell carcinoma with VEGFR-TKIs: a comparison of clinical pharmacology and drug-drug interactions of anti-angiogenic drugs. *Cancer Treat Rev* 2020;84:101966.

ABSTRACT – Anti-angiogenic treatment is an important option that has changed the therapeutic landscape in various tumors, particularly in patients affected by renal cell carcinoma (RCC). Agents that block signaling pathways governing tumor angiogenesis have raised high expectations among clinicians. Vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs) comprise a heterogeneous class of drugs with distinct pharmacological profiles, including potency, selectivity, pharmacokinetics and drug-drug interactions. Among them, tivozanib is one of the last TKIs introduced in the clinical practice; this drug selectively targets VEGFRs, it is characterized by a favorable pharmacokinetics and safety profile and has been approved as first-line treatment for patients with metastatic RCC (mRCC). In this article, we describe the clinical pharmacology of selected VEGFR-TKIs used for the treatment of mRCC, highlighting the relevant differences; moreover we aim to define the main pharmacologic characteristics of these drug.
I.F.: 8,332
N. citazioni = 20

352. Donskov F, Xie W, Overby A, et al. Synchronous versus metachronous metastatic disease: impact of time to meta-

stasis on patient outcome. Results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol Oncol* 2020;3:530-9.

ABSTRACT – Background: Patients with metastatic renal cell carcinoma (mRCC) may present with primary metastases (synchronous disease) or develop metastases during follow-up (metachronous disease). The impact of time to metastasis on patient outcome is poorly characterised. Objective: To characterise overall survival (OS) and time to treatment failure (TTF) based on time to metastasis in mRCC patients treated with targeted therapy (tyrosine kinase inhibitors [TKIs]). Design, setting, and participants: We used the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) to compare synchronous (metastases within ≤3 mo of initial diagnosis of cancer) versus metachronous disease (evaluated by >3-12 mo, >1-2 yr, >2-7 yr, and >7 yr intervals). Outcome measurements and statistical analysis: OS and TFF were assessed using Kaplan-Meier curves. Cox multivariable regressions analyses (MVAs) were adjusted for baseline factors. Results and limitations: Of 7386 patients with mRCC treated with first-line TKIs, 3906 (53%) and 3480 (47%) had synchronous and metachronous metastasis, respectively. More patients with synchronous versus metachronous disease had higher T stage (T1-2: 19% vs 34%), N1 disease (21% vs 6%), presence of sarcomatoid differentiation (15.8% vs 7.9%), Karnofsky performance status <80 (25.9% vs 15.1%), anaemia (62.5% vs 42.3%), elevated neutrophils (18.9% vs 10.9%), elevated platelets (21.6% vs 11.4%), bone metastases (40.4% vs 29.8%), and IMDC poor risk (40.6% vs 11.3%). Synchronous versus metachronous disease by intervals >3-12 mo, >1-2 yr, >2-7 yr, and >7 yr correlated with poor TTF (5.6 mo vs 7.3, 8.0, 10.8, and 13.3 mo, p < 0.0001) and poor OS (median 16.7 mo vs 23.8, 30.2, 34.8, and 41.7 mo, p < 0.0001). In MVAs, the adjusted hazard ratios (95% confidence intervals) were 1.00 (reference), 0.98 (0.90-1.06), 0.81 (0.73-0.91), 0.74 (0.68-0.81), and 0.60 (0.54-0.67), respectively, for OS (p < 0.0001), and 1.00 (reference), 0.99 (0.92-1.06), 0.98 (0.90-1.07), 0.83 (0.77-0.89), and 0.66 (0.60-0.72), respectively, for TTF (p < 0.0001). Data were collected retrospectively. Conclusions: Timing of metastases after initial RCC diagnosis may impact the outcomes from targeted therapy in mRCC. Patient summary: We looked at the impact of the timing of metastatic outbreak on survival outcomes in kidney cancer patients treated with targeted therapy. We found that the longer time to metastatic development was associated with improved outcome.

I.F.^{2020}: 7,47

N. citazioni = 11

353. Gibellini L, De Biasi S, **Porta C**, Lo Tartaro D, Depenni R, Pellacani G, Sabbatini R, Cossarizza A. Single-Cell Approaches to Profile the Response to Immune Checkpoint Inhibitors. *Front Immunol* 2020;11:490.

ABSTRACT – Novel treatments based upon the use of immune checkpoint inhibitors have an impressive efficacy in different types of cancer. Unfortunately, most patients do not derive benefit or lasting responses, and the reasons for the lack of therapeutic success are not known. Over the past two decades, a pressing need to deeply profile either the tumor microenvironment or cells responsible for the immune response has led investigators to integrate data obtained from traditional approaches with those obtained with new, more sophisticated, single-cell technologies, including high parameter flow cytometry, single-cell sequencing and high resolution imaging. The introduction and use of these technologies had, and still have a prominent impact in the field of cancer immunotherapy, allowing delving deeper into the molecular and cellular crosstalk between cancer and immune system, and fostering the identification of predictive biomarkers of response. In this review, besides the molecular and cellular cancer-immune system interactions, we are discussing how cutting-edge single-cell approaches are helping to point out the heterogeneity of immune cells in the tumor microenvironment and in blood.

I.F.: 6,429

N. citazioni = 21

354. Cosmai L, **Porta C**, Privitera C, Gesualdo L, Procopio G, Gori S, Laghi A. Acute kidney injury from contrast-enhanced CT procedures in patients with cancer: white paper to highlight its clinical relevance and discuss applicable preventive strategies. *ESMO Open* 2020;5:e000618.

ABSTRACT – Patients with cancer are subjected to several imaging examinations which frequently require the administration of contrast medium (CM). However, it has been estimated that acute kidney injury (AKI) due to the injection of iodinated CM accounts for 11% of all cases of AKI, and it is reported in up to 2% of all CT examinations. Remarkably, the risks of developing AKI are increased in the elderly, in patients with chronic kidney disease or diabetes, and with dehydration or administration of nephrotoxic chemotherapeutics. Given the common occurrence of postcontrast acute kidney injury (PC-AKI) in clinical practice, primary care physicians and all specialists involved in managing patients with cancer should be aware of the strategies to reduce the risk of this event. In 2018, a panel of four experts from the specialties of radiology, oncology and nephrology were speakers at the annual meeting of the Italian Society of Medical Radiology (Società Italiana di Radiologia Medica e Interventistica), with the aim of commenting on existing evidence and providing their experience on the incidence and management of PC-AKI in patients with cancer. The discussion represented the basis for this white paper, which is intended to be a practical guide organised by statements describing methods to reduce renal injury risks related to CM-enhanced CT examinations in patients with cancer.

I.F.: 5,329

N. citazioni = 3

355. Caliò A, Brunelli M, Segala D, Pedron S, Remo A, Ammendola S, Munari E, Pierconti F, Mosca A, Bollito E, Sidoni A, Fisogni S, Sacco C, Canu L, Sentinelli S, Fraccon AP, Fiorentino M, Scott C, Milella M, **Porta C**, Argani P, Martignoni G. Comprehensive analysis of 34 MiT family translocation renal cell carcinomas and review of the literature: investigating prognostic markers and therapy targets. *Pathology* 2020;52:297-309.

BSTRACT – Recently cabozantinib, a tyrosine kinase inhibitor with activity against VEGF, MET, AXL, and downregulating cathepsin K in vitro, has been proposed for the treatment of advanced clear and non-clear renal cell carcinomas. Since it is well known that cathepsin K is expressed in the majority of MiT family translocation renal cell carcinomas, we investigated cathepsin K, MET, AXL, and VEGF in a large series of those tumours, looking for possible predictive markers. We collected the clinicopathological features of 34 genetically confirmed MiT family translocation renal cell carcinomas [26 Xp11 and 8 t(6;11) renal cell carcinomas] and studied them using an immunohistochemical panel including PAX8, cathepsin K, HMB45, Melan-A, CD68 (PG-M1), CK7, CA9, MET, AXL and

by FISH for VEGFA and MET. Cathepsin K was expressed in 14 of 26, HMB45 in 8 of 25, and Melan-A in 4 of 23 Xp11 renal cell carcinomas, whereas labelling for CK7 and CA9 was minimal. In t(6;11) renal cell carcinoma, cathepsin K and melanogenesis markers were constantly positive, whereas CK7 and CA9 were negative. None of the 34 carcinomas showed CD68 (PG-M1) and AXL expression. One aggressive Xp11 renal cell carcinoma showed increased VEGFA gene copy number (4-5 copies) with concurrent gains of TFE3 and TFEB. None of the 34 carcinomas showed MET gene amplification, whereas staining for MET was found in 7 of 8 t(6;11) and in 16 of 24 Xp11 renal cell carcinomas, and in the latter cases, when the expression was >50%, correlated with aggressiveness (p=0.0049). In Xp11 renal cell carcinomas, the aggressiveness was also correlated with larger tumour size (p=0.0008) and the presence of necrosis (p=0.027) but not nucleolar grading (p=1). Interestingly, in patients with tumours exhibiting two of three parameters (necrosis, larger tumour size and MET immunolabelling >50%) an aggressive clinical behaviour was observed in 88% of cases. In conclusion, cathepsin K, CD68 (PG-M1), CK7, CA9, and PAX8 is a useful panel for the diagnosis. Larger tumour size, the presence of necrosis and MET immunohistochemical expression correlate with aggressive behaviour in Xp11 renal cell carcinomas, especially in combination. VEGF, MET, cathepsin K but not AXL may be potential predictive markers for targeted therapy in MiT family translocation renal cell carcinomas.
I.F.: 3,744
N. citazioni = 17

356. **Porta C**, Verzoni E, Zai S, Messina C, Ferrari V, Gri N, Procopio G. Use of a natural multicomponent mouthwash plus oral hygiene vs oral hygiene alone to prevent everolimus-induced stomatitis: the STOP multicenter, randomized trial. *Tumori* 2020;300891620915786 [published online ahead of print, 2020 May 3].

ABSTRACT – Background: Stomatitis is highly prevalent in patients with cancer treated with the mammalian target of rapamycin inhibitor everolimus; it usually has an early onset and may compromise treatment dose intensity and patients' quality of life. Within the randomized controlled Stomatitis Prevention trial (STOP, ISRCTN14568888), we investigated the possibility of using a commercial natural multicomponent mouthwash (Orasol Plus®) to prevent the development of stomatitis of any grade in patients with advanced renal cell carcinoma (RCC) treated with everolimus. Methods: Overall, 62 patients were randomized to receive either Orasol Plus in addition to oral hygiene or oral hygiene alone (31 patients per treatment arm). Results: In the whole study population, 28 episodes of stomatitis were observed (41.9%); in only 2 patients, stomatitis occurred more than once (2 episodes). As expected, the episodes of stomatitis occurred early in the course of treatment with everolimus. Treatment with Orasol Plus prevented the onset of everolimus-induced stomatitis: only 8 episodes of stomatitis were observed in the treated group with Orasol Plus in addition to oral hygiene vs 20 episodes in the group treated with oral hygiene only (p = 0021). Also, a reduction in the average duration of mucositis in patients treated with Orasol Plus compared to patients treated with oral hygiene only was observed (8 days vs 11.2 days, p = 0.0416). Conclusion: This study showed that the use of a natural multicomponent mouthwash coupled with regular oral hygiene was able to reduce the severity and duration of everolimus-induced stomatitis in patients with RCC.
I.F.: 1,707

357. **Porta C**. Editorial debate: Challenges an oncologist has to face during the SARS-CoV-2 pandemic within a universal healthcare system. *ESMO Open* 2020;5:e000790.

BSTRACT – In these dramatic days of the SARS-CoV-2 pandemic, what is our role as oncologists in a country like Italy, characterised by a very high prevalence of the Covid-19 infection and high mortality rates, and a universal healthcare system? The answer looks easy: continue to guarantee the best care to cancer patients in order to avoid leaving anyone behind. True, but it's not as simple as it looks. Our healthcare system is overwhelmed by the number of critically ill patients, by the need for beds and ventilators in our intensive care units (ICUs), not to mention the very serious situation facing many physicians and nurses working in war-like conditions, becoming infected and sometimes dying from Covid-19. Yet, almost no one is allowed to mention the word "triage" in the media; we simply cannot induce panic by suggesting that we are unable to continue treating all patients coming to the ICU the same way. It is hard to admit, but triage is still a cornerstone in the management of catastrophes such as the current pandemic, although it will always be an unresolved ethical issue. Should we do triage too, as oncologists, in our wards? I think the answer is yes, although this is a tough decision for all of us, especially in a universal healthcare system like ours. Right or wrong, too many cancer patients still receive treatments which won't have any impact on their survival; indeed, the survival gain of many later-line therapies is extremely limited, at best. Furthermore, we know that mortality within 30 days from chemotherapy is as high as 8.1%, even in a top European institution such as the Royal Marsden in London. However, many of us are used to administering relatively useful anticancer treatments, because ultimately these treatments are reimbursed (at least in a country such as Italy); this is because patients often ask for further therapies (especially when not adequately informed about their prognosis), and because it is definitely easier to prescribe a new agent, instead of trying to explain that end-of-life care is sometimes the most ethical, although tough, choice to pursue. Now, in order to protect our patients from the unnecessary harm that may result from being admitted to hospital during a pandemic, as well as to preserve valuable resources for the management of Covid-19 patients, we should start revising this attitude. After having consumed a very large amount of research resources, at the expense of other disciplines such as infectious diseases, it is now time to reconsider our role in medicine, and go back to the roots of a close and personal relationship with our patients. Furthermore, we should cease to consider patients as a source of economical income for our institutions, and instead do what is best for them and not what is economically convenient.
I.F.: 5,329
N. citazioni = 1

358. Schmidinger M, **Porta C**, Oudard S, Denechere G, Brault Y, Serfass L, Costa N, Larkin J. Real-world experience with Sunitinib treatment in patients with metastatic renal cell carcinoma: clinical outcome according to risk score. *Clin Genitourin Cancer* 2020;18:e588-97.

ABSTRACT – Background: ADONIS is an ongoing observational study in 9 European countries, designed to evaluate treatment patterns/outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with first-line sunitinib and/or second-line axitinib post sunitinib. We present an evaluation of sunitinib efficacy by risk group, in the real-world setting examined in ADONIS. Patients and methods: Patients were enrolled at the start of first-line sunitinib treatment or second-line axitinib post sunitinib treatment. Evaluation of sunitinib efficacy was assessed by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and

Memorial Sloan Kettering Cancer Center risk criteria. Results: For all patients in this analysis (N = 467), the median progression-free survival was 23.8 months (95% confidence interval [CI], 16.5-28.5 months), 11.8 months (95% CI, 8.1-17.4 months), and 4.6 months (95% CI, 2.5-7.7 months) for IMDC favorable-, intermediate-, and poor-risk groups, respectively. The median overall survival was 97.1 months (95% CI, 46.3 months-not evaluable [NE]), 33.5 months (95% CI, 20.5-46.6 months), and 10.0 months (95% CI, 4.5-19.8 months) for the respective risk groups. Data on individual risk factors were available for a subgroup of patients, allowing analysis by intermediate risk by 1 versus 2 risk factors. When including this subgroup (n = 120), the median overall survival for IMDC favorable-, intermediate-1, and intermediate-2 risk factors was 21.6 months (95% CI, 16.3 months-NE), 20.5 months (15.5 months-NE), and 15.1 months (4.1 months-NE), respectively. Conclusions: For patients overall and by risk-group stratification, survival estimates were aligned with previously published data. In patients with intermediate-1 risk, overall survival was very similar to patients with favorable risk. However, further exploration of outcome data from different sources is needed to confirm these observations.
I.F.: 2,695
N. citazioni = 5

359. Motzer RJ, Escudier B, McDermott DF, Arén Frontera O, Melichar B, Powles T, Donskov F, Plimack ER, Barthélémy P, Hammers HJ, George S, Grünwald V, **Porta C**, Neiman V, Ravaud A, Choueiri TK, Rini BI, Salman P, Kollmannsberger CK, Tykodi SS, Grimm MO, Gurney H, Leibowitz-Amit R, Geertsen PF, Amin A, Tomita Y, McHenry MB, Saggi SS, Tannir NM. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. *J Immunother Cancer* 2020;8:e000891.

ABSTRACT – Background: The extent to which response and survival benefits with immunotherapy-based regimens persist informs optimal first-line treatment options. We provide long-term follow-up in patients with advanced renal cell carcinoma (aRCC) receiving first-line nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) in the phase 3 CheckMate 214 trial. Survival, response, and safety outcomes with NIVO+IPI versus SUN were assessed after a minimum of 42 months of follow-up. Methods: Patients with aRCC were enrolled from October 16, 2014, through February 23, 2016. Patients stratified by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk and region were randomized to nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every 3 weeks for four doses, followed by nivolumab (3 mg/kg) every 2 weeks; or SUN (50 mg) once per day for 4 weeks (6-week cycle). Primary endpoints: overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) per independent radiology review committee in IMDC intermediate-risk/poor-risk patients. Secondary endpoints: OS, PFS, and ORR in the intention-to-treat (ITT) population and safety. Favorable-risk patient outcomes were exploratory. Results: Among ITT patients, 550 were randomized to NIVO+IPI (425 intermediate/poor risk; 125 favorable risk) and 546 to SUN (422 intermediate/poor risk; 124 favorable risk). Among intermediate-risk/poor-risk patients, OS (HR, 0.66; 95% CI, 0.55-0.80) and PFS (HR, 0.75; 95% CI, 0.62-0.90) benefits were observed, and ORR was higher (42.1% vs 26.3%) with NIVO+IPI versus SUN. In ITT patients, both OS benefits (HR, 0.72; 95% CI, 0.61-0.86) and higher ORR (39.1% vs 32.6%) were observed with NIVO+IPI versus SUN. In favorable-risk patients, HR for death was 1.19 (95% CI, 0.77-1.85) and ORR was 28.8% with NIVO+IPI versus 54.0% with SUN. Duration of response was longer (HR, 0.46-0.54), and more patients achieved complete response (10.1%-12.8% vs 1.4%-5.6%) with NIVO+IPI versus SUN regardless of risk group. The incidence of treatment-related adverse events was consistent with previous reports. Conclusions: NIVO+IPI led to improved efficacy outcomes versus SUN in both intermediate-risk/poor-risk and ITT patients that were maintained through 42 months' minimum follow-up. A complete response rate >10% was achieved with NIVO+IPI regardless of risk category, with no new safety signals detected in either arm. These results support NIVO+IPI as a first-line treatment option with the potential for durable response. Trial registration number: NCT02231749.
I.F.: 13,751
N. citazioni = 79

360. Aeppli S, Eboulet EI, Eisen T, Escudier B, Fischer S, Larkin J, Grunwald V, McDermott D, Oldenburg J, Omlin A, **Porta C**, Rini B, Schmidinger M, Sternberg C, Rothermundt C. Impact of COVID-19 pandemic on treatment patterns in metastatic clear cell renal cell carcinoma. *ESMO Open* 2020;5(Suppl 3):e000852.

ABSTRACT – Background: The coronavirus pandemic has provoked discussions among healthcare providers how to manage cancer patients when faced with the threat of severe acute respiratory syndrome related coronavirus 2 (SARS-CoV-2) infection. Immune checkpoint inhibitor (ICI) containing regimens are standard of care in the majority of metastatic clear cell renal cell carcinoma (mccRCC) patients. It remains unclear whether therapies should be modified in response to the COVID-19 pandemic. Methods: We performed an online survey among physicians involved in the treatment of mccRCC, and 41 experts responded. Questions focused on criteria relevant for treatment decision outside the pandemic and the modifications of systemic therapy during COVID-19. Findings: For the majority of experts (73%), the combination of International metastatic renal cell carcinoma Database Consortium (IMDC) risk category and patient fitness are two important factors for decision-making. The main treatment choice in fit, favourable risk patients outside the pandemic is pembrolizumab/axitinib for 53%, avelumab/axitinib, sunitinib or pazopanib for 13% of experts each. During the pandemic, ICI-containing regimens are chosen less often in favour of a tyrosine kinase inhibitors (TKI) monotherapy, mainly sunitinib or pazopanib (35%).In fit, intermediate/poor-risk patients outside the pandemic, over 80% of experts choose ipilimumab/nivolumab, in contrast to only 41% of physicians during COVID-19, instead more TKI monotherapies are given. In patients responding to established therapies with ICI/ICI or ICI/TKI combinations, most participants modify treatment regimen by extending cycle length, holding one ICI or even both. Conclusion: mccRCC treatment modifications in light of the coronavirus pandemic are variable, with a shift from ICI/ICI to ICI/TKI or TKI monotherapy.
I.F.: 5,329
N. citazioni = 14

361. Iacovelli R, Ciccarese C, Bria E, Bracarda S, **Porta C**, Procopio G, Tortora G. Patients with sarcomatoid renal cell carcinoma - re-defining the first-line of treatment: a meta-analysis of randomised clinical trials with immune checkpoint inhibitors. *Eur J Cancer* 2020;136:195-203.

ABSTRACT – Background: Sarcomatoid renal cell carcinoma (sRCC)

represents a rare form of renal cell carcinoma marked by an aggressive biology, poor prognosis and little benefit from anti-angiogenic targeted therapy. More promising results come from the recent therapeutic strategy based on immune checkpoint inhibitor (ICI) combinations. Materials and methods: For this meta-analysis, we searched MEDLINE/PubMed, the Cochrane Library and American Society of Medical Oncology (ASCO) Meeting abstracts for phase II or III randomised clinical trials. Data extraction was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis statement. The hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) with the relative 95% confidence intervals were extracted from studies. Summary HRs were calculated using random- or fixed-effects models, depending on the heterogeneity of the included studies. Results: Four studies were selected for final analysis, including 467 patients (226 treated in with ICI combinations and 241 received sunitinib in the control arms). ICI-based combinations were associated with an improved PFS and OS compared with sunitinib, with a reduction of more than 40% of progression (HR = 0.56; p < 0.0001) and mortality (HR = 0.56; p = 0.001) risk. Moreover, ICI-based combinations are associated with a objective response rate (ORR) of more than 50% (versus 20% with sunitinib), corresponding to a doubled risk of achieving an ORR compared with controls (relative risk [RR] = 2.15; p < 0.00001). Finally, immunotherapy significantly increased the possibility to obtain complete responses (RR = 8.15, p = 0.0002) with an incidence of 11%. Conclusion: Our data support the efficacy of ICI-based combinations for sRCC therapy, redefining the first-line treatment.

I.F.: 7,275

N. citazioni = 21

362. Vitale MG, Pipitone S, Venturelli M, Baldessari C, **Porta C**, Iannuzzi F, Basso U, Scagliarini S, Zucali PA, Galli L, Rossetti S, Caserta C, Bracarda S, Iacovelli R, Masini C, Cortellini A, Di Girolamo S, Buti S, Fornarini G, Carrozza F, Santoni M, Caputo F, Giaquinta S, Balduzzi S, D'Amico R, Vitale G, Mighali P, Sabbatini R. Correlation between immune-related adverse event (IRAE) occurrence and clinical outcome in patients with metastatic renal cell carcinoma (mRCC) treated with Nivolumab: IRAENE trial, an Italian multi-institutional retrospective study. *Clin Genitourin Cancer* 2020;19:1329-38.

ABSTRACT – Background: Immunotherapy has brought clinical benefits to patients with metastatic renal cell cancer (mRCC). Most patients tolerate immunotherapy but serious immune-related adverse events (irAEs) have been reported. Some studies indicate a correlation between irAEs and clinical response in other cancer types (eg, lung cancer and melanoma). For patients with mRCC, the impact of irAE on clinical outcome is unknown. Patients and methods: A retrospective review of 167 patients with mRCC treated with nivolumab as standard of care between March 2017 and January 2018 in 16 Italian centers was performed. irAEs were assessed using Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. Results: Any grade and grade 3/4 irAEs occurred in 46% and 8.9% of patients, respectively. The median time to appearance of irAEs was 10 weeks; 38.8% of patients required steroid treatment. The most common irAEs were cutaneous (33.7%) and gastrointestinal (23.3%). The median overall survival and progression-free survival were 20.13 and 7.86 months, respectively. Patients with irAEs showed a greater overall survival (hazard ratio, 0.38; 95% confidence interval [CI], 0.23-0.63) and progression-free survival (hazard ratio, 0.44; 95% CI, 0.29-0.66) benefit as well as better overall response rate (27.3% vs. 13.7%; odds ratio, 2.36; 95% CI, 1.03-5.44) and disease control rate (68.8% vs. 48%; odds ratio, 2.4; 95% CI, 1.23-4.67) if compared with those without irAEs. No correlation was found between steroid use and clinical outcomes. Conclusions: Our analysis revealed that the appearance of irAEs was associated with better outcomes in patients treated with nivolumab. This data may be limited by sample size and the retrospective nature of the study.

I.F.: 2,695

N. citazioni = 7

363. Massari F, Mollica V, Rizzo A, Cosmai L, Rizzo M, **Porta C**. Safety evaluation of immune-based combinations in patients with advanced renal cell carcinoma: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2020;19:1329-38.

ABSTRACT – Introduction: Immune-based combinations, including nivolumab plus ipilimumab, pembrolizumab plus axitinib, and (at a lesser extent) avelumab plus axitinib, should be regarded among the new standards of care for first line therapy of metastatic renal cell carcinoma. Toxicity profiles are different among all these above combinations, as well as between them and targeted agents monotherapies, including sunitinib (i.e. the control arm of all the above studies). Areas covered: We performed a systematic review and meta-analysis with the aim to compare adverse events from immune-based combinations versus sunitinib monotherapy across four recent randomized controlled trials (CheckMate-214, Keynote-426, IMmotion-151, and JAVELIN Renal 101) of front-line treatment for metastatic renal cell carcinoma, with particular attention to those from the ipilimumab plus nivolumab combination. Expert Opinion/Commentary: Beyond efficacy and activity, the ipilimumab plus nivolumab combination appears feasible, being endowed by an acceptable safety profile, in line with that of the other available options for the treatment of metastatic RCC. The different patterns of toxicities emerging from this systematic review and meta-analysis need to be kept in mind while choosing the appropriate treatment for each individual patient. Furthermore, prevention, prompt identification and treatment of immune-related adverse events remains an are to be improved.

I.F.: 3.383

N. citazioni = 38

364. Cives M, Mannavola F, Lospalluti L, Sergi MC, Cazzato G, Filoni E, Cavallo F, Giudice G, Stucci LS, **Porta C**, Tucci M. Non-melanoma skin cancers: biological and clinical features. *Int J Mol Sci* 2020;21:5394.

ABSTRACT – Non-melanoma skin cancers (NMSCs) include basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and Merkel cell carcinoma (MCC). These neoplasms are highly diverse in their clinical presentation, as well as in their biological evolution. While the deregulation of the Hedgehog pathway is commonly observed in BCC, SCC and MCC are characterized by a strikingly elevated mutational and neoantigen burden. As result of our improved understanding of the biology of non-melanoma skin cancers, innovative treatment options including inhibitors of the Hedgehog pathway and immunotherapeutic agents have been recently investigated against these malignancies, leading to their approval by regulatory authorities. Herein, we review the most relevant biological and clinical features of NMSC, focusing on innovative treatment approaches.

I.F.: 4,556

N. citazioni = 19

365. **Porta C**, Giannatempo P, Rizzo M, Lucarelli G, Ditonno P, Battaglia M. An evaluation of UGN-101, a sustained-release hydrogel polymer-based formulation containing mitomycin-C, for the treatment of upper urothelial carcinomas. *Expert Opin Pharmacother* 2020;21:2199-204.

ABSTRACT – Introduction: The treatment of low-grade upper tract urothelial carcinomas (UTUCs) after either surgery, or nephron-sparing techniques remains an unmet need in Genitourinary (GU) Oncology. UGN-101 is a novel drug in development for the treatment of UTUCs; it is composed of a sustained-release hydrogel polymer-based formulation containing the antitumor antibiotic mitomycin-C (MM-C); cold UGN-101 is liquid, but at body temperature, it becomes a gel, and thus, when administered through a ureteral catheter, it sticks to the upper tract urothelium, slowly releasing MM-C. Areas covered: Here, the authors review the preclinical rationale for the development of UGN-101, as well as presently available clinical results for the treatment of low-grade UTUCs. Expert opinion: The positive results of the recently completed OLYMPUS trial suggest the feasibility, activity (59% of complete responses, with just 6 of these complete responders on follow-up who recurred), and safety (68% of patients experiencing mild to moderate urinary adverse events) of UGN-101 instillations into the upper urinary tract. Our expectations are that UGN-101 will soon become a standard of treatment for low-grade UTUC at risk of relapse after either surgery, or nephron-sparing techniques.
I.F.: 2,878

366. Pezzicoli G, Tucci M, Lovero D, Silvestris F, **Porta C**, Mannavola F. Large extracellular vesicles. A new frontier of liquid biopsy in Oncology. *Int J Mol Sci* 2020;21:E6543.

ABSTRACT – Extracellular Vesicles (EVs) are emerging as pivotal elements in cancer. Many studies have focused on the role of Small- (S)-EVs but in recent years Large-(L)-EVs have progressively gained increasing interest due to their peculiar content and functions. Tumor-derived L-EVs carry a lot of oncogenic proteins, nucleic acids and lipids to recipient cells and are involved in the reshaping of the tumor microenvironment as well as in the metabolic rewiring and the promotion of the pro-metastatic attitude of cancer cells. Several techniques have been developed for the isolation of L-EVs and commercial kits are also available for efficient and easy recovery of these vesicles. Also, the improvement in DNA sequencing and "omics sciences" profoundly changed the way to analyze and explore the molecular content of L-EVs, thus providing novel and potentially useful cancer biomarkers. Herein, we review the most recent findings concerning the role of L-EVs in cancer and discuss their possible use in oncology as "liquid biopsy" tools as compared to the other classes of EVs.
I.F.: 4,556
N. citazioni = 8

367. Pal SK, Escudier BJ, Atkins MB, Hutson TE, **Porta C**, Verzoni E, Needle MN, Powers D, McDermott DF, Rini BI. Final overall survival results from a phase 3 study to compare Tivozanib to Sorafenib as third- or fourth-line therapy in subjects with metastatic renal cell carcinoma. *Eur Urol* 2020;78:783-5.

ABSTRACT – Tivozanib is a potent and selective inhibitor of the VEGF receptor. In an open-label, randomized phase 3 trial, we compared tivozanib to sorafenib in patients with metastatic renal cell carcinoma (mRCC) who had received two or three prior therapies. We have previously reported that the study met its primary endpoint, demonstrating an improvement in progression-free survival with tivozanib versus sorafenib (5.6 mo vs 3.9 mo; hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.56-0.94; p=0.016). The current report reflects the final assessment of overall survival, showing no difference between treatment with tivozanib and sorafenib (HR 0.97, 95% CI 0.75-1.24). Given its activity and distinct tolerability profile, tivozanib represents a treatment option for patients with previously treated mRCC. PATIENT SUMMARY: We show that tivozanib, a targeted therapy, can delay tumor growth relative to an already approved targeted therapy (sorafenib) in patients with kidney cancer who have received two or three prior treatments. No difference in survival was observed.
I.F.: 17,947
N. citazioni = 6

368. Capri S, Porta C, Condorelli C, Premoli E, Khare A, Kalra M, Modi N, Ratto B. An updated cost-effectiveness analysis of pazopanib versus sunitinib as first-line treatment for locally advanced or metastatic renal cell carcinoma in Italy. *J Med Econ* 2020;23:1579-87.

ABSTRACT – Objective: To assess the cost-effectiveness of pazopanib versus sunitinib as a first-line treatment for patients with metastatic renal cell carcinoma (mRCC) from an Italian National Health Service perspective, considering the evolving Italian landscape in terms of new reimbursement agreements trend. Methods: This analysis is an update of the previously published cost-effectiveness analysis to incorporate recent 2019 costs and additional changes regarding drug discounting. A partitioned-survival analysis model with three different health states (progression-free survival, post-progression survival, and dead) was utilized. Outcomes included progression-free life years, post-progression life years, overall life years, quality-adjusted life years (QALYs), and costs calculated for both treatments. Cost-effectiveness was assessed in terms of incremental costs per QALY gained and the net monetary benefit (NMB) of pazopanib versus sunitinib. In the base case analysis, a time horizon of 5 years was used and future costs and QALYs were discounted at a 3% annual discount rate. An impact of methodological and parameter uncertainly on base case results was evaluated using probabilistic and deterministic sensitivity analyses. Results: In the base case, pazopanib had higher QALYs (+0.060) at lower costs (-€5,857) versus sunitinib, hence it dominated sunitinib. At willingness-to-pay thresholds of €30,000 and €50,000 per QALY, the NMB with pazopanib were €7,647 and €8,841 per patient, respectively, versus sunitinib. The probability that pazopanib is cost-effective versus sunitinib was estimated to be 97.5% at a cost-effectiveness threshold of €20,000, 95.4% at a threshold of €30,000, and 90.2% at a threshold of €50,000 per QALY. Cost-effectiveness results were robust to changes in key parameter values and assumptions as demonstrated by deterministic sensitivity analyses. Conclusions: Pazopanib is likely to represent a cost-effective treatment option compared with sunitinib as a first-line treatment for patients with metastatic RCC in Italy.
I.F.: 1,958
N. citazioni = 2

369. Internò V, Tucci M, Pezzicoli G, Silvestris F, **Porta C**,

Mannavola F. Liquid biopsy as a tool exploring in real-time both genomic perturbation and resistance to EGFR antagonists in colorectal cancer. *Front Oncol* 2020;10:581130.

ABSTRACT – The treatment of metastatic colorectal cancer (mCRC) has improved since the introduction of the epithelial growth factor receptor (EGFR) inhibitors as cetuximab and panitumumab. However, only patients with peculiar genomic profiles benefit from these targeting therapies. In fact, the molecular integrity of RAS genes is a predominant factor conditioning both primary and acquired resistance in non-responders although additional molecular derangements induced by selective anti-EGFR pressure may concur to the failure of those disease treatment, liquid biopsy (LB) appears as a surrogate of tissue biopsy, provides the genomic information to reveal tumor resistance to anti-EGFR agents, the detection of minimal residual disease before adjuvant therapies, and the discovery of tumor molecular status suitable for rechallenging treatments with EGFR antagonists. LB investigates circulating tumor cells (CTCs), cell-free tumor DNA (ctDNA), and tumor-derived exosomes. In mCRC, ctDNA analysis has been demonstrated as a useful method in the mutational tracking of defined genes as well as on tumor burden and detection of molecular alterations driving the resistance to anti-EGFR targeting treatments. However, despite their efficiency in molecular diagnosis and prognostic evaluation of mCRC, the affordability of these procedures is prevalently restricted to research centers, and the lack of consensus validation prevents their translation to clinical practice. Here, we revisit the major mechanisms responsible for resistance to EGFR blockade and review the different methods of LB potentially useful for treatment options in mCRC.
I.F.: 4,848
N. citazioni = 4

370. **Porta C**, Bamias A, Danesh FR, Dębska-Ślizień A, Gallieni M, Gertz MA, Kielstein JT, Tesarova P, Wong G, Cheung M, Wheeler DC, Winkelmayer WC, Małyszko J; Conference Participants. KDIGO Controversies Conference on onco-nephrology: understanding kidney impairment and solid-organ malignancies, and managing kidney cancer. *Kidney Int* 2020;98:1108-19.

ABSTRACT – The association between kidney disease and cancer is multifaceted and complex. Persons with chronic kidney disease (CKD) have an increased incidence of cancer, and both cancer and cancer treatments can cause impaired kidney function. Renal issues in the setting of malignancy can worsen patient outcomes and diminish the adequacy of anticancer treatments. In addition, the oncology treatment landscape is changing rapidly, and data on tolerability of novel therapies in patients with CKD are often lacking. Caring for oncology patients has become more specialized and interdisciplinary, currently requiring collaboration among specialists in nephrology, medical oncology, critical care, clinical pharmacology/pharmacy, and palliative care, in addition to surgeons and urologists. To identify key management issues in nephrology relevant to patients with malignancy, KDIGO (Kidney Disease: Improving Global Outcomes) assembled a global panel of multidisciplinary clinical and scientific expertise for a controversies conference on onco-nephrology in December 2018. This report covers issues related to kidney impairment and solid organ malignancies as well as management and treatment of kidney cancer. Knowledge gaps, areas of controversy, and research priorities are described.
I.F.: 8,945
N. citazioni = 5

371. Franzin R, Netti GS, Spadaccino F, **Porta C**, Gesualdo L, Stallone G, Castellano G, Ranieri E. The use of immune checkpoint inhibitors in Oncology and the occurrence of AKI: where do we stand? *Front Immunol* 2020;11:574271.

ABSTRACT – Immune checkpoint inhibitors (ICIs) are a novel class of immunotherapy drugs that have improved the treatment of a broad spectrum of cancers as metastatic melanoma, non-small lung cancer or renal cell carcinoma. These humanized monoclonal antibodies target inhibitory receptors (e.g. CTLA-4, PD-1, LAG-3, TIM-3) and ligands (PD-L1) expressed on T lymphocytes, antigen presenting cells and tumor cells and elicit an anti-tumor response by stimulating immune system. Nevertheless, the improved overall survival is complicated by the manifestation of Immune-related Adverse Effects (irAEs). During treatment with ICIs, the most common adverse kidney effect is represented by the development of acute kidney injury (AKI) with the acute tubulointerstitial nephritis as recurrent histological feature. The mechanisms involved in ICIs-induced AKI include the re-activation of effector T cells previously stimulated by nephrotoxic drugs (i.e. by antibiotics), the loss of tolerance versus self-renal antigens, the increased PD-L1 expression by tubular cells or the establishment of a pro-inflammatory milieu with the release of self-reactive antibodies. For renal transplant recipient treated with ICIs, the increased incidence of rejection is a serious concern. Therefore, the combination of ICIs with mTOR inhibitors represents an emerging strategy. Finally, it is relevant to anticipate which patients under ICIs would experience severe irAEs and from a kidney perspective, to predict patients with higher risk of AKI. Here, we provide a detailed overview of ICIs-related nephrotoxicity and the recently described multicenter studies. Several factors have been reported as biomarkers of ICIs-irAEs, in this review we speculate on potential biomarkers for ICIs-associated AKI.
I.F.: 5,085
N. citazioni = 18

372. Incorvaia L, Fanale D, Badalamenti G, **Porta C**, Olive D, De Luca I, Brando C, Rizzo M, Messina C, Rediti M, Russo A, Bazan V, Iovanna JL. Baseline plasma levels of soluble PD-1, PD-L1, and BTN3A1 predict response to nivolumab treatment in patients with metastatic renal cell carcinoma: a step toward a biomarker for therapeutic decisions. *Oncoimmunology* 2020;9:1832348.

ABSTRACT – Despite a proportion of renal cancer patients can experiment marked and durable responses to immune-checkpoint inhibitors, the treatment efficacy is widely variable and identifying the patient who will benefit from immunotherapy remains an issue. We performed a prospective study to investigate if soluble forms of the immune-checkpoints PD-1 (sPD-1), PD-L1 (sPD-L1), pan-BTN3As, BTN3A1, and BTN2A1, could be candidate to predict the response to immune-checkpoint blockade therapy. We evaluated the plasma levels in a learning cohort of metastatic clear cell renal carcinoma (mccRCC) patients treated with the anti-PD-1 agent nivolumab by ad hoc developed ELISA's. Using specific cut-offs determined through ROC curves, we showed that high baseline levels of sPD-1 (>2.11 ng/ml), sPD-L1 (>0.66 ng/ml), and sBTN3A1 (>6.84 ng/ml) were associated with a longer progression-free survival (PFS) to nivolumab treatment [median PFS, levels above thresholds: sPD-1, 20.7 months ($p < .0001$); sPD-L1, 19 months ($p < .0001$); sBTN3A1, 17.5 months ($p = .002$)]. High sPD-1 and sBTN3A1 levels

were also associated with best overall response by RECIST and objective response of >20%. The results were confirmed in a validation cohort of 20 mccRCC patients. The analysis of plasma dynamic changes after nivolumab showed a statistically significant decrease of sPD-1 after 2 cycles (Day 28) in the long-responder patients. Our study revealed that the plasma levels of sPD-1, sPD-L1, and sBTN3A1 can predict response to nivolumab, discriminating responders from non-responders already at therapy baseline, with the advantages of non-invasive sample collection and real-time monitoring that allow to evaluate the dynamic changes during cancer evolution and treatment.
I.F.: 5,869
N. citazioni = 14

373. Gentile M, Centonza A, Lovero D, Palmirotta R, **Porta C**, Silvestris F, D'Oronzo S. Application of "omics" sciences to the prediction of bone metastases from breast cancer: State of the art. *J Bone Oncol* 2020;26:10033.

ABSTRACT – Breast cancer (BC) is the most frequent malignancy and the first cause of cancer-related death in women. The majority of patients with advanced BC develop skeletal metastases which may ultimately lead to serious complications, termed skeletal-related events, that often dramatically impact on quality of life and survival. Therefore, the identification of biomarkers able to stratify BC patient risk to develop bone metastases (BM) is fundamental to define personalized diagnostic and therapeutic strategies, possibly at the earliest stages of the disease. In this regard, the advent of "omics" sciences boosted the investigation of several putative biomarkers of BC osteotropism, including deregulated genes, proteins and microRNAs. The present review revisits the current knowledge on BM development in BC and the most recent studies exploring potential BM-predicting biomarkers, based on the application of omics sciences to the study of primary breast malignancies.
I.F.: 3,066
N. citazioni = 1

374. Cosmai L, **Porta C**, Foramitti M, Rizzo M, Gallieni M. The basics of onco-nephrology in the renal clinic. *J Nephro*l 2020;33:1143-9.

ABSTRACT – Onconephrology is a rapidly evolving subspecialty that covers all areas of renal involvement in cancer patients. The complexity of the field may benefit from well-defined multidisciplinary management by a dedicated team. Patients with cancer frequently suffer from concurrent chronic kidney disease (CKD), with a prevalence ranging from 12% to 53% at the time of cancer diagnosis. Taking into account the incidence of cancer and the prevalence of CKD in the Italian population, we estimate that about 44,000 patients suffered from both diseases in 2020. Since there is an increasing necessity to address the needs of this population in dedicated outpatient clinics, it is critical to highlight some basic characteristics and to suggest areas of development. Our experience in the nephrological management of cancer patients clearly suggests the need to implement dedicated multidisciplinary teams and to create onconephrology clinics (at least within larger, referral, hospitals). Furthermore, it must be kept in mind that not only is CKD common in cancer patients, but also that the concomitant presence of these two conditions too often excludes cancer patients from clinical trials, thus limiting their access to therapies that could potentially improve their outcomes. Indeed, the Renal Insufficiency and Cancer Medications (IRMA) study found that cancer patients with CKD or on dialysis are often undertreated, or are exposed to either ineffective or toxic anticancer agents. Finally, the aim of this article is to initiate a debate about what an onconephrology outpatient clinic might look like, in order to ensure the highest quality of care for this growing patient population.
I.F.: 3,489

375. Albiges L, Tannir NM, Burotto M, McDermott D, Plimack ER, Barthélémy P, **Porta C**, Powles T, Donskov F, George S, Kollmannsberger CK, Gurney H, Grimm MO, Tomita Y, Castellano D, Rini BI, Choueiri TK, Saggi SS, McHenry MB, Motzer RJ. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open* 2020;5:e001079.

ABSTRACT – Purpose: To report updated analyses of the phase III CheckMate 214 trial with extended minimum follow-up assessing long-term outcomes with first-line nivolumab plus ipilimumab (NIVO+IPI) versus (vs) sunitinib (SUN) in patients with advanced renal cell carcinoma (aRCC). Methods: Patients with aRCC with a clear cell component were stratified by International Metastatic Renal Cell Carcinoma Database Consortium risk and randomised to NIVO (3 mg/kg) plus IPI (1 mg/kg) every three weeks ×4 doses, followed by NIVO (3 mg/kg) every two weeks; or SUN (50 mg) once per day ×4 weeks (6-week cycle). Efficacy endpoints included overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) per independent radiology review committee in patients with intermediate/poor-risk disease (I/P; primary), intent-to-treat patients (ITT; secondary) and in patients with favourable-risk disease (FAV; exploratory). Results: Overall, 1096 patients were randomised (ITT: NIVO+IPI, n=550, SUN, n=546; I/P: NIVO+IPI, n=425, SUN, n=422; FAV: NIVO+IPI, n=125, SUN, n=124). After 4 years minimum follow-up, OS (HR; 95% CI) remained superior with NIVO+IPI vs SUN in ITT (0.69; 0.59 to 0.81) and I/P patients (0.65; 0.54 to 0.78). Four-year PFS probabilities were 31.0% vs 17.3% (ITT) and 32.7% vs 12.3% (I/P), with NIVO+IPI vs SUN. ORR remained higher with NIVO+IPI vs SUN in ITT (39.1% vs 32.4%) and I/P (41.9% vs 26.8%) patients. In FAV patients, the HRs (95% CI) for OS and PFS were 0.93 (0.62 to 1.40) and 1.84 (1.29 to 2.62); ORR was lower with NIVO+IPI vs SUN. However, more patients in all risk groups achieved complete responses with NIVO+IPI: ITT (10.7% vs 2.6%), I/P (10.4% vs 1.4%) and FAV (12.0% vs 6.5%). Probability (95% CI) of response ≥4 years was higher with NIVO+IPI vs SUN (ITT, 59% (0.51 to 0.66) vs 30% (0.21 to 0.39); I/P, 59% (0.50 to 0.67) vs 24% (0.14 to 0.36); and FAV, 60% (0.41 to 0.75) vs 38% (0.22 to 0.54)) regardless of risk category. Safety remained favourable with NIVO+IPI vs SUN. Conclusion: After long-term follow-up, NIVO+IPI continues to demonstrate durable efficacy benefits vs SUN, with manageable safety.
I.F.: 5,329
N. citazioni = 102

376. Mantovani S, Varchetta S, Mele D, Donadon M, Torzilli G, Soldani C, Franceschini B, **Porta C**, Chiellino S, Pedrazzoli P, Santambrogio R, Barabino M, Cigala C, Piccolo G, Opocher E, Maestri M, Sangiovanni A, Bernuzzi S, Lhospice F, Kraiem M, Mondelli MU, Oliviero B. An anti-MICA/B antibody and IL-15 rescue altered NKG2D-dependent NK cell responses in hepatocellular carcinoma. *Cancers (Basel)* 2020;12:3583.

ABSTRACT – Natural killer (NK) cells play a pivotal role in cancer immune surveillance, and activating the receptor/ligand interaction may contribute to control the development and evolution of hepatocellular carcinoma (HCC). We investigated the role of the natural killer group 2 member D (NKG2D) activating receptor and its ligand, the major histocompatibility complex class I chain-related protein A and B (MICA/B) in patients with cirrhosis and HCC subjected to surgical resection, patients with cirrhosis and no HCC, and healthy donors (HD). The NKG2D-mediated function was determined in peripheral blood (PB), in tumor-infiltrating lymphocytes (NK-TIL), and in matched surrounding liver tissue (NK-LIL). A group of patients treated with sorafenib because of clinically advanced HCC was also studied. A humanized anti-MICA/B monoclonal antibody (mAb) was used in in vitro experiments to examine NK cell-mediated antibody-dependent cellular cytotoxicity. Serum concentrations of soluble MICA/B were evaluated by ELISA. IL-15 stimulation increased NKG2D-dependent activity which, however, remained dysfunctional in PB NK cells from HCC patients, in line with the reduced NKG2D expression on NK cells. NK-TIL showed a lower degranulation ability than NK-LIL, which was restored by IL-15 stimulation. Moreover, in vitro IL-15 stimulation enhanced degranulation and interferon-γ production by PB NK from patients at month one of treatment with sorafenib. Anti-MICA/B mAb associated with IL-15 was able to induce PB NK cytotoxicity for primary HCC cells in HD and patients with HCC, who also showed NK-TIL degranulation for autologous primary HCC cells. Our findings highlight the key role of the NKG2D-MICA/B axis in the regulation of NK cell responses in HCC and provide evidence in support of a potentially important role of anti-MICA/B mAb and IL-15 stimulation in HCC immunotherapy.
I.F.: 6,126
N. citazioni = 5

377. Małyszko J, Bamias A, Danesh FR, Dębska-Ślizień A, Gallieni M, Gertz MA, Kielstein JT, Tesarova P, Wong G, Cheung M, Wheeler DC, Winkelmayer WC, **Porta C**. KDIGO Controversies Conference on onco-nephrology: kidney disease in hematological malignancies and the burden of cancer after kidney transplantation. *Kidney Int* 2020;98:1407-1418.

ABSTRACT – The bidirectional relationship between cancer and chronic kidney disease (CKD) is complex. Patients with cancer, particularly those with hematological malignancies such as multiple myeloma and lymphoma, are at increased risk of developing acute kidney injury and CKD. On the other hand, emerging evidence from large observational registry analyses have consistently shown that cancer risk is increased by at least 2- to 3-fold in kidney transplant recipients, and the observed increased risk occurs not only in those who have received kidney transplants but also in those on dialysis and with mild- to moderate-stage CKD. The interactions between cancer and CKD have raised major therapeutic and clinical challenges in the management of these patients. Given the magnitude of the problem and uncertainties, and current controversies within the existing evidence, Kidney Disease: Improving Global Outcomes (KDIGO) assembled a global panel of multidisciplinary clinical and scientific expertise for a controversies conference on onco-nephrology to identify key management issues in nephrology relevant to patients with malignancy. This report covers the discussed controversies in kidney disease in hematological malignancies, as well as cancer after kidney transplantation. An overview of future research priorities is also discussed.
I.F.: 8,945
N. citazioni = 4

378. Montemagno C, Hagege A, Borchiellini D, Thamphya B, Rastoin O, Ambrosetti D, Iovanna J, Rioux-Leclercq N, **Porta C**, Negrier S, Ferrero JM, Chamorey E, Pagès G, Dufies M. Soluble forms of PD-L1 and PD-1 as prognostic and predictive markers of sunitinib efficacy in patients with metastatic clear cell renal cell carcinoma. *Oncoimmunology* 2020;9:1846901.

ABSTRACT – Metastatic clear cell renal cell carcinoma (mccRCC) benefits from several treatment options in the first-line setting with VEGFR inhibitors and/or immunotherapy including anti-PD-L1 or anti-PD1 agents. Identification of predictive biomarkers is highly needed to optimize patient care. Circulating markers could reflect the biology of metastatic disease. Therefore, we evaluated soluble forms of PD-L1 (sPD-L1) and PD-1 (sPD-1) in mccRCC patients. The levels of sPD-L1 and sPD-1 were evaluated from plasma samples of mccRCC patients before they received a first-line treatment (T0) by the VEGFR inhibitor sunitinib (50 patients) or by the anti-VEGF bevacizumab (37 patients). The levels of sPD-L1 and sPD-1 were correlated to clinical parameters and progression-free survival (PFS). High levels of sPD-1 or sPDL1 were not correlated to PFS under bevacizumab while they were independent prognostic factors of PFS in the sunitinib group. Patients with high T0 plasmatic levels of sPD-L1 had a shorter PFS (11.3 vs 22.5 months, p = .011) in the sunitinib group. Equivalent shorter PFS was found with high levels of sPD-1 (8.6 vs 14.1 months, p = .009). mccRCC patients with high plasmatic levels of sPD-L1 or sPD-1 are poor responders to sunitinib. sPD-L1 or sPD-1 could be a valuable tool to guide the optimal treatment strategy including VEGFR inhibitor.
I.F.: 5,869
N. citazioni = 11

379. Lucarelli G, Ferro M, Loizzo D, Bianchi C, Terracciano D, Cantiello F, Bell LN, Battaglia S, **Porta C**, Gernone A, Perego RA, Maiorano E, Cobelli O, Castellano G, Vincenti L, Ditonno P, Battaglia M. Integration of lipidomics and transcriptomics reveals reprogramming of the lipid metabolism and composition in clear cell renal cell carcinoma. *Metabolites* 2020;10:509.

ABSTRACT – Clear cell renal cell carcinoma (ccRCC) is fundamentally a metabolic disease. Given the importance of lipids in many cellular processes, in this study we delineated a lipidomic profile of human ccRCC and integrated it with transcriptomic data to connect the variations in cancer lipid metabolism with gene expression changes. Untargeted lipidomic analysis was performed on 20 ccRCC and 20 paired normal tissues, using LC-MS and GC-MS. Different lipid classes were altered in cancer compared to normal tissue. Among the long chain fatty acids (LCFAs), significant accumulations of polyunsaturated fatty acids (PUFAs) were found. Integrated lipidomic and transcriptomic analysis showed that fatty acid desaturation and elongation pathways were enriched in neoplastic tissue. Consistent with these findings, we observed increased expression of stearoyl-CoA desaturase(SCD1) and FA elongase 2 and 5 in ccRCC. Primary renal cancer cells treated with a small molecule SCD1 inhibitor (A939572) proliferated at a slower rate than untreated cancer cells. In addition, after cisplatin treatment, the death rate of tumor cells treated with A939572 was significantly greater than that of untreated cancer cells. In conclusion, our findings delineate a ccRCC lipidomic signature and showed that SCD1 inhibition significantly reduced cancer cell proliferation and increased cisplatin sensitivity, suggesting that this pathway

can be involved in ccRCC chemotherapy resistance.
I.F.: 4,097
N. citazioni = 13

380. Santoni M, Piva F, Cimadamore A, Giulietti M, Battelli N, Montironi R, Cosmai L, **Porta C**. Exploring the spectrum of kidney ciliopathies. *Diagnostics (Basel)* 2020 Dec 16;10:1099.

ABSTRACT – Ciliopathies are a group of multi-organ diseases caused by the disruption of the primary cilium. This event leads to a variety of kidney disorders, including nephronophthisis, renal cystic dysplasia, and renal cell carcinoma (RCC). Primary cilium contributes to the regulation of the cell cycle and protein homeostasis, that is, the balance between protein synthesis and degradation by acting on the ubiquitin-proteasome system, autophagy, and mTOR signaling. Many proteins are involved in renal ciliopathies. In particular, fibrocystin (PKHD1) is involved in autosomal recessive polycystic kidney disease (ARPKD), while polycystin-1 (PKD1) and polycystin-2 (PKD2) are implicated in autosomal dominant polycystic kidney disease (ADPKD). Moreover, primary cilia are associated with essential signaling pathways, such as Hedgehog, Wnt, and Platelet-Derived Growth Factor (PDGF). In this review, we focused on the ciliopathies associated with kidney diseases, exploring genes and signaling pathways associated with primary cilium and the potential role of cilia as therapeutic targets in renal disorders.
I.F.: 3,706
N. citazioni = 1

381. Fusaro M, Gallieni M, **Porta C**, Nickolas TL, Khairallah P. Vitamin K effects in human health: new insights beyond bone and cardiovascular health. *J Nephrol* 2020;33:239-49.

ABSTRACT – Vitamin K is a cofactor for the function of the enzyme γ-glutamyl carboxylase, necessary for the activation of multiple vitamin K dependent-proteins. Vitamin K dependent-proteins (VKDPs) have important roles in bone health, vascular health, metabolism, reproduction as well as in cancer progression. Vitamin K deficiency is common in different conditions, including kidney disease, and it may influence the activity of VKDPs. This review discusses vitamin K status in human health and the physiologic and pathologic roles of VKDPs, beyond the established effects in skeletal and cardiovascular health.
I.F.: 3,902
N. citazioni = 20 + 1 (da: Correction to)

382. Cosmai L, **Porta C**, Foramitti M, Perrone V, Mollica L, Gallieni M, Capasso G. Preventive strategies for acute kidney injury in cancer patients. *Clin Kidney J* 2020;14:70-83.

ABSTRACT – Acute kidney injury (AKI) is a common complication of cancer that occurs in up to 50% of neoplastic patients during the natural history of their disease; furthermore, it has a huge impact on key outcomes such as overall prognosis, length of hospitalization and costs. AKI in cancer patients has different causes, either patient-, tumour- or treatment-related. Patient-related risk factors for AKI are the same as in the general population, whereas tumour-related risk factors are represented by compression, obstruction, direct kidney infiltration from the tumour as well by precipitation, aggregation, crystallization or misfolding of paraprotein (as in the case of multiple myeloma). Finally, treatment-related risk factors are the most common observed in clinical practice and may present also with the feature of tumour lysis syndrome or thrombotic microangiopathies. In the absence of validated biomarkers, a multidisciplinary clinical approach that incorporates adequate assessment, use of appropriate preventive measures and early intervention is essential to reduce the incidence of this life-threatening condition in cancer patients.
I.F.: 3,388
N. citazioni = 6

383. Aeppli S, Schmaus M, Eisen T, Escudier B, Grünwald V, Larkin J, McDermott D, Oldenburg J, **Porta C**, Rini BI, Schmidinger M, Sternberg CN, Rothermundt C, Putora PM. First-line treatment of metastatic clear cell renal cell carcinoma: a decision-making analysis among experts. *ESMO Open* 2021;6:100030.

ABSTRACT – Background: The treatment landscape of metastatic clear cell renal cell carcinoma (mccRCC) has been transformed by targeted therapies with tyrosine kinase inhibitors (TKI) and more recently by the incorporation of immune checkpoint inhibitors (ICI). Today, a spectrum of single agent TKI to TKI/ICI and ICI/ICI combinations can be considered and the choice of the best regimen is complex. Materials and methods: We performed an updated decision-making analysis among 11 international kidney cancer experts. Each expert provided their treatment strategy and relevant decision criteria in the first line treatment of mccRCC. After the collection of all input a list of unified decision criteria was determined and compatible decision trees were created. We used a methodology based on diagnostic nodes, which allows for an automated cross-comparison of decision trees, to determine the most common treatment recommendations as well as deviations. Results: Diverse parameters were considered relevant for treatment selection, various drugs and drug combinations were recommended by the experts. The parameters, chosen by the experts, were performance status, International Metastatic renal cell carcinoma Database Consortium (IMDC) risk group, PD-L1 status, zugzwang and contraindication to immunotherapy. The systemic therapies selected for first line treatment were sunitinib, pazopanib, tivozanib, cabozantinib, ipilimumab/nivolumab or pembrolizumab/axitinib. Conclusion: A wide spectrum of treatment recommendations based on multiple decision criteria was demonstrated. Significant inter-expert variations were observed. This demonstrates how data from randomized trials are implemented differently when transferred into daily practice.
I.F.: 6,883
N. citazioni = 17

384. Rini BI, Motzer RJ, Powles T, McDermott DF, Escudier B, Donskov F, Hawkins R, Bracarda S, Bedke J, De Giorgi U, **Porta C**, Ravaud A, Parnis F, Grande E, Zhang W, Huseni M, Carroll S, Sufan R, Schiff C, Atkins MB. Atezolizumab plus Bevacizumab versus Sunitinib for patients with untreated metastatic renal cell carcinoma and sarcomatoid features: a prespecified subgroup analysis of the IMmotion151 clinical trial. *Eur Urol* 2021;79:659-62.

ABSTRACT – Patients with metastatic renal cell carcinoma with sarcomatoid features (sRCC) have a poor prognosis and have shown limited responsiveness to inhibition of the VEGF pathway. We conducted a prespecified analysis of the randomised, phase 3 IMmotion151 trial in previously untreated patients with advanced or metastatic RCC to assess

the effectiveness of atezolizumab + bevacizumab versus sunitinib in a subgroup of patients with sarcomatoid features. Patients whose tumour had any component of sarcomatoid features were included and received atezolizumab + bevacizumab (n = 68) or sunitinib (n = 74). Baseline characteristics were similar between the groups. Median progression-free survival was significantly longer in the group receiving atezolizumab + bevacizumab overall (8.3 vs 5.3 mo; hazard ratio [HR] 0.52 95% confidence interval [CI] 0.34-0.79) and in the subset of patients with PD-L1-positive tumours (8.6 vs 5.6 mo; HR 0.45, 95% CI 0.26-0.77). More patients receiving atezolizumab + bevacizumab achieved an objective response (49% vs 14%), including complete responses (10% vs 3%), and reported greater symptom improvements versus sunitinib. Safety was consistent with the known profiles of each drug and with that reported in the overall safety-evaluable population of IMmotion151. This analysis supports enhanced activity of atezolizumab + bevacizumab in patients with sRCC. PATIENT SUMMARY: In this report, we looked at patients with a specific type of kidney cancer (tumours with sarcomatoid features) that has been hard to treat. A treatment with two drugs (atezolizumab and bevacizumab) appeared to help patients live longer without the disease getting worse than another drug (sunitinib) that is often used. Patients who took the two drugs also said they were better able to carry out their everyday activities than patients who took sunitinib. The combination of these two drugs may work better in patients with this type of advanced kidney cancer.

I.F.: 24,267
N. citazioni = 25

385. Del Re M, Cucchiara F, Rofi E, Fontanelli L, Petrini I, Gri N, Pasquini G, Rizzo M, Gabelloni M, Belluomini L, Crucitta S, Ciampi R, Frassoldati A, Neri E, **Porta C**, Danesi R. A multiparametric approach to improve the prediction of response to immunotherapy in patients with metastatic NSCLC. *Cancer Immunol Immunother* 2021;70:1667-78.

*ABSTRACT – Background: It is still unclear how to combine biomarkers to identify patients who will truly benefit from anti-PD-1 agents in NSCLC. This study investigates exosomal mRNA expression of PD-L1 and IFN-γ, PD-L1 polymorphisms, tumor mutational load (TML) in circulating cell-free DNA (cfDNA) and radiomic features as possible predictive markers of response to nivolumab and pembrolizumab in metastatic NSCLC patients. Methods: Patients were enrolled and blood (12 ml) was collected at baseline before receiving anti-PD-1 therapy. Exosome-derived mRNA and cfDNA were extracted to analyse PD-L1 and IFN-γ expression and tumor mutational load (TML) by digital droplet PCR (ddPCR) and next-generation sequencing (NGS), respectively. The PD-L1 single nucleotide polymorphisms (SNPs) c.-14-368 T > C and c.*395G > C, were analysed on genomic DNA by Real-Time PCR. A radiomic analysis was performed on the QUIBIM Precision® V3.0 platform. Results: Thirty-eight patients were enrolled. High baseline IFN-γ was independently associated with shorter median PFS (5.6 months vs. not reached p = 0.0057), and levels of PD-L1 showed an increase at 3 months vs. baseline in patients who progressed (p = 0.01). PD-L1 baseline levels showed significant direct and inverse relationships with radiomic features. Radiomic features also inversely correlated with PD-L1 expression in tumor tissue. In subjects receiving nivolumab, median PFS was shorter in carriers of c.*395GG vs. c.*395GC/CC genotype (2.3 months vs. not reached, p = 0.041). Lastly, responders had higher non-synonymous mutations and more links between co-occurring genetic somatic mutations and ARID1A alterations as well. Conclusions: A combined multiparametric approach may provide a better understanding of the molecular determinants of response to immunotherapy.*

I.F.: 6,63
N. citazioni = 7

386. Dudani S, de Velasco G, Wells JC, Gan CL, Donskov F, **Porta C**, Fraccon A, Pasini F, Lee JL, Hansen A, Bjarnason GA, Beuselinck B, Pal SK, Yuasa T, Kroeger N, Kanesvaran R, Reaume MN, Canil C, Choueiri TK, Heng DYC. Evaluation of clear cell, papillary, and chromophobe renal cell carcinoma metastasis sites and association with survival. *JAMA Netw Open* 2021;4:e2021869.

ABSTRACT – Importance: There exists considerable biological and clinical variability between histologic variants of metastatic renal cell carcinoma (mRCC). Data reporting on patterns of metastasis in histologic variants of mRCC are sparse. Objective: To characterize sites of metastasis and their association with survival across the 3 most common histologic variants of mRCC: clear cell (ccRCC), papillary (pRCC), and chromophobe (chrRCC). Design, setting, and participants: In this multicenter, international cohort study, the International mRCC Database Consortium (IMDC) database was used to identify consecutive patients starting systemic therapy for mRCC between 2002 and 2019. Patients with mixed histologic subtype were excluded. Statistical analysis was performed from February to June 2020. Exposures: Data regarding histologic subtype and sites of metastatic involvement at the time of first systemic therapy initiation were collected. Main outcomes and measures: The primary outcomes were prevalence of metastatic site involvement and overall survival (OS) from time of systemic therapy initiation. Patients with multiple sites of metastatic involvement were included in analyses of all groups to which they had metastases. Results: A total of 10 105 patients were eligible for analysis. Median (interquartile range) age at diagnosis was 60 (53-67) years, 7310 (72.4%) were men and 8526 (84.5%) underwent nephrectomy. Of these, 9252 (92%) had ccRCC, 667 (7%) had pRCC, and 186 (2%) had chrRCC. The median number of sites of metastasis was 2 (range, 0-7). In ccRCC, the most common sites of metastasis were lung (70%; 6189 of 8804 patients [448 missing]), lymph nodes (45%; 3874 of 8655 patients [597 missing]), bone (32%; 2847 of 8817 patients [435 missing]), liver (18%; 1560 of 8804 [448 missing]), and adrenal gland (10%; 678 of 6673 patients [2579 missing]). Sites of metastasis varied between subtypes. Lung, adrenal, brain, and pancreatic metastases were more frequent in ccRCC, lymph node involvement was more common in pRCC, and liver metastases were more frequent in chrRCC. Median OS for ccRCC varied by site of metastatic involvement, ranging between 16 months (95% CI, 13.7-18.8 months) for the pleura and 50 months (95% CI, 41.1-55.5 months) for the pancreas. Compared with ccRCC, patients with pRCC tended to have lower OS, regardless of metastatic site. Conclusions and relevance: Sites of metastatic involvement differ according to histologic subtype in mRCC and are associated with OS. These data highlight the clinical and biological variability between histologic subtypes of mRCC. Patterns of metastatic spread may reflect differences in underlying disease biology. Further work to investigate differences in immune, molecular, and genetic profiles between metastatic sites and histologic subtypes is encouraged.

II.F.: 13,353
N. citazioni = 18

387. Mosca A, De Giorgi U, Procopio G, Basso U, Cartenì G, Bersanelli M, Naglieri E, Galli L, Caffo O, Fornarini G, Boccardo F, **Porta C**. An Italian, multicenter, real-world, retrospective study of first-line pazopanib in unselected

metastatic renal-cell carcinoma patients: the 'Pamerit' study. *Jpn J Clin Oncol* 2021;51:484-91.

ABSTRACT – Objective: Despite the current immunotherapy era, VEGFR inhibitors maintain effectiveness in metastatic renal cell cancer. Real-world data concerning pazopanib are limited. The aim of this study is to add information about efficacy and safety of pazopanib as first-line treatment in metastatic renal cell cancer patients not enrolled into clinical trials. Methods: Retrospective analysis (the PAMERIT study) of first-line pazopanib in real-world metastatic renal cell cancer patients among 39 Centers in Italy. Outcomes were progression-free survival, overall survival, objective response rate and treatment-related adverse events. Kaplan-Meier curves, log-rank test and multivariable Cox's models were used and adjusted for age, histology, previous renal surgery, International Metastatic RCC Database Consortium score and pazopanib initial dose. Results: Among 474 patients, 87.3% had clear cell metastatic renal cell cancer histology. Most of them (84.6%) had upfront renal surgery. Median progression-free survival and overall survival were 15.8 and 34.4 months, respectively, significantly correlating with International Metastatic RCC Database Consortium's good prognosis (P < 0.001), ECOG PS 0 (P < 0.001), age (<75 years, P = 0.005), surgery (P < 0.001) and response to pazopanib (P < 0.001). After 3 months of pazopanib, overall disease control rate have been observed in 76.6% patients. Among International Metastatic RCC Database Consortium's favorable group patients, 57/121 (47%) showed complete/partial response. No unexpected AEs emerged. Conclusions: In this real-world study, metastatic renal cell cancer patients treated with first-line pazopanib reached greater progression-free survival and overall survival than in pivotal studies and had high response rates when belonging to International Metastatic RCC Database Consortium's favorable group, without new toxicities. Pazopanib has been confirmed a valid first-line option for International Metastatic RCC Database Consortium's good prognosis metastatic renal cell cancer patients who cannot be submitted to immunotherapy.
I.F.: 2,925
N. citazioni = 1

388. Santoni M, Piva F, **Porta C**, Bracarda S, Heng DY, Matrana MR, Grande E, Mollica V, Aurilio G, Rizzo M, Giulietti M, Montironi R, Massari F. Artificial neural networks as a way to predict future kidney cancer incidence in the United States. *Clin Genitourin Cancer* 2021;19:e84-91.

ABSTRACT – Introduction: The incidence of kidney cancer is increasing; it could be counteracted with new ways to predict and detect it. We aimed to implement an artificial neural network in order to predict new cases of renal-cell carcinoma (RCC) in the population using population rate, obesity, smoking incidence, uncontrolled hypertension, and life expectancy data in the United States. Patients and methods: Statistics were collected on US population numbers, life expectancy, obesity, smoking, and hypertension. We used MATLAB R2018 (MathWorks) software to implement an artificial neural network. Data were repeatedly and randomly divided into training (70%) and validation (30%) subsets. Results: The number of new RCC cases will grow from 44,400 (2020) to 55,400 (2050), an increase of +24.7%. Our data show that preventing hypertension would have the greatest impact on reduction of the incidence, estimated at -775 and -575 cases per year in 2020 and in 2030, respectively. The prevention of obesity and smoking would have a more limited impact, estimated at -64 and -180 cases per year in 2020 and in 2030, respectively, for obesity, and -173 and -21 cases per year in 2020 and in 2030, respectively, for smoking. Conclusions: Our predictions underline the need for accurate studies on RCC-related risk factors to reduce the incidence.
I.F.: 3,121
N. citazioni = 7

389. Guida A, Sabbatini R, Gibellini L, De Biasi S, Cossarizza A, **Porta C**. Finding predictive factors for immunotherapy in metastatic renal-cell carcinoma: what are we looking for? *Cancer Treat Rev* 2021;94:102157.

ABSTRACT – A major breakthrough in cancer immunotherapy was the development of monoclonal antibodies targeting inhibitory immune checkpoint proteins. This approach demonstrated significant antitumor activity and efficacy in different cancer types, including metastatic renal cell carcinoma (mRCC). In the majority of patients, this drug is able to restore the patient's tumour-specific T-cell-mediated response thus improving both overall survival and objective response rate. However, a lack of clinical response occurs in a number of patients, raising questions about how to predict and increase the number of patients who receive long-term clinical benefit from immune checkpoint therapy or not. The aim of this review is to summarize available data about immune biomarkers in patients with mRCC treated with immunotherapy.
I.F.: 13,608
N. citazioni = 1

390. Motzer R, Alekseev B, Rha SY, **Porta C**, Eto M, Powles T, Grünwald V, Hutson TE, Kopyltsov E, Méndez-Vidal MJ, Kozlov V, Alyasova A, Hong SH, Kapoor A, Alonso Gordoa T, Merchan JR, Winquist E, Maroto P, Goh JC, Kim M, Gurney H, Patel V, Peer A, Procopio G, Takagi T, Melichar B, Rolland F, De Giorgi U, Wong S, Bedke J, Schmidinger M, Dutcus CE, Smith AD, Dutta L, Mody K, Perini RF, Xing D, Choueiri TK; CLEAR Trial Investigators. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med* 2021;384:1289-300.

*ABSTRACT – **Background**: Lenvatinib in combination with pembrolizumab or everolimus has activity against advanced renal cell carcinoma. The efficacy of these regimens as compared with that of sunitinib is unclear. Methods: In this phase 3 trial, we randomly assigned (in a 1:1:1 ratio) patients with advanced renal cell carcinoma and no previous systemic therapy to receive lenvatinib (20 mg orally once daily) plus pembrolizumab (200 mg intravenously once every 3 weeks), lenvatinib (18 mg orally once daily) plus everolimus (5 mg orally once daily), or sunitinib (50 mg orally once daily, alternating 4 weeks receiving treatment and 2 weeks without treatment). The primary end point was progression-free survival, as assessed by an independent review committee in accordance with Response Evaluation Criteria in Solid Tumors, version 1.1. Overall survival and safety were also evaluated. Results: A total of 1069 patients were randomly assigned to receive lenvatinib plus pembrolizumab (355 patients), lenvatinib plus everolimus (357), or sunitinib (357). Progression-free survival was longer with lenvatinib plus pembrolizumab than with sunitinib (median, 23.9 vs. 9.2 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.32 to 0.49; P<0.001) and was longer with lenvatinib plus everolimus than with sunitinib (median, 14.7 vs. 9.2 months; hazard ratio, 0.65; 95% CI, 0.53 to 0.80; P<0.001). Overall survival was longer with lenvatinib plus pembro-*

lizumab than with sunitinib (hazard ratio for death, 0.66; 95% CI, 0.49 to 0.88; P = 0.005) but was not longer with lenvatinib plus everolimus than with sunitinib (hazard ratio, 1.15; 95% CI, 0.88 to 1.50; P = 0.30). Grade 3 or higher adverse events emerged or worsened during treatment in 82.4% of the patients who received lenvatinib plus pembrolizumab, 83.1% of those who received lenvatinib plus everolimus, and 71.8% of those who received sunitinib. Grade 3 or higher adverse events occurring in at least 10% of the patients in any group included hypertension, diarrhea, and elevated lipase levels. Conclusions: Lenvatinib plus pembrolizumab was associated with significantly longer progression-free survival and overall survival than sunitinib.

I.F.: 176,079

N. citazioni = 231

391. Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, Oyervides Juárez VM, Hsieh JJ, Basso U, Shah AY, Suárez C, Hamzaj A, Goh JC, Barrios C, Richardet M, **Porta C**, Kowalyszyn R, Feregrino JP, Żołnierek J, Pook D, Kessler ER, Tomita Y, Mizuno R, Bedke J, Zhang J, Maurer MA, Simsek B, Ejzykowicz F, Schwab GM, Apolo AB, Motzer RJ; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2021;384:829-41.

ABSTRACT – Background: The efficacy and safety of nivolumab plus cabozantinib as compared with those of sunitinib in the treatment of previously untreated advanced renal-cell carcinoma are not known. Methods: In this phase 3, randomized, open-label trial, we randomly assigned adults with previously untreated clear-cell, advanced renal-cell carcinoma to receive either nivolumab (240 mg every 2 weeks) plus cabozantinib (40 mg once daily) or sunitinib (50 mg once daily for 4 weeks of each 6-week cycle). The primary end point was progression-free survival, as determined by blinded independent central review. Secondary end points included overall survival, objective response as determined by independent review, and safety. Health-related quality of life was an exploratory end point. Results: Overall, 651 patients were assigned to receive nivolumab plus cabozantinib (323 patients) or sunitinib (328 patients). At a median follow-up of 18.1 months for overall survival, the median progression-free survival was 16.6 months (95% confidence interval [CI], 12.5 to 24.9) with nivolumab plus cabozantinib and 8.3 months (95% CI, 7.0 to 9.7) with sunitinib (hazard ratio for disease progression or death, 0.51; 95% CI, 0.41 to 0.64; P<0.001). The probability of overall survival at 12 months was 85.7% (95% CI, 81.3 to 89.1) with nivolumab plus cabozantinib and 75.6% (95% CI, 70.5 to 80.0) with sunitinib (hazard ratio for death, 0.60; 98.89% CI, 0.40 to 0.89; P = 0.001). An objective response occurred in 55.7% of the patients receiving nivolumab plus cabozantinib and in 27.1% of those receiving sunitinib (P<0.001). Efficacy benefits with nivolumab plus cabozantinib were consistent across subgroups. Adverse events of any cause of grade 3 or higher occurred in 75.3% of the 320 patients receiving nivolumab plus cabozantinib and in 70.6% of the 320 patients receiving sunitinib. Overall, 19.7% of the patients in the combination group discontinued at least one of the trial drugs owing to adverse events, and 5.6% discontinued both. Patients reported better health-related quality of life with nivolumab plus cabozantinib than with sunitinib. Conclusions: Nivolumab plus cabozantinib had significant benefits over sunitinib with respect to progression-free survival, overall survival, and likelihood of response in patients with previously untreated advanced renal-cell carcinoma.

I.F.: 176,079

N. citazioni = 247

392. **Porta C**, Cosmai L, Rizzo M. Individualizing renal cell carcinoma treatment through biomarkers discovery in the era of immune checkpoint inhibitors: where do we stand? *Curr Opin Urol* 2021;31:236-41.

ABSTRACT – Purpose of review: The treatment landscape of metastatic renal cell carcinoma has greatly evolved over the past fifteen years, leading to a significant improvement in the outcome of our patients. However, there is still an urgent need for predictive biomarkers that could guide our treatment selection, especially in the present era of immune-based treatments. Recent findings: A number of putative biomarkers of immunotherapy activity have been proposed over the past few years, including PD-L1 immunohistochemical expression, tumor mutational burden, neoantigens load, insertions and deletions, complex gene signatures, as well as lymphocytic subpopulations (either circulating or tumor-infiltrating). However, despite preliminary intriguing findings, no biomarker for immune checkpoint activity has emerged so far, that could be used in everyday clinical practice, mainly due to preliminary, or frankly, conflicting results. Summary: The quest for an 'ideal' biomarker, which should be characterized by adequate specificity, sensibility, predictive (and not just prognostic) value, robustness, reproducibility, ease of evaluation and low cost, is still ongoing.

I.F.: 2,808

N. citazioni = 1

393. Internò V, De Santis P, Stucci LS, Rudà R, Tucci M, Soffietti R, **Porta C**. Prognostic factors and current treatment strategies for renal cell carcinoma metastatic to the brain: an overview. *Cancers (Basel)* 2021;13:2114.

ABSTRACT – Renal cell carcinoma (RCC) is one of primary cancers that frequently metastasize to the brain. Brain metastasis derived from RCC has the propensity of intratumoral hemorrhage and relatively massive surrounding edema. Moreover, it confers a grim prognosis in a great percentage of cases with a median overall survical (mOS) around 10 months. The well-recognized prognostic factors for brain metastatic renal cell carcinoma (BMRCC) are Karnofsky Performance Status (KPS), the number of brain metastasis (BM), the presence of a sarcomatoid component and the presence of extracranial metastasis. Therapeutic strategies are multimodal and include surgical resection, radiotherapy, such as stereotactic radiosurgery due to the radioresistance of RCC and systemic strategies with tyrosin kinase inhibitors (TKI) or Immune checkpoint inhibitors (ICI) whose efficacy is not well-established in this setting of patients due to their exclusion from most clinical trials. To date, in case of positive prognostic factors and after performing local radical therapies, such as complete resection of BM or stereotactic radiosurgery (SRS), the outcome of these patients significantly improves, up to 33 months in some patients. As a consequence, tailored clinical trials designed for BMRCC are needed to define the correct treatment strategy even in this poor prognostic subgroup of patients.

I.F.: 6,575

N. citazioni = 2

394. Rebuzzi SE, Signori A, Banna GL, Maruzzo M, De Giorgi U, Pedrazzoli P, Sbrana A, Zucali PA, Masini C, Naglieri E, Procopio G, Merler S, Tomasello L, Fratino L, Baldessari C, Ricotta R, Panni S, Mollica V, Sorarù M, Santoni M, Cortellini A, Prati V, Soto Parra HJ, Stellato M,

Atzori F, Pignata S, Messina C, Messina M, Morelli F, Prati G, Nolè F, Vignani F, Cavo A, Roviello G, Pierantoni F, Casadei C, Bersanelli M, Chiellino S, Paolieri F, Perrino M, Brunelli M, Iacovelli R, **Porta C**, Buti S, Fornarini G. Inflammatory indices and clinical factors in metastatic renal cell carcinoma patients treated with nivolumab: the development of a novel prognostic score (Meet-URO 15 study). *Ther Adv Med Oncol* 2021;13:17588359211019642.

ABSTRACT – Background: Despite the survival advantage, not all metastatic renal cell carcinoma (mRCC) patients achieve a long-term benefit from immunotherapy. Moreover, the identification of prognostic biomarkers is still an unmet clinical need. Methods: This multicenter retrospective study investigated the prognostic role of peripheral-blood inflammatory indices and clinical factors to develop a novel prognostic score in mRCC patients receiving at least second-line nivolumab. The complete blood count before the first cycle of therapy was assessed by calculating neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic inflammation index (SII), and systemic inflammation response index (SIRI). Clinical factors included pre-treatment International Metastatic RCC Database Consortium (IMDC) score, line of therapy, and metastatic sites. Results: From October 2015 to November 2019, 571 mRCC patients received nivolumab as second- and further-line treatment in 69% and 31% of cases. In univariable and multivariable analyses all inflammatory indices, IMDC score, and bone metastases significantly correlated with overall survival (OS). The multivariable model with NLR, IMDC score, and bone metastases had the highest c-index (0.697) and was chosen for the developing of the score (Schneeweiss scoring system). After internal validation (bootstrap re-sampling), the final index (Meet-URO score) composed by NLR, IMDC score, and bone metastases had a c-index of 0.691. It identified five categories with distinctive OSs: group 1 (median OS - mOS = not reached), group 2 (mOS = 43.9 months), group 3 (mOS = 22.4 months), group 4 (mOS = 10.3 months), and group 5 (mOS = 3.2 months). Moreover, the Meet-URO score allowed for a fine risk-stratification across all three IMDC groups. Conclusion: The Meet-URO score allowed for the accurate stratification of pretreated mRCC patients receiving nivolumab and is easily applicable for clinical practice at no additional cost. Future steps include its external validation, the assessment of its predictivity, and its application to first-line combinations.

I.F.: 5,485

N. citazioni = 9

395. Pezzicoli G, Moscaritolo F, Silvestris E, Silvestris F, Cormio G, **Porta C**, D'Oronzo S. Uterine carcinosarcoma: An overview. *Crit Rev Oncol Hematol* 2021;163:103369.

ABSTRACT – Uterine carcinosarcoma (UCS), also known as malignant mixed Müllerian tumor, is a rare gynecological malignancy characterized by poor prognosis. This "biphasic" neoplasm presents an admixture of epithelial and mesenchymal/sarcomatoid tumor cells which partially share their molecular signature and exhibit a typical epithelial-to-mesenchymal transition gene expression profile. Due to the rarity of this cancer, at present there is a scarcity of specific treatment guidelines. Surgical resection remains the best curative option for localized disease, whereas the addition of peri-operative radiotherapy, chemotherapy and chemoradiation has been shown to further improve disease outcomes. In the metastatic setting, palliative chemotherapy is currently the treatment of choice, although no consensus exists about the best regimen to be delivered. Besides standard treatment options for the advanced disease, mechanistic insights into UCS pathogenesis and identification of its histopathological and molecular features boosted the development of novel, and potentially more effective, therapeutic agents, that will be here discussed.

I.F.: 6,625

396. Armani G, Pozzi E, Pagani A, **Porta C**, Rizzo M, Cicognini D, Rovati B, Moccia F, Pedrazzoli P, Ferraris E. The heterogeneity of cancer endothelium: The relevance of angiogenesis and endothelial progenitor cells in cancer microenvironment. *Microvasc Res* 2021;138:104189.

ABSTRACT – Tumor-associated vessels constitution is the result of angiogenesis, the hallmark of cancer essential for tumor to develop in dimension and to spread throughout the organism. Tumor endothelium is configured as an active functioning organ capable of determine interaction with the immune response and all the other components of the variegate cancer microenvironment, determining reciprocal influence. Angiogenesis is here analyzed in its molecular and cellular mechanisms, multiple mediators and principal players, represented by Endothelial Cells. It is discussed the striking heterogeneity of cancer endothelium, due to morphological and molecular aberrations that it often presents and its multiple origin. Among the cells that participate to the composition of tumor vasculature, Endothelial Progenitor Cells represent an important source for physical sustain and paracrine signaling in the process of angiogenesis. Treatment options are reviewed, with particular focus on novel therapeutic strategies for overcoming tumor resistance to anti-angiogenic agents.

I.F.: 3,75

397. Stucci LS, Internò V, Tucci M, Perrone M, Mannavola F, Palmirotta R, **Porta C**. The ATM Gene in Breast Cancer: Its Relevance in Clinical Practice. *Genes (Basel)* 2021;12:727.

ABSTRACT – Molecular alterations of the Ataxia-telangiectasia (AT) gene are frequently detected in breast cancer (BC), with an incidence ranging up to 40%. The mutated form, the Ataxia-telangiectasia mutated (ATM) gene, is involved in cell cycle control, apoptosis, oxidative stress, and telomere maintenance, and its role as a risk factor for cancer development is well established. Recent studies have confirmed that some variants of ATM are associated with an increased risk of BC development and a worse prognosis. Thus, many patients harboring ATM mutations develop intermediate- and high-grade disease, and there is a higher rate of lymph node metastatic involvement. The evidence concerning a correlation of ATM gene mutations and the efficacy of therapeutic strategies in BC management are controversial. In fact, ATM mutations may sensitize cancer cells to platinum-derived drugs, as BRCA1/2 mutations do, whereas their implications in objective responses to hormonal therapy or target-based agents are not well defined. Herein, we conducted a review of the role of ATM gene mutations in BC development, prognosis, and different treatment strategies.

I.F.: 4,141

N. citazioni = 2

398. Negri F, Missale G, Antoni AD, **Porta C**. Hepatocellular cancer therapy in patients with HIV infection: Disparities in cancer care, trials enrolment, and cancer-related research.

Transl Oncol 2021;14:101153.

ABSTRACT – In the highly active antiretroviral therapy (HAART) era, hepatocellular carcinoma (HCC) is arising as a common late complication of human immunodeficiency virus (HIV) infection, with a great impact on morbidity and mortality. Though HIV infection alone may not be sufficient to promote hepatocarcinogenesis, the complex interaction of HIV with hepatitis is a main aspect influencing HCC morbidity and mortality. Data about sorafenib effectiveness and safety in HIV-infected patients are limited, particularly for patients who are on HAART. However, in properly selected subgroups, outcomes may be comparable to those of HIV-uninfected patients. Scarce data are available for those other systemic treatments, either tyrosine kinase inhibitors, as well as immune checkpoint inhibitors (ICIs), which have been added to our therapeutic armamentarium. This review examines the influence of HIV infection on HCC development and natural history, summarizes main data on systemic therapies, offers some insight into possible mechanisms of T cell exhaustion and reversal of HIV latency with ICIs and issues about clinical trials enrollment. Nowadays, routine exclusion of HIV-infected patients from clinical trial participation is totally inappropriate, since it leaves a number of patients deprived of life-prolonging therapies.
I.F.: 4,803

399. Negri F, Gnetti L, Pedrazzi G, Silini EM, **Porta C**. Sorafenib and hepatocellular carcinoma: is alpha-fetoprotein a biomarker predictive of tumor biology and primary resistance? *Future Oncol* 2021;17:3579-84

ABSTRACT – Background: Alpha-fetoprotein (AFP) is the only biomarker with proven prognostic value in advanced hepatocellular carcinoma. Preliminary data indicate crosstalk between AFP and VEGF signaling. Methods: The authors looked at 69 patients with advanced hepatocellular carcinoma who were previously tested for VEGFR2 expression, had available baseline AFP serum concentrations and were treated with sorafenib within clinical trials. Results: Shorter progression-free survival and overall survival were associated with increased AFP level and elevated VEGFR2 staining. At multivariate analysis of AFP level was the only independent prognostic factor for progression-free survival and overall survival. Conclusion: The authors' study confirms the adverse prognostic role of elevated baseline AFP and also suggests a possible role of AFP in primary resistance to sorafenib therapy.
I.F.: 3,674

400. Guadalupi V, Cartenì G, Iacovelli R, **Porta C**, Pappagallo G, Ricotta R, Procopio G. Second-line treatment in renal cell carcinoma: clinical experience and decision making. *Ther Adv Urol* 2021 Jun 18;13:17562872211022870.

ABSTRACT – Currently, conventional treatments for metastatic RCC (mRCC) include immune-based combination regimens and/or targeted therapies, the latter mainly acting on angiogenesis, a key element of the process of tumor growth and spread. Although these agents proved able to improve patients' outcomes, drug resistance and disease progression are still experienced by a substantial number of VEGFR-TKIs-treated mRCC patients. Following the inhibition of the VEGF/VEGFRs axis, two strategies have emerged: either specifically targeting resistance pathways, at the same time continuing to inhibit angiogenesis, or using a completely different approach aimed at re-activating the immune system through the use of inhibitors of specific negative immune checkpoints. These two approaches, practically represented by the use of either cabozantinib or nivolumab, seem to remain a rational therapeutic approach also when first-line immune-based combinations are used. The objective of this study is to design a preferential therapeutic pathway for the second-line treatment of mRCC. The procedure applied in this project was a group discussion, based on the Nominal Group Technique (NGT) method in a meeting session, aimed at defining the therapeutic choice for the second-line treatment of mRCC. The NGT process defined the most relevant parameters that, according to the interviewed panelists, clinicians should consider for the selection of the second-line therapy in the context of advanced renal cell carcinoma of mRCC. The algorithm developed for the treatment selection as a result of this process should thus be considered by clinicians as reference for therapy selection. Plain language summary: The result of this paper was the definition of an algorithm intended to suggest a preferential therapeutic pathway considering both the outputs of the Nominal Group Technique (NGT) process and the actual clinical practice and the experience of selected panelists. During the NGT process and the discussion phase, panelists defined the most important parameters to be included in the algorithm that are important for the treatment definition. Cabozantinib and nivolumab are identified as the most reasonable therapeutic options for patients progressing after first-line treatment and are the medication options included in the algorithm for therapy selection.
I.F.: 3,13
N. citazioni = 1

401. Scicchitano P, Sergi MC, Cameli M, Miglioranza MH, Ciccone MM, Gentile M, **Porta C***, Tucci M* (*co-Senior Authors). Primary soft tissue sarcoma of the heart: an emerging chapter in Cardio-Oncology. *Biomedicines* 2021;9:774.

ABSTRACT – Primary malignant cardiac tumors are rare, with a prevalence of about 0.01% among all cancer histotypes. At least 60% of them are primary soft tissue sarcomas of the heart (pSTS-h) that represent almost 1% of all STSs. The cardiac site of origin is the best way to classify pSTS-h as it is directly linked to the surgical approach for cancer removal. Indeed, histological differentiation should integrate the classification to provide insights into prognosis and survival expectancy of the patients. The prognosis of pSTS-h is severe and mostly influenced by the primary localization of the tumor, the difficulty in achieving complete surgical and pharmacological eradication, and the aggressive biological features of malignant cells. This review aims to provide a detailed literature overview of the most relevant issues on primary soft tissue sarcoma of the heart and highlight potential diagnostic and therapeutic future perspectives.
I.F.: 4,757
N. citazioni = 1

402. Caffo O, Ortega C, Nolè F, Gasparro D, Mucciarini C, Aieta M, Zagonel V, Iacovelli R, De Giorgi U, Facchini G, Veccia A, Palesandro E, Verri E, Buti S, Razzini G, Bozza G, Maruzzo M, Ciccarese C, Schepisi G, Rossetti S, Maines F, Fratino L, Ermacora P, Nicodemo M, Giordano M, Sartori D, Scapoli D, Sabbatini R, Lo Re G, Morelli F, D'Angelo A, Vittimberga I, Lippe P, Carrozza F, Messina C, Galli L, Valcamonico F, **Porta C**, Pappagallo G, Aglietta M. Docetaxel and prednisone with or without enzalutamide as

first-line treatment in patients with metastatic castration-resistant prostate cancer: CHEIRON, a randomised phase II trial. *Eur J Cancer* 2021;155:56-63.

ABSTRACT – Background: Pre-clinical data suggest that docetaxel and enzalutamide interfere with androgen receptor translocation and signalling. The aim of this study is to assess the efficacy of their concurrent administration in the first-line treatment for metastatic castration-resistant prostate cancer (mCRPC). Methods: In this open-label, randomised, phase II trial, previously untreated mCRPC patients were randomised 1:1 to receive eight 21-d courses of docetaxel 75 mg/m2, oral prednisone 5 mg twice daily and oral enzalutamide 160 mg/d (arm DE), or the same treatment without enzalutamide (arm D). The primary end-point was the percentage of patients without investigator-assessed disease progression 6 months after the first docetaxel administration. Results: The 246 eligible patients were randomly assigned to receive docetaxel, prednisone and enzalutamide (n = 120) or docetaxel and prednisone (n = 126). The 6-month progression rate was 12.5% (95% confidence interval [CI] 8.1-20.6) in arm DE and 27.8% (95% CI 22.8-39.4) in arm D (chi-squared test 10.01; P = 0.002). The most frequent grade III-IV adverse events were fatigue (12.5% in arm DE versus 5.6% in arm D), febrile neutropenia (9.3% versus 4.0%) and neutropenia (7.6% versus 5.6%). Conclusions: The combination of enzalutamide and docetaxel appears to be more clinically beneficial than docetaxel alone in previously untreated mCRPC patients, although serious adverse events were more frequent. Our findings suggest that first-line treatment with this combination could lead to an additional clinical benefit when prompt and prolonged disease control is simultaneously required. Clearly, these results should be considered cautiously because of the study's phase II design and the absence of an overall survival benefit. Trial registration numbers: EudraCT 2014-000175-43 - NCT02453009.
I.F.: 10,002
N. citazioni = 1

403. Cafforio P, Palmirotta R, Lovero D, Cicinelli E, Cormio G, Silvestris E, **Porta C**, D'Oronzo S. Liquid biopsy in cervical cancer: hopes and pitfalls. *Cancers (Basel)* 2021;13:3968.

ABSTRACT – Cervical cancer (CC) is the fourth most common cancer in women worldwide, with about 90% of cancer-related deaths occurring in developing countries. The geographical influence on disease evolution reflects differences in the prevalence of human papilloma virus (HPV) infection, which is the main cause of CC, as well as in the access and quality of services for CC prevention and diagnosis. At present, the most diffused screening and diagnostic tools for CC are Papanicolaou test and the more sensitive HPV-DNA test, even if both methods require gynecological practices whose acceptance relies on the woman's cultural and religious background. An alternative (or complimentary) tool for CC screening, diagnosis, and follow-up might be represented by liquid biopsy. Here, we summarize the main methodologies developed in this context, including circulating tumor cell detection and isolation, cell tumor DNA sequencing, coding and non-coding RNA detection, and exosomal miRNA identification. Moreover, the pros and cons of each method are discussed, and their potential applications in diagnosis and prognosis of CC, as well as their role in treatment monitoring, are explored. In conclusion, it is evident that despite many advances obtained in this field, further effort is needed to validate and standardize the proposed methodologies before any clinical use.
I.F.: 6,575
N. citazioni = 2

404. Bersanelli M, Iacovelli R, Buti S, Houede N, Laguerre B, Procopio G, Lheureux S, Fischer R, Negrier S, Ravaud A, Oudard S, Escudier B, Albiges L, **Porta C**. Metastatic renal cell carcinoma rapidly progressive to Sunitinib: what to do next? *Eur Urol Oncol* 2021;4:274-81.

ABSTRACT – Background: From 10% to 26% of patients with metastatic renal cell carcinoma (mRCC) experience rapidly progressive disease (PD) on treatment with sunitinib. Objective: To investigate the benefit of subsequent treatment with another tyrosine kinase inhibitor (TKI) or a mammalian target of rapamycin (mTOR) inhibitor in such primary refractory patients. Design, setting and participants: A total of 150 mRCC patients with rapidly PD on first-line sunitinib (within two cycles, n=93, or four cycles, n=57) were identified: median age 59yr; nephrectomy 86%; histological subtypes: clear cell (77.8%), papillary (14%), and sarcomatoid features (18%); according to the Memorial Sloan-Kettering Cancer Center and French classifications: good risk (11% and 7%, respectively), intermediate (68% and 63%, respectively), and poor (21% and 29%, respectively). Outcome measurements and statistical analysis: Data were retrospectively collected by a questionnaire from 19 European oncology centers between March 2005 and March 2011. Progression-free survival (PFS) and overall survival (OS) were calculated (Kaplan-Meier method). Results and limitations: Median OS from the start of first-line treatment was 7.4mo. Second-line treatment was administered to 86 (57%) patients (44 mTOR inhibitors: 23 everolimus and 21 temsirolimus; 39 TKIs alone or in combination; three chemotherapy). Second-line PFS was not significantly different between TKIs and mTOR inhibitors (2.0 vs 0.9mo; p=0.536). Median OS from the start of second-line treatment was 5.0mo for mTOR inhibitors and 6.6mo for TKIs (p=0.15). Conclusions: Treatment with further TKIs or mTOR inhibitors for mRCC patients primarily refractory to first-line sunitinib in the observed time period achieved very minimal benefit, suggesting avoiding TKI rechallenge and possibly preferring alternative strategies, such as immune checkpoint inhibitors, after PD to a treatment line including a TKI in this setting. Patient summary: The present work collected data about 150 patients affected by metastatic renal cell carcinoma, who received one of the current standard of care as first-line treatment, namely, the antiangiogenic drug sunitinib, and experienced rapid worsening of the disease. We investigated and described the subsequent outcome of such patients treated with two different types of drug, administered as second-line therapy, to better understand the best strategy to adopt for patients who got no benefit from sunitinib and to describe the current therapeutic approach in such cases.
I.F.: 8,208
N. citazioni = 4

405. Mandriani B, Pelle' E, Pezzicoli G, Strosberg J, Abate-Daga D, Guarini A, Cives M*, **Porta C*** (*co-Senior Authors). Adoptive T-cell immunotherapy in digestive tract malignancies: current challenges and future perspectives. *Cancer Treat Rev* 2021;100:102288.

ABSTRACT – Multiple systemic treatments are currently available for advanced cancers of the digestive tract, but none of them is curative. Adoptive T-cell immunotherapy refers to the extraction, modification and re-infusion of autologous or allogenic T lymphocytes for therapeutic purposes. A number of clinical trials have investigated either non-engineered T cells (i.e., lymphokine-activated killer cells, cytokine induced killer

cells, or tumor-infiltrating lymphocytes) or engineered T cells (T cell receptor-redirected T cells or chimeric antigen receptor T cells) in patients with digestive tract malignancies over the past two decades, with variable degrees of success. While the majority of completed trials have been primarily aimed at assessing the safety of T-cell transfer strategies, a new generation of studies is being designed to formally evaluate the antitumor potential of adoptive T-cell immunotherapy in both the metastatic and adjuvant settings. In this review, we provide an overview of completed and ongoing clinical trials of passive T-cell immunotherapy in patients with cancers of the digestive tract, focusing on present obstacles and future strategies for achieving potential success.
I.F.: 13,608
N. citazioni = 3

406. Pezzicoli G, Triggiano G, Sergi MC, Mannavola F, **Porta C**, Tucci M. Biliary tract cancers: moving from the present standards of care towards the use of immune checkpoint inhibitors. *Am J Transl Res* 2021;13:8598-610.

ABSTRACT – Biliary tract cancers (BTCs) are aggressive and chemoresistant tumors associated with poor prognosis. Thus, more active and effective treatments are urgently needed, among which immunotherapy holds promise for the near future. Preclinical data show that BTCs are mainly immunosuppressed cancers, thus suggesting that their immunogenic potential may be unleashed with the appropriate strategy. Immune checkpoint inhibitors (ICIs) could theoretically be effective in BTCs by blocking those inhibitory checkpoints that limit the activation and the expansion of the effector cells of the immune response. Many currently ongoing trials aim to demonstrate the efficacy of ICIs and to incorporate immunotherapy into the routine management of BTCs. Presently available results are controversial and there is no consensus on the role of ICIs in monotherapy, while combinations of immunotherapy with chemotherapy look more promising. Nevertheless, despite the many proposed over time, there are no predictive biomarkers presently available, thus, the early identification of those patients showing a good response is of great significance.
I.F.: 3,94

407. Ciccarese C, Iacovelli R, **Porta C**, Procopio G, Bria E, Astore S, Cannella MA, Tortora G. Efficacy of VEGFR-TKIs plus immune checkpoint inhibitors in metastatic renal cell carcinoma patients with favorable IMDC prognosis. *Cancer Treat Rev* 2021;100:102295.

ABSTRACT – Background: Combinations of PD-1/PD-L1 immune checkpoint inhibitors (ICI) with VEGFR-TKIs as first-line therapy significantly improve outcomes of metastatic renal cell carcinoma (mRCC) patients. The benefit of these combinations is well evident in the IMDC intermediate- and poor-risk population, but remains unclear in the subgroup of patients with favorable prognosis. Our meta-analysis aims at evaluating whether the addition of ICIs to VEGFR-TKIs is able to improve the outcome compared to VEGFR-TKIs alone in mRCC patients with favorable prognosis. Methods: This meta-analysis searched MEDLINE/PubMed, the Cochrane Library and ASCO Meeting abstracts for randomized clinical trials (RCTs) testing the combination of VEGFR-TKI + ICI in mRCC. Data extraction was conducted according to the PRISMA statement. Summary hazard ratio (HR) was calculated using random- or fixed-effects models, depending on studies heterogeneity. Results: Four RCTs were selected. VEGFR-TKI + ICI combinations improved PFS compared to sunitinib (fixed-effect, HR = 0.63; p < 0.00001). However, VEGFR-TKI + ICI combinations did not significantly prolong OS (fixed-effect; HR = 0.99; 95% CI 0.74-1.33; p = 0.95). Conclusion: VEGFR-TKI + ICI combinations improved PFS but not OS as first-line therapy for mRCC patients with favorable IMDC prognosis. Longer follow-up and further studies will increase the power of our analysis, suggesting the best first-line therapy for mRCC patients with favorable prognosis.
I.F.: 13,608
N. citazioni = 2

408. Basso U, Procopio G, Fornarini G, Massari F, Bearz A, Fratino L, Milella M, Bassanelli M, Ermacora P, Bimbatti D, Verzoni E, Rizzo M, **Porta C**. Safety and Efficacy of Tivozanib in First-Line mRCC: A Multicenter Compassionate-Use Study (Meet-Uro 16). *Oncology* 2021;99:747-55.

ABSTRACT – Introduction: Tivozanib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptor 1 (VEGFR-1), VEGFR-2, and VEGFR-3, recently approved in Europe for the first-line treatment of metastatic renal cell carcinoma (mRCC). Methods: Retrospective analysis of safety and activity of tivozanib administered at 1.34 mg daily (3 weeks on, 1 week off) within a compassionate-use program to patients with mRCC with no prior systemic treatment in Italy. Results: From August 2018 to April 2019, 64 patients have started tivozanib in 9 oncology units. The median age was 67.5 years (range 40-85), 62.5% males. According to International Metastatic Renal Cell Carcinoma Database Consortium criteria, 27.1% of patients were good prognosis, 57.6% intermediate, and 15.3% poor. Primary tumor had been removed in 71.9% of patients. Histology was clear cell 89%, papillary 4.7%, and unclassified 6.3%. The response rate was 34.4%, stable disease 40.6%, and progression 15.6%. Grade 3-4 toxicities were 7.8% hypertension, 4.7% anemia, 3.1% mucositis, 3.1% asthenia, 1.6% diarrhea, 1.6% anorexia, 1.6% worsening of renal function, and 3.1% cardiac events. Dose reduction to 0.89 mg was applied to 17.2% of patients, and the discontinuation rate due to toxicity was 5.8%. Median progression-free survival was 12.4 months, with 68.7% of patients alive at 12 months. The developing of hypertension predicted increased progression-free survival at multivariate analysis (HR, 0.128; 95% CI, 0.03-0.59; p = 0.008). Conclusions: Tivozanib showed good activity and favorable safety profile in a real-world cohort of unselected patients with mRCC. Predictive biomarkers of response to antiangiogenic therapy are urgently needed in order to identify RCC patients who could still receive a monotherapy with VEGFR inhibitors in the first line.
I.F.: 3,734

409. Lauricella E, Cives M, Bracigliano A, Clemente O, Felici V, Lippolis R, Amoruso B, Pelle' E, Mandriani B, Esposto C, Forte C, Perri F, **Porta C**, Tafuto S. The psychological impact of COVID-19 pandemic on patients with neuroendocrine tumors: Between resilience and vulnerability. *J Neuroendocrinol* 2021;33:e13041.

ABSTRACT – The COVID-19 pandemic has added another layer of complexity to the fears of patients with neuroendocrine tumors (NETs). Little is known regarding the psychological impact of the COVID-19 outbreak on patients with gastroenteropancreatic or bronchopulmonary (BP) NETs. We longitudinally surveyed the mental symptoms and concerns of NET patients during the plateau phase of the first (W1) and second epidemic waves (W2) in Italy. Seven specific constructs (depression,

anxiety, stress, health-related quality of life, NET-related quality of life, patient-physician relationship, psychological distress) were investigated using validated screening instruments, including DASS-21, EORTC QLQ-C30, EORTC QLQ GI.NET21, PDRQ9 and IES-R. We enrolled 197 patients (98 males) with a median age of 62 years. The majority of the patients had G1/G2 neoplasms. Some 38% of the patients were on active treatment. At W1, the prevalence of depression, anxiety and stress was 32%, 36% and 26% respectively. The frequency of depression and anxiety increased to 38% and 41% at W2, whereas no modifications were recorded in the frequency of stress. Poor educational status was associated with higher levels of anxiety at both W1 (odds ratio [OR] = 1.33 ± 0.22; p = .07) and W2 (OR = 1.45 ± 0.26; p = .03). Notably, post-traumatic stress symptoms were observed in the 58% of the patients, and both single marital status (OR = 0.16, 95% confidence interval [CI] = 0.06-0.48; p = .0009) and low levels of formal education (OR = 0.47, 95% CI = 0.23-0.99; p = .05) predicted their occurrence. No significant deteriorations of health-related quality of life domains were observed from W1 to W2. High patient care satisfaction was documented despite the changes in health systems resource allocation. NET patients have an increased risk of developing post-traumatic stress symptoms as result of the COVID-19 pandemic. Specific screening measures and psychological interventions should be implemented in NET clinics to prevent, recognize and treat mental distress in this vulnerable population.
I.F.: 3,87
N. citazioni = 1

410. Powles T, Albiges L, Bex A, Grünwald V, **Porta C**, Procopio G, Schmidinger M, Suárez C, de Velasco G; ESMO Guidelines Committee. ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. *Ann Oncol* 2021;32:1511-9.
I.F.: 51,769
N. citazioni = 14

411. Marconcini R, Pezzicoli G, Stucci LS, Sergi MC, Lospalluti L, **Porta C**, Tucci M. Combination of immunotherapy and other targeted therapies in advanced cutaneous melanoma. *Hum Vaccin Immunother* 2021;6:1-9.

ABSTRACT – Cutaneous Melanoma (CM) is an aggressive cancer whose incidence is increasing worldwide. However, the knowledge of its biology and genes driving cell growth and survival allowed to develop new drugs that have improved PFS and OS of advanced disease. Both BRAF targeting agents and immune checkpoint inhibitors (ICIs) have been adopted for the treatment of metastatic disease and the adjuvant setting. Several melanoma patients show innate or acquired drug-resistance and thus new strategies are required for overcoming this complication. New ICIs have been developed, and strategies of combination or sequencing are under investigation in ongoing clinical trials. In addition, pre-clinical data have demonstrated that many strategies induce the release of neoantigens within the tumor microenvironment, thus suggesting the combination of new agents with ICIs. Here, we review the ongoing strategies in advanced CM including a dedicated section on treatment of brain metastases.
I.F.: 4,526

412. Negri F, **Porta C**. Donafenib in Chinese patients with advanced hepatocellular carcinoma (HCC): Really a new standard of care, or should we change paradigm for drug development in HCC? *Oncol Rev* 2021;15:564.

CONTENT - Liver cancer is the sixth most common cancer worldwide, with over half of the new cases and death occurring in China. Hepatocellular carcinoma (HCC) accounts for 75-85% of primary liver cancers. Most patients are diagnosed at an advanced stage with poor survival rates; thus, the diagnosis and treatment of HCC is a main public health concern, especially in China. Donafenib is a novel oral small-molecule inhibitor of multiple tyrosine kinases, such as vascular endothelial growth factor receptors, platelet-derived growth factor receptor, and Raf kinases, thereby blocking both angiogenesis and tumor cell proliferation. Donafenib is a derivative of sorafenib with a trideuterated N-methyl group, that may improve molecular stability and enhance the pharmacokinetic features. Preclinical, phase Ia and Ib trials have shown favorable efficacy and safety profile. Qin et al. recently reported in the Journal of Clinical Oncology the results from an open-label, randomized phase II-III trial, in which donafenib was compared with sorafenib, as firstline therapy in Chinese patients with unresectable or metastatic HCC. The trial showed the superiority of donafenib over sorafenib in increasing overall survival (OS) and thus the authors propose donafenib as 'new frontline standard for Chinese patients with advanced HCC'. Is this statement correct? Probably yes … Is this true also for non-Asian patients? Probably no … But, more importantly, which are the most relevant considerations we can draw from this study (and all the other first-line trials available)? Despite the significant OS advantage observed (median OS: 12.1 vs 10.3 months; HR: 0.831; 95% CI: 0.699 to 0.988; P=0.0245), patients enrolled in the donafenib trial clearly differed from those enrolled in other globally-conducted first-line pivotal trials.5,6 Indeed, although no differences were observed between treatment arms in terms of BCLC C stage, Child-Pugh score, and percentage of patients presenting with high AFP level, >90% of the enrolled patients were HBV positive, a well-known negative prognostic factor; furthermore, patients were also younger, median age being 53 years in both study arms, while it was constantly over 60 years (often well above this figure) in the sorafenib SHARP trial, the lenvatinib REFLECT trial, and the atezolizumab plus bevacizumab IMbrave 150 trial, this latter study having shown a significant OS advantage (again over sorafenib) in all main patients' subgroups, including HBV-positive and Asian patients. Once again, in our opinion, '… the issue is not the right drug [or combination], but the right patient'. Having, for the first time, at least three different options for the medical treatment of HCC patients, our choice should rely on more thorough biological and etiopathogenic considerations. Possibly, donafenib could be the treatment option of choice in HBV-infected

patients, a population which is more and more uncommon in western country, where the growing incidence of nonalcoholic fatty liver disease, now a recognized inflammatory disease, could theoretically benefit more from an immunotherapy-containing regimen; whether bevacizumab or lenvatinib is the best drug to combine with immunotherapy remains to be proven. Recent studies have indeed clearly demonstrated the immunomodulatory activity of lenvatinib, suggesting potential synergism with immune checkpoint inhibitors. Furthermore, the combination of lenvatinib with the anti-PD-1 antibody pembrolizumab yielded impressive results not only in kidney cancer, but also in HCC, with a 46% objective response rate (95% CI, 36.0% to 56.3%), a 9.3-month median progression-free survival, and a 22-month median OS of 22 months, per mRECIST, within a phase Ib study. In our opinion, these considerations and hypotheses should be taken into account when designing the new generation of trials in HCC.
I.F.: n.r.
N. citazioni = 1

413. Riva S, Arenare L, Di Maio M, Efficace F, Montesarchio V, Frontini L, Giannarelli D, Bryce J, Del Campo L, De Lorenzo F, Iannelli E, Traclò F, Gitto L, Jommi C, Vaccaro CM, Barberio D, Cinieri S, **Porta C**, Del Mastro L, Zagonel V, Cogoni AA, Bordonaro R, Gimigliano A, Piccirillo MC, Guizzaro L, Gallo C, Perrone F. Cross-sectional study to develop and describe psychometric characteristics of a patient-reported instrument (PROFFIT) for measuring financial toxicity of cancer within a public healthcare system. *BMJ Open* 2021;11:e049128.

ABSTRACT – Objectives: To measure and explain financial toxicity (FT) of cancer in Italy, where a public healthcare system exists and patients with cancer are not expected (or only marginally) to pay out-of-pocket for healthcare. Setting: Ten clinical oncological centres, distributed across Italian macroregions (North, Centre, South and Islands), including hospitals, university hospitals and national research institutes. Participants: From 8 October 2019 to 11 December 2019, 184 patients, aged 18 or more, who were receiving or had received within the previous 3 months active anticancer treatment were enrolled, 108 (59%) females and 76 (41%) males. Intervention: A 30-item prefinal questionnaire, previously developed within the qualitative tasks of the project, was administered, either electronically (n=115) or by paper sheet (n=69). Primary and secondary outcome measures: According to the protocol and the International Society for Pharmacoeconomics and Outcomes Research methodology, the final questionnaire was developed by mean of explanatory factor analysis and tested for reliability, internal consistency (Cronbach's α test and item-total correlation) and stability of measurements over time (test-retest reliability by intraclass correlation coefficient and weighted Cohen's kappa coefficient). Results: After exploratory factor analysis, a score measuring FT (FT score) was identified, made by seven items dealing with outcomes of FT. The Cronbach's alpha coefficient for the FT score was 0.87 and the item-total correlation coefficients ranged from 0.53 to 0.74. Further, nine single items representing possible determinants of FT were also retained in the final instrument. Test-retest analysis revealed a good internal validity of the FT score and of the 16 items retained in the final questionnaire. Conclusions: The Patient-Reported Outcome for Fighting FInancial Toxicity (PROFFIT) instrument consists of 16 items and is the first reported instrument to assess FT of cancer developed in a country with a fully public healthcare system. Trial registration number: NCT03473379.
I.F.: 3,006
N. citazioni = 1

414. Pezzicoli G, Filoni E, Gernone A, Cosmai L, Rizzo M, **Porta C**. Playing the Devil's Advocate: Should We Give a Second Chance to mTOR Inhibition in Renal Clear Cell Carcinoma? - ie Strategies to Revert Resistance to mTOR Inhibitors. *Cancer Manag Res* 2021;13:7623-36.

ABSTRACT – In the last decade, the inhibition of the mechanistic target of Rapamycin (mTOR) in renal clear cell carcinoma (RCC) has disappointed the clinician's expectations. Many clinical trials highlighted the low efficacy and unmanageable safety profile of first-generation mTOR inhibitors (Rapalogs), thus limiting their use in the clinical practice only to those patients who already failed several therapy lines. In this review, we analyze the major resistance mechanisms that undermine the efficacy of this class of drugs. Moreover, we describe some of the possible strategies to overcome the mechanisms of resistance and their clinical experimentation, with particular focus on novel mTOR inhibitors and the combinations of mTOR inhibitors and other anti-cancer drugs.
I.F.: 3,602
N. citazioni = 1

415. Bersanelli M, Buti S, Rizzo M, Cortellini A, Cattrini C, Massari F, Masini C, Vitale MG, Fornarini G, Caffo O, Atzori F, Gatti A, Macrini S, Mucciarini C, Galli L, Morelli F, Stellato M, Fanelli M, Corti F, Zucali PA, Toscani I, Dalla Volta A, Gernone A, Baldessari C, La Torre L, Zara D, Gennari A, Bracarda S, Procopio G, **Porta C**. GU-CA-COVID: a clinical audit among Italian genitourinary oncologists during the first COVID-19 outbreak. *Ther Adv Urol* 2021;13:17562872211054302.

ABSTRACT – Background: Considering the growing genitourinary (GU) cancer population undergoing systemic treatment with immune checkpoint inhibitors (ICIs) in the context of the COVID-19 pandemic, we planned a clinical audit in 24 Italian institutions treating GU malignancies. Objective: The primary objective was investigating the clinical impact of COVID-19 in GU cancer patients undergoing ICI-based therapy during the first outbreak of SARS-CoV-2 contagion in Italy. Design, setting and participants: The included centers were 24 Oncology Departments. Two online forms were completed by the responsible Oncology Consultants, respectively, for metastatic renal cell carcinoma (mRCC) and metastatic urothelial carcinoma (mUC) patients receiving at least one administration of ICIs between 31 January 2020 and 30 June 2020. Results and limitation: In total, 287 mRCC patients and 130 mUC patients were included. The COVID-19 incidence was, respectively, 3.5%, with mortality 1%, in mRCC patients and 7.7%, with mortality 3.1%, in mUC patients. In both groups, 40% of patients developing COVID-19 permanently discontinued anticancer treatment. The pre-test SARS-CoV-2 probability in the subgroup of patients who underwent nasal/pharyngeal swab ranged from 14% in mRCC to 26% in mUC. The main limitation of the work was its

nature of audit: data were not recorded at the single-patient level. Conclusion: GU cancer patients undergoing active treatment with ICIs have meaningful risk factors for developing severe events from COVID-19 and permanent discontinuation of therapy after the infection. Treatment delays due to organizational issues during the pandemic were unlikely to affect the treatment outcome in this population.
I.F.: 3,13

416. Rizzo M, Giannatempo P, **Porta C**. Biological therapeutic advances for the treatment of advanced urothelial cancers. *Biologics* 2021;15:441-50.

ABSTRACT - In recent years, diagnostic and therapeutic advances have contributed to a reduction in mortality rates of patients with metastatic urothelial carcinoma (mUC). Immune checkpoint inhibitors have demonstrated efficacy and safety as both first-line and first-line switch maintenance therapy for mUC. For platinum-refractory patients, in addition to immunotherapy, other targeted agents (antibody-drug conjugates and fibroblast growth factor receptor inhibitors) have been approved after demonstrating a clinically relevant advantage in overall response rate, progression-free survival, and overall survival compared to standard of care. Sequential treatment strategies are finally feasible for patients with advanced urothelial carcinoma. This review will summarize the results of the most important phase II-III clinical trials for first-line, switch maintenance, second-line, and subsequent lines of therapy, and describe the most promising clinical trials currently ongoing in these treatment scenarios.
I.F.: n.r.
N. citazioni = 1

417. **Porta C**, Nardone V, Gray SG, Correale P, Mutti L. RAMES study: is there really a role for VEGF inhibition in mesothelioma? *Lancet Oncol* 2021;22:e532.

CONTENT - We read with interest the results of the randomised, phase 2, RAMES mesothelioma trial by Carmine Pinto and colleagues published in The Lancet Oncology. The rationale for targeting angiogenesis to treat mesothelioma is based on our seminal works on VEGF as a key autocrine growth factor in this tumour type. However, despite the strong rationale, so far just a single study (MAPS) demonstrated a slight survival improvement for patients with mesothelioma who received VEGF inhibition combined with combination chemotherapy compared with chemotherapy alone in the first-line setting. We appreciate the effort of performing clinical trials in a difficult setting such as the second-line treatment of mesothelioma, which still remains a lethal disease with unusually poor prognosis even in the first-line setting. In our opinion, the results of this study should be looked at with a degree of caution, especially with respect to the selection criteria of choice of the control group, survival fragility index, and censoring rate, which all represent common individual issues whenever we attempt to translate the results of clinical trials for mesothelioma into everyday clinical practice. In this regard, for the RAMES study, the gain achieved in terms of progression-free survival (median 3.1 months) was higher than the gain in overall survival (median 1.7 months), thus confirming that progression-free survival cannot be considered as a surrogate endpoint for overall survival in mesothelioma4 and indicating that the results of this study should not be considered positive. Furthermore, the patient population enrolled in this trial presents, in our opinion, a clear selection bias, with an imbalance in subgroups with Eastern Cooperative Oncology Group performance status of 0 and age younger than 70 years between the two treatment groups. Indeed, performance status of 0 and age younger than 70 years (two well known prognostic factors in mesothelioma)5 was more frequent in the ramucirumab group. Moreover, a performance status of 0 is quite uncommon in mesothelioma, even at diagnosis;5 if patients with a performance status of 0 are removed from the analysis of the trial, patients with a performance status of 1–2 (hazard ratio [HR] 0.95) and age younger than 70 years (HR 1.08) would have received very limited benefit from the addition of ramucirumab. Finally, and perhaps more relevantly, gemcitabine alone might not be considered an optimal second-line control group in late (>6 months) progressors, in lieu of a possible first-line drug rechallenge. Taking into account all these points, we feel that despite the positive presentation of the RAMES trial, in reality further work is required to identify those (realistically few) patients who could truly benefit from the addition of antiangiogenics, and a much deeper insight into biology, and different trial designs (to validate preclinical hypotheses), are needed to fully bring drugs such as ramucirumab into the treatment paradigm for mesothelioma.
I.F.: 54,433
N. citazioni = 1

418. Kanesvaran R, **Porta C**, Wong A, Powles T, Ng QS, Schmidinger M, Ye D, Malhotra H, Miura Y, Lee JL, Chong FLT, Pu YS, Yen CC, Saad M, Lee HJ, Kitamura H, Bhattacharyya GS, Curigliano G, Poon E, Choo SP, Peters S, Lim E, Yoshino T, Pentheroudakis G. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with renal cell carcinoma. *ESMO Open* 2021;6:100304.

ABSTRACT - The most recent version of the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of renal cell carcinoma was published in 2019 with an update planned for 2021. It was therefore decided by both the ESMO and the Singapore Society of Oncology (SSO) to convene a special, virtual guidelines meeting in May 2021 to adapt the ESMO 2019 guidelines to take into account the ethnic differences associated with the treatment of renal cell carcinomas in Asian patients. These guidelines represent the consensus opinions reached by experts in the treatment of patients with renal cell carcinoma representing the oncological societies of China (CSCO), India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). The voting was based on scientific evidence and was independent of the current treatment practices and drug access restrictions in the different Asian countries. The latter were discussed when appropriate.
I.F.: 6,883

419. Buti S, Bersanelli M, Massari F, De Giorgi U, Caffo O, Aurilio G, Basso U, Carteni G, Caserta C, Galli L, Boccardo F, Procopio G, Facchini G, Fornarini G, Berruti A, Fea E, Naglieri E, Petrelli F, Iacovelli R, **Porta C**, Mosca A. First-line pazopanib in patients with advanced non-clear cell renal carcinoma: An Italian case series. *World J Clin Oncol* 2021;12:1037-46.

ABSTRACT - Background: Non-clear cell (ncc) metastatic renal-cell carcinoma (RCC) has dismal results with standard systemic therapies and a generally worse prognosis when compared to its clear-cell counterpart. New systemic combination therapies have emerged for metastatic RCC

(mRCC), but the pivotal phase III trials excluded patients with nccRCC, which constitute about 30% of metastatic RCC cases. Aim: To provide a piece of real-life evidence on the use of pazopanib in this patient subgroup. Methods: The present study is a multicenter retrospective observational analysis aiming to assess the activity, efficacy, and safety of pazopanib as first-line therapy for advanced nccRCC patients treated in a real-life setting. Results: Overall, 48 patients were included. At the median follow-up of 40.6 mo, the objective response rate was 27.1%, the disease control rate was 83.3%, and the median progression-free survival and overall survival were 12.3 (95% confidence interval [CI]: 3.6-20.9) and 27.7 (95%CI: 18.2-37.1) mo, respectively. Grade 3 adverse events occurred in 20% of patients, and no grade 4 or 5 toxicities were found. Conclusion: Pazopanib should be considered as a good first-line option for metastatic RCC with variant histology.

I.F.: n.r.

420. Pezzicoli G, Rizzo M, Perrone M, Minei S, Mutti L, **Porta C**. A Glimpse in the Future of Malignant Mesothelioma Treatment. *Front Pharmacol* 2021;12:809337.

ABSTRACT - Malignant mesothelioma (MMe) is a rare neoplasm with few therapeutic options available. The landscape of effective therapy for this disease remained unchanged in the last two decades. Recently, however, the introduction of Immune Checkpoint Inhibitors (ICIs) led to small, but nevertheless, promising improvements. However, many efforts are still needed to radically improve the prognosis of MMe. In this review, we analyze all those therapeutic strategies for MMe that are still in a preclinical or early clinical phase of development. In particular, we focus on novel antiangiogenic drugs and their possible combination with immunotherapy. Furthermore, we describe also more complex strategies such as microRNA-loaded vectors, oncolytic viruses, and engineered lymphocytes.

I.F.: 5,988

421. Oudard S, Benhamouda N, Escudier B, Ravel P, Tran T, Levionnois E, Negrier S, Barthelemy P, Berdah JF, Gross-Goupil M, Sternberg CN, Bono P, **Porta C**, Giorgi U, Parikh O, Hawkins R, Highley M, Wilke J, Decker T, Tanchot C, Gey A, Terme M, Tartour E. Decrease of pro-angiogenic monocytes predicts clinical response to anti-angiogenic treatment in patients with metastatic renal cell carcinoma. *Cells* 2021;11:17.

ABSTRACT - The modulation of subpopulations of pro-angiogenic monocytes (VEGFR-1+CD14 and Tie2+CD14) was analyzed in an ancillary study from the prospective PazopanIb versus Sunitinib patient preferenCE Study (PISCES) (NCT01064310), where metastatic renal cell carcinoma (mRCC) patients were treated with two anti-angiogenic drugs, either sunitinib or pazopanib. Blood samples from 86 patients were collected prospectively at baseline (T1), and at 10 weeks (T2) and 20 weeks (T3) after starting anti-angiogenic therapy. Various subpopulations of myeloid cells (monocytes, VEGFR-1+CD14 and Tie2+CD14 cells) decreased during treatment. When patients were divided into two subgroups with a decrease (defined as a >20% reduction from baseline value) (group 1) or not (group 2) at T3 for VEGFR-1+CD14 cells, group 1 patients presented a median PFS and OS of 24 months and 37 months, respectively, compared with a median PFS of 9 months (p = 0.032) and a median OS of 16 months (p = 0.033) in group 2 patients. The reduction in Tie2+CD14 at T3 predicted a benefit in OS at 18 months after therapy (p = 0.04). In conclusion, in this prospective clinical trial, a significant decrease in subpopulations of pro-angiogenic monocytes was associated with clinical response to anti-angiogenic drugs in patients with mRCC.

I.F.: 7,666

N. citazioni = 1

422. Guarini C, Grassi T, Pezzicoli G, **Porta C**. Beyond RAS and BRAF: HER2, a New Actionable Oncotarget in Advanced Colorectal Cancer. *Int J Mol Sci* 2021;22:6813.

ABSTRACT - The human epidermal growth factor receptor 2 (HER2) is a well-established oncogenic driver and a successful therapeutic target in several malignancies, such as breast and gastric cancers. HER2 alterations, including amplification and somatic mutations, have also been detected in a small but not negligible subset of patients affected by advanced colorectal cancer (aCRC). However, to date, there are no available oncotargets in this malignancy beyond RAS and BRAF that are available. Here we present an overview on the present predictive and prognostic role of HER2 expression in aCRC, as well as on its consequent potential therapeutic implications from preclinical investigations towards ongoing trials testing anti-HER2 agents in aCRC. While HER2's role as a molecular predictive biomarker for anti-EGFR therapies in CRC is recognized, HER2 prognostic value remains controversial. Moreover, thanks to the impressive and growing body of clinical evidence, HER2 is strongly emerging as a new potential actionable oncotarget in aCRC. In conclusion, in the foreseeable future, HER2-targeted therapeutic strategies may integrate the algorithm of aCRC treatment towards an increasingly tailored therapeutic approach to this disease.

I.F.: 6,208

N. citazioni = 2

423. Laface C, Laforgia M, Molinari P, Ugenti I, Gadaleta CD, **Porta C**, Ranieri G. Hepatic arterial infusion of chemotherapy for advanced hepatobiliary cancers: state of the art. *Cancers (Basel)* 2021;13:3091.

ABSTRACT - Liver functional failure is one of the leading causes of cancer-related death. Primary liver tumors grow up mainly in the liver, and thus happens for liver metastases deriving from other organs having a lower burden of disease at the primary site. Systemic chemotherapy usually offers a modest benefit in terms of disease control rate, progression-free survival, and overall survival at the cost of a significant percentage of adverse events. Liver malignancies are mostly perfused by the hepatic artery while the normal liver parenchyma by the portal vein network. On these bases, the therapeutic strategy consisting of hepatic arterial infusion (HAI) of chemotherapy takes place. In literature, HAI chemotherapy was applied for the treatment of advanced hepatobiliary cancers with encouraging results. Different chemotherapeutic agents were used such as Oxaliplatin, Cisplatin, Gemcitabine, Floxuridine, 5-Fluorouracil, Epirubicin, individually or in combination. However, the efficacy of this treatment strategy remains controversial. Therefore, this review aims to summarize the current knowledge on this approach from different points of view, such as techniques, drugs pharmacology and pharmacokinetics, and clinical outcomes for advanced hepatobiliary cancers.

I.F.: 6,575

N. citazioni = 1

424. Lovero D, D'Oronzo S, Palmirotta R, Cafforio P, Brown J, Wood S, **Porta C**, Lauricella E, Coleman R, Silvestris F. Correlation between targeted RNAseq signature of breast cancer CTCs and onset of bone-only metastases. *Br J Cancer* 2022;126:419-29.

ABSTRACT – Background: Bone is the most frequent site of metastases from breast cancer (BC), but no biomarkers are yet available to predict skeletal dissemination. Methods: We attempted to identify a gene signature correlated with bone metastasis (BM) onset in circulating tumour cells (CTCs), isolated by a DEPArray-based protocol from 40 metastatic BC patients and grouped according to metastasis sites, namely "BM" (bone-only), "ES" (extra-skeletal) or BM + ES (bone + extra-skeletal). Results: A 134-gene panel was first validated through targeted RNA sequencing (RNAseq) on sub-clones of the MDA-MB-231 BC cell line with variable organotropism, which successfully shaped their clustering. The panel was then applied to CTC groups and, in particular, the "BM" vs "ES" CTC comparison revealed 31 differentially expressed genes, including MAF, CAPG, GIPC1 and IL1B, playing key prognostic roles in BC. Conclusion: Such evidence confirms that CTCs are suitable biological sources for organotropism investigation through targeted RNAseq and might deserve future applications in wide-scale prospective studies.
I.F.^{2021}: 9,075
N. citazioni = 2

425. Albiges L, Tannir NM, Burotto M, McDermott D, Plimack ER, Barthélémy P, **Porta C**, Powles T, Donskov F, George S, Kollmannsberger CK, Gurney H, Grimm MO, Tomita Y, Castellano D, Rini BI, Choueiri TK, Leung D, Saggi SS, Lee CW, McHenry MB, Motzer RJ. First-line Nivolumab plus Ipilimumab versus Sunitinib in patients without nephrectomy and with an evaluable primary renal tumor in the CheckMate 214 trial. *Eur Urol* 2022:81:266-71.

ABSTRACT - We present an exploratory post hoc analysis from the phase 3 CheckMate 214 trial of first-line nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib in a subgroup of 108 patients with advanced renal cell carcinoma (aRCC) without prior nephrectomy and with an evaluable primary tumor, a population under-represented in clinical trials. Patients with clear cell aRCC were randomized to NIVO+IPI every 3 wk for four doses followed by NIVO monotherapy, or sunitinib every day for 4 wk (6-wk cycle). Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and primary tumor shrinkage were assessed. PFS and ORR were assessed per independent radiology review committee using RECIST version 1.1. With minimum study follow-up of 4 yr for intent-to-treat patients, OS favored NIVO+IPI (n = 53) over sunitinib (n = 55; hazard ratio 0.63, 95% confidence interval 0.40-1.0) among patients without prior nephrectomy. ORR was higher (34% vs 15%; p = 0.0041) and median duration of response was longer with NIVO+IPI versus sunitinib (20.5 vs 14.1 mo); the best overall response was partial response in either arm. A ≥30% reduction in the diameter of intact target renal tumors was achieved in 35% of patients with NIVO+IPI versus 20% with sunitinib. Safety was consistent with the global study population. In conclusion, in patients with aRCC without prior nephrectomy and with an evaluable primary tumor, NIVO+IPI showed survival benefits and renal tumor reduction versus sunitinib. This trial is registered at ClinicalTrials.gov as NCT02231749. PATIENT SUMMARY: In an exploratory analysis of a large global trial (CheckMate 214), we observed positive outcomes (both survival and tumor response to treatment) with nivolumab plus ipilimumab over sunitinib in a subgroup of patients with advanced kidney cancer who did not undergo removal of their primary kidney tumor. This subset of patients represents a population that has not been studied in clinical trials and for whom outcomes with new immunotherapy combination regimens are not yet known. We conclude that treatment with nivolumab plus ipilimumab offers these patients a survival benefit versus sunitinib, consistent with that observed in the overall study, as well as a notable kidney tumor reduction.
I.F.^{2021}: 24,267
N. citazioni = 1

426. Brunelli M, Tafuri A, Cima L, Cerruto MA, Milella M, Zivi A, Buti S, Bersanelli M, Fornarini G, Vellone VG, Rebuzzi SE, Procopio G, Verzoni E, Bracarda S, Sabbatini R, Baldessari C, Eccher A, Passalacqua R, Perrucci B, Giganti MO, Donini M, Panni S, Tucci M, Prati V, Ortega C, Caliò A, Alongi F, Munari E, Pappagallo G, Iacovelli R, Mosca A, **Porta C**, Martignoni G, Antonelli A. MDM2 gene amplification as selection tool for innovative targeted approaches in PD-L1 positive or negative muscle-invasive urothelial bladder carcinoma. *J Clin Pathol* 2022;75:39-44.

ABSTRACT – Aims: According to The Cancer Genome Atlas (TCGA), around 9% of bladder carcinomas usually show abnormalities of the murine double minute 2 (MDM2) gene, but a few studies have been investigated them. We profiled MDM2 gene amplification in a series of urothelial carcinomas (UC) considering the molecular subtypes and expression of programmed death ligand 1 (PD-L1). Methods: 117 patients with muscle-invasive UC (pT2-3) without (N0) or with (N+) lymph-node metastases were revised. Only cases with availability of in toto specimens and follow-up were studied. Tissue microarray was built. p53, ER, RB1, GATA-3, CK20, CK5/6, CD44 and PD-L1 (clone sp263) immunoexpression was evaluated. Fluorescent in situ hybridisation was assessed by using the HER-2/neu, FGFR-3, CDKN2A and MDM2 probes. True (ratio 12q/CEP12 >2) MDM2 gene amplification was distinguished from polyploidy/gains (ratio <2, absolute copy number of MDM-2 >2). MDM2 and PD-L1 values were correlated to the TCGA molecular phenotypes. Statistical analysis was performed. Results: 6/50 (12%) cases (5 N0 and 1 N+) were amplified for MDM2 without matching to molecular phenotypes. Of 50, 14 (37%) cases expressed PD-L1 at 1% cut-off; 3/50 (9%) at >50% cut-off; of these, 2 cases on side of neoplasia among inflammatory cells. Only one out of six (17%) cases amplified for MDM2 showed expression (>50% cut-off) of PD-L1. MDM2 amplification was independent to all documented profiles (k test=0.3) and was prevalent in recurrent UC. Conclusion: MDM2 amplification has been seen in both PD-L1 positive and negative muscle-invasive bladder UC independently from the TCGA molecular phenotypes. MDM2 and PD-L1 might be assessed in order to predict a better response to combo/single targeted therapies.
I.F.^{2021}: 4,463

427. Lasagna A, Ghiara M, A Mahagna A, A Lombardini A, Cuzzocrea F, **Porta C**. Skeletal muscle metastases: pitfalls and challenges of a highly inhospitable environment. *Future Oncol* 2022;18:897-901.
I.F.^{2021}: 3,674

428. Bersanelli M, Casartelli C, Buti S, **Porta C**. Renal cell

carcinoma and viral infections: A dangerous relationship? *World J Nephrol* 2022;11:1-12.

ABSTRACT - Virus-related cancers in humans are widely recognized, but in the case of renal cancer, the link with the world of viruses is not clearly established in humans, despite being known in animal biology. In the present review, we aimed to explore the literature on renal cell carcinoma (RCC) for a possible role of viruses in human RCC tumorigenesis and immune homeostasis, hypothesizing the contribution of viruses to the immunogenicity of this tumor. A scientific literature search was conducted using the PubMed, Web of Science, and Google Scholar databases with the keywords "virus" or "viruses" or "viral infection" matched with ("AND") "renal cell carcinoma" or "kidney cancer" or "renal cancer" or "renal carcinoma" or "renal tumor" or "RCC". The retrieved findings evidenced two main aspects testifying to the relationship between RCC and viruses: The presence of viruses within the tumor, especially in non-clear cell RCC cases, and RCC occurrence in cases with pre-existing chronic viral infections. Some retrieved translational and clinical data suggest the possible contribution of viruses, particularly Epstein-Barr virus, to the marked immunogenicity of sarcomatoid RCC. In addition, it was revealed the possible role of endogenous retrovirus reactivation in RCC oncogenesis, introducing new fascinating hypotheses about this tumor's immunogenicity and likeliness of response to immune checkpoint inhibitors.

I.F.: n.r.

429. Freifeld Y, Pedrosa I, Mclaughlin M, Correa RM, Louie AV, Maldonado JA, Tang C, Kadow B, Kutikov A, Uzzo RG, **Porta C**, Bucknell NW, Siva S, Brugarolas J, Margulis V, Timmerman R, Hannan R. Stereotactic ablative radiation therapy for renal cell carcinoma with inferior vena cava tumor thrombus. *Urol Oncol* 2022;40:166e9-13.

ABSTRACT - Background: Inferior vena cava tumor thrombus (IVC-TT) is a rare yet deadly sequel of renal cell carcinoma (RCC) with limited treatment options. The standard treatment is extirpative surgery, which has high rates of morbidity and mortality. As a result, many patients are unfit or unwilling to undergo surgery and face poor prognosis. This stresses the need for alternative options for local disease control. Our study aims to assess the feasibility and oncological outcomes of stereotactic ablative radiation (SAbR) for IVC-TT. Methods: A retrospective study reviewing six leading international institutions' experience in treating RCC with IVC-TT with SAbR. Primary end point was overall survival using Kaplan-Meier. Results: Fifteen patients were included in the cohort. Over 50% of patients had high level IVC-TT (level III or IV), 66.7% had metastatic disease. Most eschewed surgery due to high surgical risk (7/15) or recurrent thrombus (3/15). All patients received SAbR to the IVC-TT with a median biologically equivalent dose (BED10) of 72 Gy (range: 37.5-100.8) delivered in a median of 5 fractions (range 1-5). Median overall survival was 34 months. Radiographic response was observed in 58% of patients. Symptom palliation was recorded in all patients receiving SAbR for this indication. Only grade 1 to 2 adverse events were noted. Conclusions: SAbR for IVC-TT appears feasible and safe. In patients who are not candidates for surgery, SAbR may palliate symptoms and improve outcomes. SAbR may be considered as part of a multimodal treatment approach for patients with RCC IVC-TT.

I.F.^{2021}: 2,954

430. Rebuzzi SE, Cerbone L, Signori A, Santoni M, Murianni V, De Giorgi U, Procopio G, **Porta C**, Milella M, Basso U, Massari F, Maruzzo M, Iacovelli R, Battelli N, Carmisciano L, Banna GL, Buti S, Fornarini G. Application of the Meet-URO score to metastatic renal cell carcinoma patients treated with second- and third-line cabozantinib. *Ther Adv Med Oncol* 2022;14:17588359221079580.

ABSTRACT - Background: The addition of neutrophil-to-lymphocyte ratio (NLR) and bone metastases to the International Metastatic RCC Database Consortium (IMDC) score (by the Meet-URO score) has been shown to better stratify pretreated metastatic renal cell carcinoma (mRCC) patients receiving nivolumab. This study aimed to validate the Meet-URO score in patients receiving cabozantinib to assess its predictivity and prognostic role. Methods: A multicenter retrospective analysis evaluated mRCC patients receiving second-line cabozantinib. NLR, IMDC score and bone metastases were assessed before the start of cabozantinib. The primary endpoint was overall survival (OS). Harrell's c-index was calculated to compare the accuracy of the prediction of the two scores. Results: Overall, 174 mRCC patients received cabozantinib as second and third line (51.7% and 48.3%, respectively) with a median follow-up of 6.8 months. A shorter median overall survival (mOS) was observed for the IMDC poor-risk group, NLR 3.2 and the presence of bone metastases, while the IMDC intermediate-risk group had a similar mOS to the favourable-risk one. Applying the Meet-URO score, three risk groups were identified: group 1 (55.2% of patients) with a score of 0-3, group 2 (38.5%) with a score of 4-8 and group 3 (6.3%) with a score of 9. Compared to group 1 (mOS: 39.4 months), a statistically significant worse mOS was observed in group 2 (11.2 months) and group 3 (3.2 months) patients, respectively. The Meet-URO c-index score was 0.640, showing a higher discriminative ability than the IMDC score (c-index: 0.568). Conclusion: This analysis showed that the Meet-URO score provides a more accurate prognostic stratification than the IMDC score in mRCC patients treated with second-line cabozantinib besides nivolumab. Moreover, it is an easy-to-use tool with no additional costs for clinical practice (web-calculator is available at: https://proviso.shinyapps.io/Meet-URO15_score/). Future investigations will include the application of the Meet-URO score to the first-line immunotherapy-based combination therapies.

I.F.^{2021}: 5,485

431. Orlacchio A, Guastoni C, Beretta GD, Cosmai L, Galluzzo M, Gori S, Grassedonio E, Incorvaia L, Marcantoni C, Netti GS, Passamonti M, **Porta C**, Procopio G, Rizzo M, Roma S, Romanini L, Stacul F, Casinelli A. SIRM-SIN-AIOM: appropriateness criteria for evaluation and prevention of renal damage in the patient undergoing contrast medium examinations-consensus statements from Italian College of Radiology (SIRM), Italian College of Nephrology (SIN) and Italian Association of Medical Oncology (AIOM). *Radiol Med* 2022;127:534-42.

ABSTRACT - The increasing number of examinations and interventional radiological procedures that require the administration of contrast medium (CM) in patients at risk for advanced age and/or comorbidities highlights the problem of CM-induced renal toxicity. A multidisciplinary group consisting of specialists of different disciplines-radiologists, nephrologists and oncologists, members of the respective Italian Scientific Societies-agreed to draw up this position paper, to assist clinicians increasingly facing the challenges posed by CM-related renal dysfunction

in their daily clinical practice.The major risk factor for acute renal failure following CM administration (post-CM AKI) is the preexistence of renal failure, particularly when associated with diabetes, heart failure or cancer.In accordance with the recent guidelines ESUR, the present document reaffirms the importance of renal risk assessment through the evaluation of the renal function (eGFR) measured on serum creatinine and defines the renal risk cutoff when the eGFR is < 30 ml/min/1.73 m2 for procedures with intravenous (i.v.) or intra-arterial (i.a.) administration of CM with renal contact at the second passage (i.e., after CM dilution with the passage into the pulmonary circulation).The cutoff of renal risk is considered an eGFR < 45 ml/min/1.73 m2 in patients undergoing i.a. administration with first-pass renal contact (CM injected directly into the renal arteries or in the arterial district upstream of the renal circulation) or in particularly unstable patients such as those admitted to the ICU.Intravenous hydration using either saline or Na bicarbonate solution before and after CM administration represents the most effective preventive measure in patients at risk of post-CM AKI. In the case of urgency, the infusion of 1.4% sodium bicarbonate pre- and post-CM may be more appropriate than the administration of saline.In cancer patients undergoing computed tomography, pre- and post-CM hydration should be performed when the eGFR is < 30 ml/min/1.73 m2 and it is also advisable to maintain a 5 to 7 days interval with respect to the administration of cisplatin and to wait 14 days before administering zoledronic acid.In patients with more severe renal risk (i.e., with eGFR < 20 ml/min/1.73 m2), particularly if undergoing cardiological interventional procedures, the prevention of post-CM AKI should be implemented through an internal protocol shared between the specialists who treat the patient.In magnetic resonance imaging (MRI) using gadolinium CM, there is a lower risk of AKI than with iodinated CM, particularly if doses < 0.1 mmol/kg body weight are used and in patients with eGFR > 30 ml/min/1.73 m2. Dialysis after MRI is indicated only in patients already undergoing chronic dialysis treatment to reduce the potential risk of systemic nephrogenic fibrosis.

I.F.^{2021}: 6,313

432. Iacovelli R, Ciccarese C, Procopio G, Astore S, Cannella MA, Maratta MG, Rizzo M, Verzoni E, **Porta C**, Tortora G. Current evidence for second-line treatment in metastatic renal cell carcinoma after progression to immune-based combinations. *Cancer Treat Rev* 2022;105:102379.

ABSTRACT - The recent approval of immune checkpoint inhibitor (ICI)-based combinations has redefined the first-line standard of care of metastatic renal cell carcinoma (mRCC) patients. Although the undisputed advantage of these combinations, most patients progressed, requiring subsequent therapies. The change of first-line therapy inevitably led to modification of the all mRCC treatment algorithm; to date, the most appropriate second-line options remain still unclear. The aim of our review was to provide a useful summary of the available evidence in order to overcome the doubts about treatment sequences. Retrospectively, the efficacy of second-line VEGFR-TKIs seems to be greater after failure of a dual ICIs combination rather than after ICIs plus VEGFR-TKIs, nevertheless prospective data of second-line TKIs are limited. Moreover, ICI re-challenge could be an option but, again, most data derived from retrospective series emphasizing the identification of predictive factors of response to select mRCC patients that could benefit from this strategy. Novel molecules and different ICI-based combinations are under evaluation with the aim of implementing the second-line setting. In particular, belzutifan, ciforadenant (CPI-444), and talazoparib achieved encouraging objective response rates (ORR) in phase I/II trials. Phase III trials comparing these new molecules with the standard of care are currently ongoing. The first-line regimen, and the type and duration of response emerged as crucial factors that could influence the efficacy of second-line therapy. Prognostic models that integrate clinical features and molecular biomarkers with a predictive value are warranted to guide clinicians in the decision-making process with the ultimate goal of offering to the patients the most effective therapy in a personalized, precision medicine-based, therapeutic strategy.

I.F.^{2021}: 13,608

433. Santoni M, Aurilio G, Massari F, Grande E, Matrana MR, Rizzo M, De Giorgi U, Incorvaia L, Martignetti A, Molina-Cerrillo J, Zabalza IO, Mollica V, Rizzo A, Battelli N, **Porta C**. Nivolumab versus Cabozantinib as second-line therapy in patients with advanced renal cell carcinoma: a real-world comparison. *Clin Genitourin Cancer* 2022;20:285-95.

ABSTRACT - Background: Tyrosine-kinase inhibitors (TKIs) still represent a first-line option for selected patients with metastatic Renal Cell Carcinoma (mRCC). We aimed to compare the real-world efficacy of nivolumab or cabozantinib as second-line therapy in specific mRCC subpopulations. Patients and methods: We retrospectively collected data from 11 centers from Italy, Spain and US. Overall Survival (OS) and Progression-Free Survival (PFS) were analyzed using Kaplan-Meier curves. Cox proportional models were used at univariate and multivariate analyses. Results: We collected data from 343 patients with mRCC, 123 (36%) treated with cabozantinib and 220 (64%) with nivolumab. The median OS resulted longer, but not statistically significant, with nivolumab in patients aged >70 years (21.4 vs. 15.4 months, P = .746), treated with first-line pazopanib (26.8 vs. 11.6 months, P = .450), or with good (47.0 vs. 15.5 months, P = .285) or intermediate-risk criteria (14.4 vs. 11.0 months, P = .357), while it was longer, but even not statistically significant, for cabozantinib in patients who received previous sunitinib (25.7 vs. 21.7 months, P = .638) or with bone metastases (28.4 vs. 24.4 months, P = .871). The median PFS was significantly longer with cabozantinib in patients with clear cell histology (7.8 vs. 5.4 months, P = .026) and in patients with good risk features (12.3 vs. 5.7 months, P = .022). Conclusions: Nivolumab and cabozantinib resulted active in mRCC patients, showing distinct results when stratified into clinico-pathological features.

I.F.^{2021}: 3,121

434. Motzer RJ, McDermott DF, Escudier B, Burotto M, Choueiri TK, Hammers HJ, Barthélémy P, Plimack ER, **Porta C**, George S, Powles T, Donskov F, Gurney H, Kollmannsberger CK, Grimm MO, Barrios C, Tomita Y, Castellano D, Grünwald V, Rini BI, McHenry MB, Lee CW, McCarthy J, Ejzykowicz F, Tannir NM. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. *Cancer* 2022;128:2085-97.

ABSTRACT - Background: Conditional survival estimates provide critical prognostic information for patients with advanced renal cell carcinoma (aRCC). Efficacy, safety, and conditional survival outcomes were assessed in CheckMate 214 (ClinicalTrials.gov identifier NCT02231749) with a minimum follow-up of 5 years. Methods: Patients with untreated aRCC were randomized to receive nivolumab (NIVO) (3 mg/kg) plus ipilimumab (IPI) (1 mg/kg) every 3 weeks for 4 cycles, then either NIVO monothe-

rapy or sunitinib (SUN) (50 mg) daily (four 6-week cycles). Efficacy was assessed in intent-to-treat, International Metastatic Renal Cell Carcinoma Database Consortium intermediate-risk/poor-risk, and favorable-risk populations. Conditional survival outcomes (the probability of remaining alive, progression free, or in response 2 years beyond a specified landmark) were analyzed. Results: The median follow-up was 67.7 months; overall survival (median, 55.7 vs 38.4 months; hazard ratio, 0.72), progression-free survival (median, 12.3 vs 12.3 months; hazard ratio, 0.86), and objective response (39.3% vs 32.4%) benefits were maintained with NIVO+IPI versus SUN, respectively, in intent-to-treat patients (N = 550 vs 546). Point estimates for 2-year conditional overall survival beyond the 3-year landmark were higher with NIVO+IPI versus SUN (intent-to-treat patients, 81% vs 72%; intermediate-risk/poor-risk patients, 79% vs 72%; favorable-risk patients, 85% vs 72%). Conditional progression-free survival and response point estimates were also higher beyond 3 years with NIVO+IPI. Point estimates for conditional overall survival were higher or remained steady at each subsequent year of survival with NIVO+IPI in patients stratified by tumor programmed death ligand 1 expression, grade ≥3 immune-mediated adverse event experience, body mass index, and age. Conslusions: Durable clinical benefits were observed with NIVO+IPI versus SUN at 5 years, the longest phase 3 follow-up for a first-line checkpoint inhibitor-based combination in patients with aRCC. Conditional estimates indicate that most patients who remained alive or in response with NIVO+IPI at 3 years remained so at 5 years.

I.F.^{2021}: 6,921

N. citazioni = 1

435. Loizzo D, Pandolfo SD, Rogers D, Cerrato C, di Meo NA, Autorino R, Mirone V, Ferro M, **Porta C**, Stella A, Bizzoca C, Vincenti L, Spilotros M, Rutigliano M, Battaglia M, Ditonno P, Lucarelli G. Novel insights into autophagy and prostate cancer: A comprehensive review. *Int J Mol Sci* 2022;23:3826.

ABSTRACT - Autophagy is a complex process involved in several cell activities, including tissue growth, differentiation, metabolic modulation, and cancer development. In prostate cancer, autophagy has a pivotal role in the regulation of apoptosis and disease progression. Several molecular pathways are involved, including PI3K/AKT/mTOR. However, depending on the cellular context, autophagy may play either a detrimental or a protective role in prostate cancer. For this purpose, current evidence has investigated how autophagy interacts within these complex interactions. In this article, we discuss novel findings about autophagic machinery in order to better understand the therapeutic response and the chemotherapy resistance of prostate cancer. Autophagic-modulation drugs have been employed in clinical trials to regulate autophagy, aiming to improve the response to chemotherapy or to anti-cancer treatments. Furthermore, the genetic signature of autophagy has been found to have a potential means to stratify prostate cancer aggressiveness. Unfortunately, stronger evidence is needed to better understand this field, and the application of these findings in clinical practice still remains poorly feasible.

I.F.^{2021}: 6,208

436. Di Meo NA, Loizzo D, Pandolfo SD, Autorino R, Ferro M, **Porta C**, Stella A, Bizzoca C, Vincenti L, Crocetto F, Tataru OS, Rutigliano M, Battaglia M, Ditonno P, Lucarelli G. Metabolomic approaches for detection and identification of biomarkers and altered pathways in bladder cancer. *Int J Mol Sci* 2022;23:4173.

ABSTRACT - Metabolomic analysis has proven to be a useful tool in biomarker discovery and the molecular classification of cancers. In order to find new biomarkers, and to better understand its pathological behavior, bladder cancer also has been studied using a metabolomics approach. In this article, we review the literature on metabolomic studies of bladder cancer, focusing on the different available samples (urine, blood, tissue samples) used to perform the studies and their relative findings. Moreover, the multi-omic approach in bladder cancer research has found novel insights into its metabolic behavior, providing excellent start-points for new diagnostic and therapeutic strategies. Metabolomics data analysis can lead to the discovery of a "signature pathway" associated with the progression of bladder cancer; this aspect could be potentially valuable in predictions of clinical outcomes and the introduction of new treatments. However, further studies are needed to give stronger evidence and to make these tools feasible for use in clinical practice.

I.F.^{2020}: 5,924

437. Motzer R, **Porta C**, Alekseev B, Rha SY, Choueiri TK, Mendez-Vidal MJ, Hong SH, Kapoor A, Goh JC, Eto M, Bennett L, Wang J, Pan JJ, Saretsky TL, Perini RF, He CS, Mody K, Cella D. Health-related quality-of-life outcomes in patients with advanced renal cell carcinoma treated with lenvatinib plus pembrolizumab or everolimus versus sunitinib (CLEAR): a randomised, phase 3 study. *Lancet Oncol* 2022;23:768-80.

ABSTRACT - Background: Results from the phase 3 CLEAR study showed that lenvatinib plus pembrolizumab improved progression-free survival and overall survival compared with sunitinib in patients with advanced renal cell carcinoma. We aimed to assess the health-related quality-of-life (HRQOL) outcomes from the CLEAR study. Methods: This open-label, randomised, phase 3 study was done across 200 hospitals and cancer centres in 20 countries. Patients were required to be 18 years or older, with advanced clear-cell renal cell carcinoma, and a Karnofsky performance status of 70% or higher. Patients who had received previous systemic anticancer therapy for renal cell carcinoma were not eligible. Patients were randomly assigned (1:1:1) to lenvatinib (oral 20 mg per day) plus pembrolizumab (intravenous 200 mg every 21 days), lenvatinib (oral 18 mg per day) plus everolimus (oral 5 mg per day) in 21-day cycles, or sunitinib (oral 50 mg per day, 4 weeks on followed by 2 weeks off). Patients were assigned to treatments with a computer-generated randomisation scheme and were stratified by geographical region and Memorial Sloan Kettering Cancer Center prognostic groups. The primary endpoint, previously reported, was progression-free survival, and HRQOL was a secondary endpoint. Most HRQOL analyses were done in patients who underwent randomisation, received at least one dose of study treatment, and had any HRQOL data. Completion and compliance analyses were done in the full analysis set. Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS), European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), and the EQ-5D-3 Level (EQ-5D-3L) preference questionnaire were administered at baseline and on day 1 of each subsequent 21-day cycle. This study is registered with ClinicalTrials.gov, NCT02811861, and is closed to new participants. Findings: Between Oct 13, 2016, and July 24, 2019, 355 patients were randomly assigned to the lenvatinib plus pembrolizumab group, 357 to the lenvatinib plus everolimus group, and 357 to the

sunitinib group. Median follow-up for HRQOL analyses was 12·9 months (IQR 5·6-22·3). Because of the promising efficacy and safety results of lenvatinib plus pembrolizumab in the first-line setting, we focus the HRQOL results in this report on that combination versus sunitinib. Mean change from baseline in the lenvatinib plus pembrolizumab group compared with the sunitinib group was -1·75 (SE 0·59) versus -2·19 (0·66) for FKSI-DRS, -5·93 (0·86) versus -6·73 (0·94) for EORTC QLQ-C30 global health status/quality of life (GHS/QOL), and -4·96 (0·85) versus -6·64 (0·94) for the EQ-5D visual analogue scale (VAS). Median time to first deterioration in the lenvatinib plus pembrolizumab group compared with the sunitinib group was 9·14 weeks (95% CI 6·43-12·14) versus 12·14 weeks (9·14-15·29; HR 1·13 [95% CI 0·94-1·35], log-rank p=0·20) for FKSI-DRS, 12·00 weeks (7·29-15·14) versus 9·14 weeks (6·29-12·14; 0·88 [0·74-1·05], log-rank p=0·17) for EORTC QLQ-C30 GHS/QOL, and 9·43 weeks (6·43-12·29) versus 9·14 weeks (6·29-12·00; 0·83 [0·70-0·99], log-rank p=0·041) for the EQ-5D VAS. Median time to definitive deterioration in the lenvatinib plus pembrolizumab group compared with the sunitinib group was 134·14 weeks (95% CI 120·00-not estimable) versus 117·43 weeks (90·14-131·29; HR 0·70 [95% CI 0·53-0·92], log-rank p=0·0081) for FKSI-DRS, 114·29 weeks (102·14-153·29) versus 75·14 weeks (57·29-105·14; 0·60 [0·47-0·77], log-rank p<0·0001) for EORTC QLQ-C30 GHS/QOL, and 124·86 weeks (94·71-134·57) versus 74·86 weeks (54·14-96·00; 0·67 [0·53-0·85], log-rank p=0·0012) for the EQ-5D VAS. No outcomes on any of the instruments significantly favoured sunitinib over lenvatinib plus pembrolizumab. Most HRQOL comparisons of lenvatinib plus everolimus versus sunitinib were similar or favoured sunitinib. Interpretation: These HRQOL results demonstrate that patients given lenvatinib plus pembrolizumab treatment had similar or favourable scores compared with patients given sunitinib, particularly with respect to time to definitive deterioration. These results support the efficacy and safety profile of lenvatinib plus pembrolizumab as first-line therapy for patients with advanced renal cell carcinoma.

I.F.^{2021}: 54,433

438. De Biasi S, Guida A, Lo Tartaro D, Fanelli M, Depenni R, Dominici M, Finak G, **Porta C**, Paolini A, Borella R, Bertoldi C, Cossarizza A, Sabbatini R, Gibellini L. Redistribution of CD8+ T cell subsets in metastatic renal cell carcinoma patients treated with anti-PD-1 therapy. *Cytometry A* 2022;101:597-605.

ABSTRACT - Renal-cell carcinoma (RCC) is responsible for the majority of tumors arising from the kidney parenchyma. Although a progressive improvement in median overall survival has been observed after the introduction of anti-PD-1 therapy, many patients do not benefit from this treatment. Therefore, we have investigated T cell dynamics to find immune modification induced by anti-PD-1 therapy. Here, we show that, after therapy, RCC patients (5 responders and 14 nonresponders) are characterized by a redistribution of different subsets across the memory T cell compartment.

I.F.^{2021}: 4,714

439. Brunelli M, Martignoni G, Malpeli G, Volpe A, Cima L, Raspollini MR, Barbareschi M, Tafuri A, Masi G, Barzon L, Ammendola S, Villanova M, Cerruto MA, Milella M, Buti S, Bersanelli M, Fornarini G, Rebuzzi SE, Vellone VG, Gaggero G, Procopio G, Verzoni E, Bracarda S, Fanelli M, Sabbatini R, Passalacqua R, Perrucci B, Giganti MO, Donini M, Panni S, Tucci M, Prati V, Ortega C, Caliò A, Eccher A, Alongi F, Pappagallo G, Iacovelli R, Mosca A, Umari P, Montagnani I, Gobbo S, Atzori F, Munari E, Maruzzo M, Basso U, Pierconti F, Patriarca C, Colombo P, Lapini A, Conti G, Salvioni R, Bollito E, Cossarizza A, Massari F, Rizzo M, Franco R, Zito-Marino F, Aberasturi Plata Y, Galuppini F, Sbaraglia M, Fassan M, Dei Tos AP, Colecchia M, Moch H, Scaltriti M, **Porta C**, Delahunt B, Giannarini G, Bortolus R, Rescigno P, Banna GL, Signori A, Obispo MAL, Perris R, Antonelli A. Validation of a novel three-dimensional (3D fusion) gross sampling protocol for clear cell renal cell carcinoma to overcome intratumoral heterogeneity: the Meet-Uro 18 study. *J Pers Med* 2022;12:727.

ABSTRACT - We aimed to overcome intratumoral heterogeneity in clear cell renal cell carcinoma (clearRCC). One hundred cases of clearRCC were sampled. First, usual standard sampling was applied (1 block/cm of tumor); second, the whole tumor was sampled, and 0.6 mm cores were taken from each block to construct a tissue microarray; third, the residual tissue, mapped by taking pieces 0.5 × 0.5 cm, reconstructed the entire tumor mass. Precisely, six randomly derived pieces of tissues were placed in each cassette, with the number of cassettes being based on the diameter of the tumor (called multisite 3D fusion). Angiogenic and immune markers were tested. Routine 5231 tissue blocks were obtained. Multisite 3D fusion sections showed pattern A, homogeneous high vascular density (10%), pattern B, homogeneous low vascular density (8%) and pattern C, heterogeneous angiogenic signatures (82%). PD-L1 expression was seen as diffuse (7%), low (33%) and absent (60%). Tumor-infiltrating CD8 scored high in 25% (pattern hot), low in 65% (pattern weak) and zero in 10% of cases (pattern desert). Grading was upgraded in 26% of cases (G3-G4), necrosis and sarcomatoid/rhabdoid characters were observed in, respectively, 11 and 7% of cases after 3D fusion (p = 0.03). CD8 and PD-L1 immune expressions were higher in the undifferentiated G4/rhabdoid/sarcomatoid clearRCC subtypes (p = 0.03). Again, 22% of cases were set to intermediate to high risk of clinical recurrence due to new morphological findings of all aggressive G4, sarcomatoid/rhabdoid features by using 3D fusion compared to standard methods (p = 0.04). In conclusion, we propose an easy-to-apply multisite 3D fusion sampling that negates bias due to tumor heterogeneity.

I.F.^{2021}: 3,508

440. Nardone V, **Porta C**, Giannicola R, Correale P, Mutti L. Abemaciclib for malignant pleural mesothelioma. *Lancet Oncol* 2022;23:e237.

ABSTRACT - We read with interest the paper by Dean Fennell and colleagues on abemaciclib in patients with p16ink4A-deficient mesothelioma and appreciate that our previous in vitro study findings on the role of PRMT5 in this neoplasm may have formed part of the basis for the rationale of this trial. However, we believe there are several points that should be addressed. The authors included 26 patients in this study. 12 (46%) of them were in stage 1b or 2, so one wonders if there is an explanation for omitting surgery before enrolling them onto a clinical trial. The choice of disease control rate (DCR) as an endpoint is well known not to mirror overall survival in patients with malignant pleural mesothelioma; moreover, the null hypothesis of DCR in 11 (42%) of 26 patients is definitively very modest. Nevertheless, 14 (54%; 95% CI 36–71) of 26 patients with disease control after 12 weeks and six (23%) patients after 24 weeks of treatment are very average results achieved with standard second-line therapy as previously reviewed and commented on. Moreover, the study

provides no detail on the relative risk, DCR, or overall survival of the majority of patients with early, compared with more advanced, disease. The authors report the treatment toxicity, which is not negligible at all (six (23%) of 26 patients had a serious adverse event, one of which lead to treatment discontinuation; and one patient died due to an adverse event). We also note that the authors emphasise these results and compare them with those from CONFIRM (vs placebo) and CM743 while ignoring the serious caveat (ie, choice of control group and inclusion criteria) on these treatments provided by independent groups, and once more raising concern about the risks of online medical communication. On the whole, we believe the type of patients selected, the extremely low number of patients treated, the endpoint selected, and the comparison with other second-line treatments broadly adopted for patients with malignant pleural mesothelioma should suggest more caution before drawing conclusions on the efficacy of the therapy proposed.

I.F.^{2021}: 54,433

441. Caminiti C, Bryce J, Riva S, Ng D, Diodati F, Iezzi E, Sparavigna L, Novello S, **Porta C**, Del Mastro L, Procopio G, Cinieri S, Falzetta A, Calabrò F, Lorusso V, Cogoni AA, Tortora G, Maruzzo M, Passalacqua R, Cognetti F, Adamo V, Capelletto E, Ferrari A, Bagnalasta M, Bassi M, Nicelli A, De Persis D, D'Acunti A, Iannelli Patient E, Perrone F, Mitchell SA. Cultural adaptation of the Italian version of the Patient-Reported Outcomes Common Terminology Criteria for Adverse Event (PRO-CTCAE®). *Tumori* 2022 Jun 8:3008916221099558. doi: 10.1177/03008916221099558. Online ahead of print.

ABSTRACT - Introduction: US National Cancer Institute's (NCI) Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE®) is a library of 78 symptom terms and 124 items enabling patient reporting of symptomatic adverse events in cancer trials. This multicenter study used mixed methods to develop an Italian language version of this widely accepted measure, and describe the content validity and reliability in a diverse sample of Italian-speaking patients. Methods: All PRO-CTCAE items were translated in accordance with international guidelines. Subsequently, the content validity of the PRO-CTCAE-Italian was explored and iteratively refined through cognitive debriefing interviews. Participants (n=96; 52% male; median age 64 years; 26% older adults; 18% lower educational attainment) completed a PRO-CTCAE survey and participated in a semi-structured interview to determine if the translation captured the concepts of the original English language PRO-CTCAE, and to evaluate comprehension, clarity and ease of judgement. Test-retest reliability of the finalized measure was explored in a second sample (n=135). Results: Four rounds of cognitive debriefing interviews were conducted. The majority of PRO-CTCAE symptom terms, attributes and associated response choices were well-understood, and respondents found the items easy to judge. To improve comprehension and clarity, the symptom terms for nausea and pain were rephrased and retested in subsequent interview rounds. Test-retest reliability was excellent for 41/49 items (84%); the median intraclass correlation coefficient was 0.83 (range 0.64-0.94). Discussion: Results support the semantic, conceptual and pragmatic equivalence of PRO-CTCAE-Italian to the original English version, and provide preliminary descriptive evidence of content validity and reliability.

I.F.^{2021}: 2,149

442. Motzer RJ, Powles T, Burotto M, Escudier B, Bourlon MT, Shah AY, Suárez C, Hamzaj A, **Porta C**, Hocking CM, Kessler ER, Gurney H, Tomita Y, Bedke J, Zhang J, Simsek B, Scheffold C, Apolo AB, Choueiri TK. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. *Lancet Oncol* 2022;23:888-98.

ABSTRACT - Background: In the primary analysis of CheckMate 9ER, nivolumab plus cabozantinib showed superior progression-free survival, overall survival, and objective response over sunitinib in patients with previously untreated advanced renal cell carcinoma (median follow-up of 18·1 months). Here, we report extended follow-up of overall survival and updated efficacy and safety. Methods: This open-label, randomised, phase 3 trial was done in 125 hospitals and cancer centres across 18 countries. We included patients aged 18 years or older with previously untreated advanced or metastatic clear-cell renal cell carcinoma, a Karnofsky performance status of 70% or higher, measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 assessed by the investigator, any International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk category, and available tumour tissue for PD-L1 testing. Patients were randomly assigned (1:1) to nivolumab (240 mg) intravenously every 2 weeks plus cabozantinib (40 mg) orally once daily or sunitinib (50 mg orally) once daily (4 weeks per 6-week cycle). Randomisation, stratified by IMDC risk status, tumour PD-L1 expression, and geographical region, was done by permuted block within each stratum using a block size of four, via an interactive response system. The primary endpoint was progression-free survival by blinded independent central review. Overall survival was a secondary endpoint (reported here as the preplanned final analysis according to the protocol). Efficacy was assessed in all randomly assigned patients; safety was assessed in all patients who received at least one dose of any study drug. This ongoing study, closed to recruitment, is registered with ClinicalTrials.gov, NCT03141177. Findings: Between Sept 11, 2017, and May 14, 2019, 323 patients were randomly assigned to the nivolumab plus cabozantinib group and 328 to the sunitinib group. With an extended follow-up (data cutoff of June 24, 2021; median 32·9 months [IQR 30·4-35·9]), median overall survival was 37·7 months (95% CI 35·5-not estimable) in the nivolumab plus cabozantinib group and 34·3 months (29·0-not estimable) in the sunitinib group (hazard ratio [HR] 0·70 [95% CI 0·55-0·90], p=0·0043) and updated median progression-free survival was 16·6 months (12·8-19·8) versus 8·3 months (7·0-9·7; HR 0·56 [95% CI 0·46-0·68], p<0·0001). Grade 3-4 treatment-related adverse events occurred in 208 (65%) of 320 patients with nivolumab plus cabozantinib versus 172 (54%) of 320 with sunitinib. The most common grade 3-4 treatment-related adverse events were hypertension (40 [13%] of 320 patients in the nivolumab plus cabozantinib group vs 39 [12%] of 320 in the sunitinib group), palmar-plantar erythrodysaesthesia (25 [8%] vs 26 [8%]), and diarrhoea (22 [7%] vs 15 [5%]). Grade 3-4 treatment-related serious adverse events occurred in 70 (22%) of 320 patients in the nivolumab plus cabozantinib group and 31 (10%) of 320 in the cabozantinib group. One additional treatment-related death occurred with sunitinib (sudden death). Interpretation: With extended follow-up and preplanned final overall survival analysis per protocol, nivolumab plus cabozantinib demonstrated improved efficacy versus sunitinib, further supporting the combination in the first-line treatment of advanced renal cell carcinoma.

I.F.^{2021}: 54,433

443. Geynisman DM, Burotto M, **Porta C**, Suarez C, Bourlon

MT, Huo S, Del Tejo V, Du EX, Yang X, Betts KA, Choueiri TK, McGregor B. Temporal trends in grade 3/4 adverse events and associated costs of Nivolumab plus Cabozantinib versus Sunitinib for previously untreated advanced Renal Cell Carcinoma. *Clin Drug Investig* 2022;42:611-22.

ABSTRACT - Background and objectives: Novel immunotherapy-based combination treatments have drastically improved clinical outcomes for previously untreated patients with advanced/metastatic renal cell carcinoma (aRCC). This study aimed to assess the temporal trends in grade 3/4 adverse event (AE) rates and associated costs of nivolumab plus cabozantinib combination therapy versus sunitinib monotherapy in previously untreated patients with aRCC. Methods: Individual patient data from the CheckMate 9ER trial (nivolumab plus cabozantinib: N = 320; sunitinib: N = 320) were used to calculate the proportion of patients experiencing grade 3/4 AEs. AE unit costs were obtained from the United States (US) 2017 Healthcare Cost and Utilization Project (HCUP) and inflated to 2020 US dollars. Per-patient-per-month (PPPM) all-cause and treatment-related grade 3/4 AE costs over 18-months, temporal trends, and top drivers of AE costs were evaluated in both treatment arms. Results: Overall, the proportion of patients experiencing grade 3/4 AEs decreased over time, with the highest rates observed in the first 3 months for the nivolumab plus cabozantinib and sunitinib arms. Compared with sunitinib, nivolumab plus cabozantinib was associated with consistently lower average all-cause AE costs PPPM [month 3: $2021 vs. $3097 (p < 0.05); month 6: $1653 vs. $2418 (p < 0.05); month 12: $1450 vs. $1935 (p > 0.05); month 18: $1337 vs. $1755 (p > 0.05)]. Over 18 months, metabolism and nutrition disorders ($244), laboratory abnormalities ($182), and general disorders and administration site conditions ($122) were the costliest all-cause PPPM AE categories in the nivolumab plus cabozantinib arm, and laboratory abnormalities ($443), blood and lymphatic system disorders ($254), and metabolism and nutrition disorders ($177) were the costliest in the sunitinib arm. Trends of treatment-related AE costs were consistent with all-cause AE costs. Conclusions: Nivolumab plus cabozantinib was associated with lower costs of grade 3/4 AE management PPPM than sunitinib, which accumulated over the 18-month study period.

I.F.^{2021}: 3,58

444. Rizzo M, **Porta C**. CheckMate 9ER patient-reported outcomes: the patient is not willing to give up. *Ann Palliat Med* 2022;11:2177-9.

Clinical decisions, in addition to be supported by research evidence, should accommodate patients' preferences. Before choosing a treatment, we as clinicians should ask ourselves how much the patient is ready and willing to accept in exchange for an uncertain benefit. Therefore, we must first offer patients clear and accurate information about the potential benefits and harms of the recommended treatment, and secondly we must use valid tools to assess patients' perceptions of their general health and cancer symptoms over time. In the phase 3, open label, Checkmate 9ER trial, a total of 651 patients with advanced renal cell carcinoma (RCC) systemic treatment naïve were randomized 1:1 to the combination of nivolumab—a PD-L1 inhibitor—and cabozantinib—a VEGFR inhibitor—or sunitinib—another VEGFR inhibitor. At a median follow-up of 18.1 months, the combination of nivolumab and cabozantinib yielded a relevant benefit over sunitinib in terms of progression-free survival (PFS) [24 PFS events lower every 100 patients treated—number needed to treat (NNT) 4], overall survival (OS) (10 OS events lower every 100 patients treated—NNT 10) and objective response rate (29 responses more every 100 patients treated—NNT 3). Remarkably, responses were rapid and durable, with 3 complete remissions more every 100 patients treated. However, we must not divert attention from the potential harms associated with such a combined treatment which includes two agents endowed by a completely different mechanism of action and with a not overlapping safety profile. Indeed, patients receiving nivolumab plus cabozantinib experienced an absolute increase of 10% in grade ≥3 drug-related adverse events (DRAEs), and an absolute increase of 7% in DRAEs leading to treatment discontinuation, as compared to sunitinib alone. Patient-reported outcomes (PROs) are a powerful tool for providing optimal care. PROs reflect the patient's perception of his/her general health status and cancer symptoms influenced by the toxicities and efficacy of drugs over time without the coding of the patient's response by healthcare professionals. Prof. Cella and colleagues analyzed PROs in the phase 3 CheckMate 9ER study. PROs were assessed with a cancer-specific instrument—FKSI-19 (Functional Assessment of Cancer Therapy - Kidney Symptom Index-19) —and a cancer-generic instrument—EQ-5D-3L (EuroQoL-five dimension-three level) —as exploratory endpoints. The FKSI-19 measures disease-related emotional, physical and general symptoms, ability to work, as well as Health Related Quality of Life (HRQOL); higher scores identify better health state and impacts on HRQoL. The EQ-5D-3L collects data on motility, self-care, daily activities, stress, pain, depression and the patient's self-assessment health; higher scores indicate better health state. PRO instruments (FKSI-19 and EQ-5D-3L) were dispensed before the start of therapy, before each treatment cycle (every 2 weeks for nivolumab plus cabozantinib, every 6 weeks for sunitinib), and during follow-up visits (30 and 100 days from last dose). Although PROs are administered more frequently in the nivolumab plus cabozantinib arm, the analysis included only those assessment timepoints that were common to both treatment arms (before starting therapy and every 6 weeks until week 115). PROs completion rates in both treatment arms remained high in both treatment arms through week 115. Even though the differences in FKSI-19 and EQ-5D-3L scores between the two treatments were nominally significant, they did not overcome the threshold values [minimal important differences (MIDs)] established for individual change during the validation process. However, these within-patient thresholds are not validated to establish change in FKSI-19 scores as clinically significant at the group level. Indeed, when the thresholds were applied to define deterioration of quality of life (QoL) at the individual level, the combination of nivolumab and cabozantinib successfully decreased the risk of clinically meaningful deterioration in both all scores of the FKSI-19 (including disease-related symptoms) and in EQ-5D-3L VAS compared with sunitinib irrespective of the definition used (first, confirmed, or definitive deterioration). Although PROs were assessed at the start of each treatment cycle (after 2 weeks without sunitinib vs. 1 week without nivolumab, and no break for cabozantinib), analysis of the GP5 item ("I am bothered by side effects of treatment" rated on a 5-point Likert scale) until week 55 showed a lower proportion of patients bothered by treatment side effects in the nivolumab plus cabozantinib arm. Patients in the nivolumab plus cabozantinib arm showed a decreased risk (48% less) of being notably bothered by DRAEs than patients in sunitinib arm [odds ratio (OR), 0.52; 95% CI: 0.35–0.77]. At nearly 3 years of follow-up, patients continued to report improved HRQoL with nivolumab plus cabozantinib compared with sunitinib. Thus, we believe that the effectiveness of nivolumab plus cabozantinib as first-line treatment of advanced RCC is associated with clinically meaningful improvements in patients' quality of life and disease-related symptoms. A recent analysis by Servetto and colleagues indicated that for a proportion of recent cancer treatments, regulatory approval has occurred without published QoL results or with delayed publications of QoL data. Information on QoL assessment should be described in detail in study protocols and methods sections of manuscripts, and QoL results should be reported in the main publication in order to fully explain

to the patient the benefit/harm ratio of a new treatment. The use of PROs in research and clinical practice has been limited by: (I) variability of measurements, (II) complexity and length of assessments, (III) lack of group-level thresholds, as well as (IV) inability to compare results. These limitations have been partially overcome with the creation of the Patient-Reported Outcome Measurement Information System (PROMIS), which states common measures, decreases the response burden on the patient, and simplifies scoring using item response theory and computer technology. Furthermore, we are confident that future studies will establish clinically meaningful minimum thresholds also for group-level differences and changes. Ultimately, analysis of PROs in the Checkmate 9ER trial confirms how much the patient is willing to accept in terms of short- and long-term side effects… because the patient is not willing to give up living longer.

I.F.[2021]: 1,925

445. Internò V, Triggiano G, De Santis P, Stucci LS, Tucci M, **Porta C**. Molecular aberrations stratify grade 2 Astrocytomas into several rare entities: prognostic and therapeutic implications. *Front Oncol* 2022;12:866623.

ABSTRACT - The identification of specific molecular aberrations guides the prognostic stratification and management of grade 2 astrocytomas. Mutations in isocitrate dehydrogenase (IDH) 1 and 2, found in the majority of adult diffuse low-grade glioma (DLGG), seem to relate to a favorable prognosis compared to IDH wild-type (IDH-wt) counterparts. Moreover, the IDH-wt group can develop additional molecular alterations worsening the prognosis, such as epidermal growth factor receptor amplification (EGFR-amp) and mutation of the promoter of telomerase reverse transcriptase (pTERT-mut). This review analyzes the prognostic impact and therapeutic implications of genetic alterations in adult LGG.

I.F.[2021]: 5,738

446. Mandriani B, Pellè E, Mannavola F, Palazzo A, Marsano RM, Ingravallo G, Cazzato G, Ramello MC, **Porta C**, Strosberg J, Abate-Daga D, Cives M. Development of anti-somatostatin receptors CAR T cells for treatment of neuroendocrine tumors. *J Immunother Cancer* 2022;10:e004854.

ABSTRACT - Background: Neuroendocrine tumors (NETs) overexpress somatostatin receptors (SSTRs). Methods: We developed a second-generation, ligand-based, anti-SSTR chimeric antigen receptor (CAR) incorporating the somatostatin analog octreotide in its extracellular moiety. Results: Anti-SSTR CAR T cells exerted antitumor activity against SSTR+NET cell linesin vitro. The killing activity was highly specific, as demonstrated by the lack of CAR T cell reactivity against NET cells engineered to express mutated variants of SSTR2/5 by CRISPR/Cas9. When adoptively transferred in NSG mice, anti-SSTR CAR T cells induced significant antitumor activity against human NET xenografts. Although anti-SSTR CAR T cells could recognize the murine SSTRs as shown by their killing ability against murine NET cells, no obvious deleterious effects on SSTR-expressing organs such as the brain or the pancreas were observed in mice. Conclusions: Taken together, our results establish anti-SSTR CAR T cells as a potential candidate for early phase clinical investigations in patients with NETs. More broadly, the demonstration that a known peptide drug can direct CAR T cell targeting may streamline the potential utility of multiple peptide motifs and provide a blueprint for therapeutic applications in a variety of cancers.

I.F.[2021]: 12,469

447. Internò V, Rudà R, Sergi MC, Soffietti R, **Porta C**. Newly diagnosed Glioblastoma Multiforme (GBM) during COVID-19 pandemic: changes in therapeutic approach to minimize in-hospital SARS-COV-2 contagion in pre-vaccine era. *Acta Biomed* 2022;93:e2022067.

ABSTRACT - COVID-19 pandemic revolutionized the way in which cancer patients are treated worldwide. Regarding neuro-oncological patients, usually considered frail and with lower life-expectancy in respect to other oncological patients, the international scientific community had to urgently reorganize the treatment approach in order to minimize the risk of in-hospital contagious. For GBM patients, adjuvant treatments have been evaluated with even much more attention with regard to the expected efficacy. As a consequence, an hypofractioned radiotherapy regimen has been preferred in order to reduce the daily hospital accesses and, especially in pMGMT unmethylated patients, chemotherapy with Temozolomide was avoided. Here, we made a comprehensive evaluation of the neurooncological community suggestions regarding GBM treatment in the pre-vaccine era of COVID-19 pandemic.

I.F.[2021]: n.r.

448. Santoni M, Massari F, Matrana MR, Basso U, De Giorgi U, Aurilio G, Buti S, Incorvaia L, Rizzo M, Martignetti A, Maslov D, Tawagi K, Philon E, Blake Z, **Porta C**, Battelli N. Statin use improves the efficacy of nivolumab in patients with advanced renal cell carcinoma. *Eur J Cancer* 2022;172:191-8.

ABSTRACT - Background: Statins are widely used in an ageing population, including subjects with solid malignancies. However, no conclusive evidence is currently available on their potential influence on patients' outcome. We aimed to assess whether statin exposure affects the survival of patients with metastatic renal cell carcinoma (mRCC) treated with nivolumab. Patients and methods: Medical records of patients with documented mRCC treated with second- or third-line nivolumab were reviewed at ten institutions from Italy, Spain and the USA. Patients were assessed for overall survival (OS), progression-free survival (PFS), and overall clinical benefit. Univariate and multivariate analyses were used to explore the association of variables of interest with survival. Results: A total of 219 patients with mRCC receiving nivolumab between January 2016 and September 2021 were eligible for inclusion in this study; 59 (27%) were statin users. The median OS (34.4 versus 18.6 months, p = 0.017) and PFS (11.7 versus 4.6 months, p = 0.013) resulted apparently longer in statin users. Stratified by age, longer median OS and PFS were associated with statin exposure in both patients aged ≥70 y (median OS: 21.4 versus 10.1 months, p = 0.047; median PFS: 16.4 versus 4.6 months, p = 0.022) and <70 y (median OS: 34.4 versus 21.4 months, p = 0.043; median PFS: 10.3 versus 4.6 months, p = 0.042). Overall clinical benefit resulted higher in statin users than non-users (71% versus 54%, p = 0.030). Conclusions: Our study suggests a prognostic impact of statin use in patients receiving nivolumab for mRCC.

I.F.[2021]: 10,002

449. Felici C, Mannavola F, Stucci LS, Duda L, Cafforio P, **Porta C**, Tucci M. Circulating tumor cells from melanoma patients show phenotypic plasticity and metastatic potential

in xenograft NOD.CB17 mice. *BMC Cancer* 2022;22:754.

ABSTRACT - Background: Innovative therapies have improved the overall survival in melanoma, although a high number of patients still experience disease progression or recurrence. Ex-vivo culture of circulating tumour cells (CTCs) represents a valuable laboratory resource for in-depth characterization of rare cell populations responsible for disease progression. Methods: CTCs from patients with metastatic melanoma were in-vitro established. Their stemness was demonstrated by both phenotypic and genotypic assays, as well as by functional studies. Xenograft experiments in NOD.CB17 mice injected with CTCs from a single patient were completed. Data were analysed by Student's test and results expressed as mean ± SEM. Results: CTCs share the mutational profile with primary cells, an intermediate epithelial-mesenchymal transition (EMT) phenotype and high expression of the immunosuppressive factors. A subclonal CTC population exhibited stem cell properties as high aldehyde dehydrogenase 1 activity, melanosphere-forming ability, and expression of major stemness transcription factors. Xenograft experiments confirmed the CTC ability to generate melanoma in-vivo and revealed enhanced metastatic propensity. Conclusions: CTCs play a relevant role in melanoma and may actively contribute to drive the disease progression and metastasis. Thus, they are a unique potential tool for pharmacogenomic studies to guide treatment strategies in advanced disease.
I.F.^{2021}: 4,638

450. Maroto P, **Porta C**, Capdevila J, Apolo AB, Viteri S, Rodriguez-Antona C, Martin L, Castellano D. Cabozantinib for the treatment of solid tumors: a systematic review. her *Adv Med Oncol* 2022 Jul 13;14:17588359221107112.

ABSTRACT - Background: Cabozantinib is approved, in various settings, for the treatment of renal cell carcinoma, medullary thyroid cancer, and hepatocellular carcinoma, and it has been investigated for the treatment of other cancers. With the available evidence and the real-world performance of cabozantinib compared with clinical trial data, we performed a systematic review of cabozantinib monotherapy as treatment for solid tumors in adults. Methods: This study was designed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses and registered with PROSPERO (CRD42020144680). We searched for clinical and observational studies of cabozantinib monotherapy for solid tumors using Embase, MEDLINE, and Cochrane databases (October 2020), and screened relevant congress abstracts. Eligible studies reported clinical or safety outcomes, or biomarker data. Small studies (n < 25) and studies of cabozantinib combination therapies were excluded. Quality was assessed using National Institute for Health and Care Excellence methodology, and study characteristics were described qualitatively. Results: Of 2888 citations, 114 were included (52 randomized studies, 29 observational studies, 32 nonrandomized phase I or II studies or pilot trials, and 1 analysis of data from a randomized study and a nonrandomized study). Beyond approved indications, other tumors studied were castration-resistant prostate cancer, urothelial carcinoma, Ewing sarcoma, osteosarcoma, uveal melanoma, non-small-cell lung cancer, Merkel cell carcinoma, glioblastoma, pheochromocytomas and paragangliomas, cholangiocarcinoma, gastrointestinal stromal tumor, colorectal cancer, salivary gland cancer, carcinoid and pancreatic neuroendocrine tumors, and breast, endometrial and ovarian cancers. The most common adverse events were hypertension, diarrhea, and fatigue. Conclusion: The identified evidence demonstrates the positive efficacy/effectiveness of cabozantinib monotherapy in various solid tumor types, with safety findings being consistent with those observed with other VEGFR-targeting tyrosine kinase inhibitors. When available, real-world findings were consistent with the data reported from clinical trials. A limitation of this review is the high proportion of abstracts; however, this allowed us to capture the most up-to-date findings.
I.F.^{2021}: 5,485

451. Stewart GD, Klatte T, Cosmai L, Bex A, Lamb BW, Moch H, Sala E, Siva S, **Porta C***, Gallieni M* (*co-Senior Authors). The multispeciality approach to the management of localised kidney cancer. *Lancet* 2022 Jul 19:S0140-6736(22)01059-5. doi: 10.1016/S0140-6736(22)01059-5. Online ahead of print.

ABSTRACT - Historically, kidney cancer was approached in a siloed single-speciality way, with urological surgeons managing the localised stages of the disease and medical oncologists caring for patients if metastases developed. However, improvements in the management of localised kidney cancer have occurred rapidly over the past two decades with greater understanding of the disease biology, diagnostic options, and innovations in curative treatments. These developments are favourable for patients but provide a substantially more complex landscape for patients and clinicians to navigate, with associated challenging decisions about who to treat, how, and when. As such, the skill sets needed to manage the various aspects of the disease and guide patients appropriately outstrips the capabilities of one particular specialist, and the evolution of a multispeciality approach to the management of kidney cancer is now essential. In this Review, we summarise the current best multispeciality practice for the management of localised kidney cancer and the areas in need of further research and development.
I.F.^{2021}: 202,731

452. Castellano D, Apolo AB, **Porta C**, Capdevila J, Viteri S, Rodriguez-Antona C, Martin L, Maroto P. Cabozantinib combination therapy for the treatment of solid tumors: a systematic review. *Ther Adv Med Oncol* 2022 Jul 30;14:17588359221108691.

ABSTRACT - Background: Cabozantinib monotherapy is approved for the treatment of several types of solid tumors. Investigation into the use of cabozantinib combined with other therapies is increasing. To understand the evidence in this area, we performed a systematic review of cabozantinib combination therapy for the treatment of solid tumors in adults. Methods: This study was designed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the protocol was registered with PROSPERO (CRD42020144680). On 9 October 2020, we searched for clinical trials and observational studies of cabozantinib as part of a combination therapy for solid tumors using Embase, MEDLINE, and Cochrane databases, and by screening relevant congress abstracts. Eligible studies reported clinical or safety outcomes, or biomarker data. Randomized and observational studies with a sample size of fewer than 25 and studies of cabozantinib monotherapy were excluded. For each study, quality was assessed using National Institute for Health and Care Excellence methodology, and the study characteristics were described qualitatively. This study was funded by Ipsen. Results: Of 2421 citations identified, 32 articles were included (6 with results from randomized studies, 24 with results from non-randomized phase I or II studies, and 2 with results from both). The most commonly studied tumor types were metastatic urothelial carcinoma/genitourinary tumors and castration-resistant prostate cancer (CRPC). Findings from

randomized studies suggested that cabozantinib combined with other therapies may lead to better progression-free survival than some current standards of care in renal cell carcinoma, CRPC, and non-small-cell lung cancer. The most common adverse events were hypertension, diarrhea, and fatigue. Conclusion: This review demonstrates the promising efficacy outcomes of cabozantinib combined with other therapies, and a safety profile similar to cabozantinib alone. However, the findings are limited by the fact that most of the identified studies were reported as congress abstracts only. More evidence from randomized trials is needed to explore cabozantinib as a combination therapy further.
I.F.^{2021}: 5,485

453. Santoni M, Molina-Cerrillo J, Myint ZW, Massari F, Buchler T, Buti S, Matrana MR, De Giorgi U, Rizzo M, Zabalza IO, Galli L, Zucali PA, Aurilio G, Incorvaia L, Bassanelli M, Mammone G, Salfi A, Isella L, Mollica V, Grande E, **Porta C***, Battelli N* (*co-Senior Authors). Concomitant use of statins, metformin, or proton pump inhibitors in patients with advanced Renal Cell Carcinoma treated with first-line combination therapies. *Target Oncol* 2022;17:571-81.

ABSTRACT - Background: Drug-drug interactions are a major concern in oncology and may potentially affect the outcome of patients with cancer. Objective: In this study, we aimed to determine whether the concomitant use of statins, metformin, or proton pump inhibitors affects survival in patients with metastatic renal cell carcinoma treated with first-line combination therapies. Methods: Medical records of patients with documented metastatic renal cell carcinoma between January 2016 and November 2021 were reviewed at 17 participating centers. This research was conducted in ten institutions, including both referral centers and local hospitals. Patients were assessed for overall survival, progression-free survival, and overall clinical benefit. Univariate and multivariate analyses were conducted to explore the association of variables of interest with overall survival and progression-free survival. Results: A total of 304 patients receiving dual immunotherapy (51%) or immunotherapy/vascular endothelial growth factor-tyrosine kinase inhibitor (49%) combinations were eligible for inclusion in this retrospective study. Statin use was a significant prognostic factor for longer overall survival in a univariate analysis (hazard ratio 0.48, 95% confidence interval 0.26-0.87; p = 0.016) and a multivariate analysis (hazard ratio 0.48, 95% confidence interval 0.31-0.74; p < 0.001) and was significantly associated with an overall clinical benefit (83% in statin users vs 71% in non-users; p = 0.045). Otherwise, the use of metformin or proton pump inhibitors did not affect the outcome of these patients. Conclusions: Our study suggests a prognostic impact of statin use in patients receiving first-line immuno-oncology combinations. The mechanism of this interaction warrants further elucidation.
I.F.^{2021}: 4,864

454. Del Re M, Crucitta S, Paolieri F, Cucchiara F, Verzoni E, Bloise F, Ciampi R, Mercinelli C, Capuano A, Sportiello L, Martinetti A, Procopio G, Galli L, **Porta C**, Bracarda S, Danesi R. The amount of DNA combined with TP53 mutations in liquid biopsy is associated with clinical outcome of renal cancer patients treated with immunotherapy and VEGFR-TKIs. *J Transl Med* 2022;20:371.

ABSTRACT - Background: Despite the increasing number of treatment options, reliable prognostic/predictive biomarkers are still missing for patients affected by metastatic clear cell renal cell carcinoma (mccRCC). Methods: Patients with mccRCC undergoing standard first line treatment were enrolled. Blood (12 ml) was drawn at treatment baseline and circulating free DNA (cfDNA) was extracted from plasma. Next-generation sequencing (NGS) was performed on cfDNA using the Oncomine Pan-Cancer Cell-Free Assay and clinical outcomes were correlated with liquid biopsy findings. Results: A total of 48 patients were enrolled, 12 received immunotherapy and 36 received a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI). A cfDNA cut-off of 0.883 ng/µl stratified patients based on progression-free survival (PFS) and overall survival (OS) (p = 0.001 and p = 0.008, respectively). cfDNA amount was also correlated with best response (p = 0.006). Additional cfDNA cut-points divided patients into short, intermediate and long responders, with PFS of 4.87 vs 9.13 vs 23.1 months, respectively (p < 0.001). PFS resulted to be significantly shorter in carriers of mutant TP53 compared to not carriers (p = 0.04). Patients with high cfDNA levels and mutant TP53 have the worst PFS, while patients with low cfDNA amounts and no mutations in TP53 displayed the longest PFS (p = 0.004). Conclusions: The present study demonstrates that cfDNA and TP53 are potential predictive biomarkers of response in mccRCC to be further explored in larger and/or prospective studies.
I.F.^{2021}: 8,44

455. Tannir NM, Agarwal N, **Porta C**, Lawrence NJ, Motzer R, McGregor B, Lee RJ, Jain RK, Davis N, Appleman LJ, Goodman O Jr, Stadler WM, Gandhi S, Geynisman DM, Iacovelli R, Mellado B, Sepúlveda Sánchez JM, Figlin R, Powles T, Akella L, Orford K, Escudier B. Efficacy and Safety of Telaglenastat Plus Cabozantinib vs Placebo Plus Cabozantinib in Patients With Advanced Renal Cell Carcinoma: The CANTATA Randomized Clinical Trial. J*AMA Oncol* 2022;8:1411-8.

ABSTRACT - Importance: Dysregulated metabolism is a hallmark of renal cell carcinoma (RCC). Glutaminase is a key enzyme that fuels tumor growth by converting glutamine to glutamate. Telaglenastat is an investigational, first-in-class, selective, oral glutaminase inhibitor that blocks glutamine utilization and downstream pathways. Preclinically, telaglenastat synergized with cabozantinib, a VEGFR2/MET/AXL inhibitor, in RCC models. Objective: To compare the efficacy and safety of telaglenastat plus cabozantinib (Tela + Cabo) vs placebo plus cabozantinib (Pbo + Cabo). Design, setting, and participants: CANTATA was a randomized, placebo-controlled, double-blind, pivotal trial conducted at sites in the US, Europe, Australia, and New Zealand. Eligible patients had metastatic clear-cell RCC following progression on 1 to 2 prior lines of therapy, including 1 or more antiangiogenic therapies or nivolumab plus ipilimumab. The data cutoff date was August 31, 2020. Data analysis was performed from December 2020 to February 2021. Interventions: Patients were randomized 1:1 to receive oral cabozantinib (60 mg daily) with either telaglenastat (800 mg twice daily) or placebo until disease progression or unacceptable toxicity. Main outcomes and measures: The primary end point was progression-free survival (Response Evaluation Criteria in Solid Tumors version 1.1) assessed by blinded independent radiology review. Results: A total of 444 patients were randomized: 221 to Tela + Cabo (median [range] age, 61 [21-81] years; 47 [21%] women and 174 [79%] men) and 223 to Pbo + Cabo (median [range] age, 62 [29-83] years; 68 [30%] women and 155 [70%] men). A total of 276 (62%) patients had received prior immune checkpoint inhibitors, including 128 with prior nivolumab plus ipilimumab, 93 of whom had not received prior

antiangiogenic therapy. Median progression-free survival was 9.2 months for Tela + Cabo vs 9.3 months for Pbo + Cabo (HR, 0.94; 95% CI, 0.74-1.21; P = .65). Overall response rates were 31% (69 of 221) with Tela + Cabo vs 28% (62 of 223) with Pbo + Cabo. Treatment-emergent adverse event (TEAE) rates were similar between arms. Grade 3 to 4 TEAEs occurred in 160 patients (71%) with Tela + Cabo and 172 patients (79%) with Pbo + Cabo and included hypertension (38 patients [17%] vs 40 patients [18%]) and diarrhea (34 patients [15%] vs 29 patients [13%]). Cabozantinib was discontinued due to AEs in 23 patients (10%) receiving Tela + Cabo and 33 patients (15%) receiving Pbo + Cabo. Conclusions and relevance: In this randomized clinical trial, telaglenastat did not improve the efficacy of cabozantinib in metastatic RCC. Tela + Cabo was well tolerated with AEs consistent with the known risks of both agents.
I.F.^{2021}: 33,006

456. Lauricella E, Mandriani B, Cavallo F, Pezzicoli G, Chaoul N, **Porta C***, Cives M* (*co-Senior Authors). Angiogenesis in NENs, with a focus on gastroenteropancreatic NENs: from biology to current and future therapeutic implications. *Front Oncol* 2022;12:957068.

ABSTRACT - Neuroendocrine neoplasms (NENs) are highly vascularized malignancies arising from cells of the diffuse neuroendocrine system. An intricated cross-talk exists between NEN cells and the tumor microenvironment, and three main molecular circuits (VEGF/VEGFR pathway, FGF-dependent signaling and PDGF/PDGFR axis) have been shown to regulate angiogenesis in these neoplasms. Multiple randomized trials have investigated antiangiogenic agents over the past two decades, and sunitinib is currently approved for the treatment of advanced, progressive, G1/G2 pancreatic NENs. In recent years, two phase III clinical trials have demonstrated the efficacy and safety of surufatinib, a multi-tyrosine kinase angioimmune inhibitor, in patients with well-differentiated pancreatic and extrapancreatic NENs, and two studies of this agent are currently underway in Europe and US. The HIF-2α inhibitor belzutifan has recently received regulatory approval for the treatment of tumors arising in the context of Von-Hippel Lindau syndrome including pancreatic NENs, and a study of this drug in patients with sporadic tumors is presently ongoing. Combinations of antiangiogenic agents with chemotherapeutics and targeted drugs have been tested, with accumulating toxicities being a matter of concern. The potential of antiangiogenic agents in fine-tuning the immune microenvironment of NENs to enhance the activity of immune checkpoint inhibitors has been only partially elucidated, and further research should be carried out at this regard. Here, we review the current understanding of the biology of angiogenesis in NENs and provide a summary of the latest clinical investigations on antiangiogenic drugs in this malignancy.
I.F.^{2021}: 5,738

457. Rizzo M, Varnier L, Pezzicoli G, Pirovano M, Cosmai L, **Porta C**. IL-8 and its role as a potential biomarker of resistance to anti-angiogenic agents and immune checkpoint inhibitors in metastatic renal cell carcinoma. *Front Oncol* 2022;12:990568.

ABSTRACT - The therapeutic armamentarium of metastatic Renal Cell Carcinoma (mRCC) has consistently expanded in recent years, with the introduction of VEGF/VEGFR (Vascular Endothelial Growth Factor/Vascular Endothelial Growth Factor Receptor) inhibitors, mTOR (mammalian Target Of Rapamycin) inhibitors and Immune Checkpoint (IC) inhibitors. Currently, for the first-tline treatment of mRCC it is possible to choose between a VEGFR-TKI (VEGFR-Tyrosine Kinase Inhibitor) monotherapy, an ICI-ICI (Immune Checkpoint Inhibitor) combination and an ICI-VEGFRTKI combination. However, a consistent part of patients does not derive benefit from first-line therapy with ICIs; moreover, the use of combination regimens exposes patients to significant toxicities. Therefore, there is a critical need to develop prognostic and predictive biomarkers of response to VEGFR-TKIs and ICIs, and measurement of serum IL-8 is emerging as a potential candidate in this field. Recent retrospective analyses of large phase II and phase III trials found that elevated baseline serum IL-8 correlated with higher levels of tumor and circulating immunosuppressive myeloid cells, decreased T cell activation and poor response to treatment. These findings must be confirmed in prospective clinical trials; however, they provide evidence for a potential use of serum IL-8 as biomarker of resistance to VEGFR-TKIs and ICIs. Considering the amount of new agents and treatment regimens which are transforming the management of metastatic renal cell carcinoma, serum IL-8 could become a precious resource in tailoring the best therapy for each individual patient with the disease.
I.F.^{2021}: 5,738

458. Zengin ZB, Pal SK, McDermott DF, Escudier B, Hutson TE, **Porta C**, Verzoni E, Atkins MB, Kasturi V, Rini B. Temporal characteristics of adverse events of Tivozanib and Sorafenib in previously treated kidney cancer. *Clin Genitourin Cancer* 2022;20:553-7.

ABSTRACT - Introduction: Tivozanib, vascular endothelial growth factor receptor inhibitor, met the primary endpoint of improved progression free survival compared to sorafenib in the phase 3 TIVO-3 study in patients with previously treated metastatic renal cell carcinoma. In this study we sought to understand the temporal characteristics of treatment related adverse events (TRAEs) and frequency and timing of the dose modifications. Materials and methods: In this open label, randomized, phase 3 TIVO-3 study, previously treated patients with a diagnosis of metastatic renal cell carcinoma and with measurable disease were included. Patients were randomized to receive either tivozanib 1.5 mg orally once daily in 4-week cycles or sorafenib 400 mg orally twice daily continuously. Based on updated safety analysis data (cutoff date of August 15, 2019), time to onset of the most commonly reported TRAEs, duration of toxicity, rate of dose modifications was calculated for each treatment arm. Results: Overall, 350 patients were randomly assigned to receive tivozanib or sorafenib;173 patients from the tivozanib arm and 170 patients from the sorafenib arm were included in this analysis. Patients received a median of 11.9 cycles (336 days) and 6.7 cycles (192 days) of tivozanib and sorafenib, respectively. Dose reductions, interruptions and treatment discontinuations were 25%, 50%, and 21%, and 39%, 50%, and 30% in the tivozanib and sorafenib arms, respectively, with a longer time to onset of TRAEs in the tivozanib arm. Conclusion: Tivozanib was associated with less TRAEs, fewer dose modifications, a longer time to onset and a shorter duration of TRAEs compared to sorafenib.
I.F.^{2021}: 3,121

459. McGregor B, Geynisman DM, Burotto M, **Porta C**, Suarez C, Bourlon MT, Del Tejo V, Du EX, Yang X, Sendhil SR, Betts KA, Huo S. Grade 3/4 Adverse Event Costs of Immuno-oncology Combination Therapies for Previously Untreated Advanced Renal Cell Carcinoma. *Oncologist* 2022;28:72-9.

ABSTRACT - Background: Despite 4 approved combination regimens in the first-line setting for advanced renal cell carcinoma (aRCC), adverse event (AE) costs data are lacking. Materials and methods: A descriptive analysis on 2 AE cost comparisons was conducted using patient-level data for the nivolumab-based therapies and published data for the pembrolizumab-based therapies. First, grade 3/4 AE costs were compared between nivolumab + ipilimumab vs. nivolumab + cabozantinib vs. pembrolizumab + axitinib using data from the CheckMate 214 (median follow-up [mFU]: 13.1 months), CheckMate 9ER (mFU: 12.8 months), and KEYNOTE-426 (mFU: 12.8 months) trials, respectively. Second, grade 3/4 AE costs were compared between nivolumab + ipilimumab vs. nivolumab + cabozantinib vs. pembrolizumab + lenvatinib using data from the CheckMate 214 (mFU: 26.7 months), CheckMate 9ER (mFU: 23.5 months), and KEYNOTE-581 (mFU: 26.6 months) trials, respectively. Per-patient costs for all-cause and treatment-related grade 3/4 AEs with corresponding any-grade AE rates ≥ 20% were calculated based on the Healthcare Cost and Utilization Project database and inflated to 2020 US dollars. Results: Per-patient all-cause grade 3/4 AE costs for nivolumab + ipilimumab vs. nivolumab + cabozantinib vs. pembrolizumab + axitinib were $2703 vs. $4508 vs. $5772, and treatment-related grade 3/4 AE costs were $741 vs. $2722 vs. $4440 over ~12.8 months of FU. For nivolumab + ipilimumab vs. nivolumab + cabozantinib vs. pembrolizumab + lenvatinib, per-patient all-cause grade 3/4 AE costs were $3120 vs. $5800 vs. $9285, while treatment-related grade 3/4 AE costs were $863 vs. $3162 vs. $5030 over ~26.6 months of FU. Conclusion: Patients with aRCC treated with first-line nivolumab-based therapies had lower grade 3/4 all-cause and treatment-related AE costs than pembrolizumab-based therapies, suggesting a more favorable cost-benefit profile.
I.F.^{2021}: 5,025

460. Choueiri T, **Porta C**, Suárez C, Hainsworth J, Voog E, Duran I, Reeves J, Czaykowski P, Castellano D, Chen J, Sedarati F, Powles T. Randomized phase II trial of Sapanisertib ± TAK-117 vs. Everolimus in patients with advanced renal cell carcinoma after VEGF-targeted therapy. *Oncologist* 2022;27:1048-57.

ABSTRACT - Background: Sapanisertib, a dual mTORC1/2 inhibitor, may offer more complete inhibition of the PI3K/AKT/mTOR pathway than mTORC1 inhibitors, such as everolimus. This phase II study evaluated the efficacy and safety of single-agent sapanisertib and sapanisertib plus the PI3Kα inhibitor TAK-117, vs. everolimus in patients with advanced clear cell renal cell carcinoma (ccRCC) that had progressed on or after VEGF-targeted therapy. Materials and methods: Patients with histologically confirmed, advanced ccRCC were randomized 1:1:1 to receive single-agent everolimus 10 mg once daily, single-agent sapanisertib 30 mg once weekly, or sapanisertib 4 mg plus TAK-117 200 mg, both once daily for 3 days/week, in 28-day cycles. The primary endpoint was progression-free survival (PFS). Results: Ninety-five patients were treated with everolimus or sapanisertib (n = 32 each), or sapanisertib plus TAK-117 (n = 31). There were no significant differences in PFS among the 3 groups or across any subgroups. Median PFS was 3.8 months with everolimus vs. 3.6 months with sapanisertib (HR, 1.33; 95% CI, 0.75-2.36), and 3.1 months with sapanisertib plus TAK-117 (HR, 1.37; 95% CI, 0.75-2.52). No significant differences in overall survival were seen among groups. Overall response rate was 16.7%, 0%, and 7.1%, respectively. Discontinuations due to treatment-emergent adverse events were 15.6%, 28.1%, and 29.0%. Conclusion: Sapanisertib with or without TAK-117 was less tolerable and did not improve efficacy vs. everolimus in patients with advanced ccRCC who had relapsed after or were refractory to VEGF-targeted therapies. Dual mTORC1/2 inhibition may not be an effective therapeutic approach for these patients.
I.F.^{2021}: 5,025

461. Sprangers B, Leaf DE, **Porta C**, Soler MJ, Perazella MA. Diagnosis and management of immune checkpoint inhibitor-associated acute kidney injury. *Nat Rev Nephrol* 2022;18:794-805.

ABSTRACT - Since their introduction into clinical practice a decade ago, immune checkpoint inhibitors (ICIs) have had an overwhelming impact on cancer treatment. Use of these agents in oncology continues to grow; however, the increased use of these agents has been associated with a parallel increase in ICI-associated immune-related adverse events, which can affect virtually any organ, including the kidneys. ICI-associated acute kidney injury (ICI-AKI) occurs in 2-5% of patients treated with ICIs. Its occurrence can have important consequences, including the temporary or permanent discontinuation of ICIs or other concomitant anticancer therapies and the need for prolonged treatment with corticosteroids. Various mechanisms have been proposed to underlie the development of ICI-AKI, including loss of tolerance to self-antigens, reactivation of drug-specific effector T cells, and the production of kidney-specific autoantibodies. ICI-AKI most commonly manifests as acute tubulointerstitial nephritis on kidney biopsy and generally shows a favourable response to early initiation of corticosteroids, with complete or partial remission achieved in most patients. The evaluation of patients with suspected ICI-AKI requires careful diagnostic work-up and kidney biopsy for patients with moderate-to-severe ICI-AKI to ensure accurate diagnosis and inform appropriate treatment.
I.F.^{2021}: 42,439

462. Rebuzzi SE, Signori A, Stellato M, Santini D, Maruzzo M, De Giorgi U, Pedrazzoli P, Galli L, Zucali PA, Fantinel E, Carella C, Procopio G, Milella M, Boccardo F, Fratino L, Sabbatini R, Ricotta R, Panni S, Massari F, Sorarù M, Santoni M, Cortellini A, Prati V, Soto Parra HJ, Atzori F, Di Napoli M, Caffo O, Messina M, Morelli F, Prati G, Nolè F, Vignani F, Cavo A, Roviello G, Llaja Obispo MA, **Porta C**, Buti S, Fornarini G, Banna GL. The prognostic value of baseline and early variations of peripheral blood inflammatory ratios and their cellular components in patients with metastatic renal cell carcinoma treated with nivolumab: The Δ-Meet-URO analysis. *Front Oncol* 2022;12:955501.

ABSTRACT - Background: Treatment choice for metastatic renal cell carcinoma (mRCC) patients is still based on baseline clinical and laboratory factors. Methods: By a pre-specified analysis of the Meet-URO 15 multicentric retrospective study enrolling 571 pretreated mRCC patients receiving nivolumab, baseline and early dynamic variations (Δ) of neutrophil, lymphocyte, and platelet absolute cell counts (ACC) and their inflammatory ratios (IR) were evaluated alongside their association with the best disease response and overall (OS) and progression-free survival (PFS). Multivariable analyses on OS and PFS between baseline and Δ ACC and IR values were investigated with receiving operating curves-based cut-offs. Results: The analysis included 422 mRCC patients. Neutrophil-to-lymphocyte ratio (NLR) increased over time due to consistent neutrophil increase (p < 0.001). Higher baseline platelets (p = 0.044) and lower

lymphocytes (p = 0.018), increasing neutrophil Δ (p for time-group interaction <0.001), higher baseline IR values (NLR: p = 0.012, SII: p = 0.003, PLR: p = 0.003), increasing NLR and systemic immune-inflammatory index (SII) (i.e., NLR x platelets) Δ (p for interaction time-group = 0.0053 and 0.0435, respectively) were associated with disease progression. OS and PFS were significantly shorter in patients with baseline lower lymphocytes (p < 0.001 for both) and higher platelets (p = 0.004 and p < 0.001, respectively) alongside early neutrophils Δ (p = 0.046 and p = 0.033, respectively). Early neutrophils and NLR Δ were independent prognostic factors for both OS (p = 0.014 and p = 0.011, respectively) and PFS (p = 0.023 and p = 0.001, respectively), alongside baseline NLR (p < 0.001 for both) and other known prognostic variables. Conclusions: Early neutrophils and NLR Δ may represent new dynamic prognostic factors with clinical utility for on-treatment decisions.
I.F.^{2021}: 5,738

463. Rizzo M, Pezzicoli G, Santoni M, Caliò A, Martignoni G, **Porta C**. MiT translocation renal cell carcinoma: A review of the literature from molecular characterization to clinical management. *Biochim Biophys Acta Rev Cancer* 2022;1877:188823.

ABSTRACT - Microphthalmia Transcription Factor (MiT) family aberration-associated renal cell carcinoma is a rare disease, whose true prevalence is unknown, due to the need of molecular confirmation, commonly by Fluorescent In Situ Hybridization (FISH), for its diagnosis. In fact, this tumor is commonly misdiagnosed, often labeled as clear cell RCC, papillary RCC and chromophobe RCC. It is typically observed in young patients, and it can have indolent or aggressive behavior. In the case of aggressive behavior, the disease is rapidly progressive, showing little-to-no response to the drugs commonly used to treat the usual types of RCC. In this review, we focus on the biological and pathological features of this neoplasm, their impact on its clinical manifestations and we analyze the few experiences of treatment reported in the literature.
I.F.^{2021}: 11,414

464. Del Re M, Crucitta S, Omarini C, Bargagna I, Mongillo M, Palleschi M, Stucci S, Meattini I, D'Onofrio R, Lorenzini G, Biondani P, De Giorgi U, **Porta C**, Livi L, Natalizio S, Fontana A, Giontella E, Angelini L, Fogli S, Danesi R. Concomitant administration of proton pump inhibitors does not significantly affect clinical outcomes in metastatic breast cancer patients treated with ribociclib. *Breast* 2022;66:157-61.

ABSTRACT - Background: Gastric pH changes by proton-pump-inhibitors (PPIs) were found to affect progression-free survival (PFS) in metastatic breast cancer (mBC) patients treated with palbociclib. The current study was aimed at investigating whether the same effect could occur in patients treated with ribociclib. Patients and methods: Patients with hormone-positive/HER-2-negative mBC candidates for first-line treatment with ribociclib were enrolled in this retrospective-cohort study. Patients were classified as "no concomitant PPIs" or "concomitant PPIs"; PPI administration covered the entire or not less than 2/3 of treatment with ribociclib. All clinical interventions were made according to clinical practice. Results: A total of 128 patients were consecutively enrolled in the study; 78 belonged to the "no concomitant PPIs" group and 50 to the "concomitant PPIs" group. One hundred and six patients were endocrine-sensitive and received ribociclib and letrozole, while 22 were endocrine-resistant and were treated with ribociclib and fulvestrant. The most prescribed PPI was lansoprazole. According to PFS, patients taking PPIs had a PFS almost superimposable to those assuming ribociclib and endocrine therapy alone (35.3 vs. 49.2 months, p = 0.594). No difference in PFS was observed in estrogen-sensitive or estrogen-resistant mBC in the presence or absence of concomitant PPI treatment (p = 0.852). No correlation with adverse events was found including grade>2 hematological toxicities. Conclusions: The present study supports the hypothesis that the concomitant use of PPIs does not compromise the efficacy of ribociclib in a real-life setting.
I.F.^{2021}: 4,254

465. Rudà R, Bruno F, Pellerino A, Pronello E, Palmiero R, Bertero L, Crasto S, Polo V, Vitaliani R, Trincia E, Internò V, **Porta C**, Soffietti R. Observational real-life study on regorafenib in recurrent glioblastoma: does dose reduction reduce toxicity while maintaining the efficacy? *J Neurooncol* 2022 Oct 30. doi: 10.1007/s11060-022-04155-9. Epub ahead of print. PMID: 36309895.

ABSTRACT - Purpose: In the phase 2 REGOMA trial, regorafenib improved overall survival, as compared with lomustine, in glioblastoma (GBM) patients at first progression after chemoradiation. Recently, some real-life trials showed similar impact on survival but a higher rate of adverse events than in REGOMA, thus raising concerns over tolerability. The aim of this study was to assess the efficacy and tolerability of a lower intensity regorafenib regimen. Patients and methods: Regorafenib daily dose was gradually increased from 80 to 160 mg across the first 2 cycles. Progression-free survival (PFS) and overall survival (OS) were defined as time from regorafenib initiation and disease progression or death. Results: Sixty-six GBM patients were included. Median age was 60.0 years. Median PFS and OS following regorafenib were 2.7 and 7.1 months, respectively. Best RANO response to regorafenib were partial response (PR) in 10 (15.1%), stable disease in 17 (25.8%), and progressive disease in 39 (59.1%) patients. Forty-six (69.7%) patients presented adverse events of any grade, and 21 (31.8%) grade 3-4 toxicity. In a multivariable analysis, higher age and absence of MGMTp methylation were significantly associated with poorer disease control after regorafenib. Conclusions: Our study is the largest observational real-life study on the use of regorafenib. Our lower intensity regimen proved as effective as the standard 160 mg daily schedule (mPFS and mOS being 2.7 vs 2.0 months and 7.1 vs 7.4 months in our study vs REGOMA, respectively). Moreover, we observed a higher rate of PRs as compared with REGOMA (15.0% vs 3.0%).
I.F.^{2021}: 4,506

466. Rizzo M, Chiellino S, Gernone A, **Porta C**. Cisplatin-based chemotherapy for the treatment of metastatic collecting duct carcinomas: a real-world, retrospective analysis. *Front Oncol* 2022;12:939953.

ABSTRACT - Collecting duct carcinomas (CDCs) are a particularly rare subtype of kidney cancer, endowed by a particularly poor prognosis. Since no active treatments have been established for CDCs, due to similarities with upper tract urothelial carcinomas, the use of the cisplatin-gemcitabine doublet is usually recommended. Here we report a retrospective analysis of 36 metastatic CDCs treated, as everyday clinical practice, with either cisplatin-gemcitabine or cisplatin-gemcitabine-paclitaxel from 2005 to 2021. Thirty-three patients received gemcitabine (1000 mg/m2, days 1 and 8) and cisplatin (70 mg/m2, day 1), while 3

were treated with paclitaxel (80 mg/m2, days 1 and 8), gemcitabine (1000 mg/m2, days 1 and 8) and cisplatin (70 mg/m2, day 1), every 21 days for a maximum of 6 cycles. Eight out of 36 patients (22.2%) experienced a partial response, while 9 others (25%) had a disease stabilization. No benefit was observed in the only 3 patients treated with the triplet. Median PFS was just 6 months, while median OS was 8 months. The commonest grade ≥3 treatment-related adverse events were: neutropenia (75%, 11.1% of febrile neutropenia), anemia (50%), thrombocytopenia (38.8%), and vomiting (8.3%). Dose omissions and dose reductions were common, and few frail patients started the treatment with a 25% dose reduction. In conclusion, our real-world experience confirmed the modest activity and relevant toxicity of cisplatin-based chemotherapy for the treatment of CDCs. More translational studies and novel study designs are thus badly needed in these still orphan tumors.
I.F.^{2021}: 5,738

467. Rebuzzi SE, Signori A, Buti S, Banna GL, Murianni V, Damassi A, Maruzzo M, Giannarelli D, Tortora G, Galli L, Rizzo M, De Giorgi U, Antonuzzo L, Bracarda S, Cartenì G, Atzori F, Tamberi S, Procopio G, Fratino L, Lo Re G, Santoni M, Baldessari C, Astone A, Calabrò F, Brunelli M, **Porta C**, Rescigno P, Basso U, Fornarini G. Validation of the Meet-URO score in patients with metastatic renal cell carcinoma receiving first-line nivolumab and ipilimumab in the Italian Expanded Access Program. *ESMO Open* 2022;7:100634.

ABSTRACT - Background: The Meet-URO score allowed a more accurate prognostication than the International Metastatic RCC Database Consortium (IMDC) for patients with pre-treated metastatic renal cell carcinoma (mRCC) by adding the pre-treatment neutrophil-to-lymphocyte ratio and presence of bone metastases. Materials and methods: A post hoc analysis was carried out to validate the Meet-URO score on the overall survival (OS) of patients with IMDC intermediate-poor-risk mRCC treated with first-line nivolumab plus ipilimumab within the prospective Italian Expanded Access Programme (EAP). We additionally considered progression-free survival (PFS) and disease response rates. Harrell's c-index was calculated to compare the accuracy of survival prediction. Results: Overall the EAP included 306 patients, with a median follow-up of 12.2 months, median OS was not reached, 1-year OS was 66.8% and median PFS was 7.9 months. By univariable analysis, both the IMDC score and the two additional variables of the Meet-URO score were associated with either OS or PFS (P < 0.001 for all comparisons). The four Meet-URO risk groups (G) had 1-year OS of 92%, 72%, 50% and 21% for G2 (29.1% of patients), G3 (28.8%), G4 (33.0%) and G5 (9.1%), respectively. OS was significantly shorter in each consecutive G (P = 0.001 for G3, P < 0.001 for both G4 and G5 compared to G2). Similarly, Meet-URO Gs 2-5 showed decreasing median PFS and response rates. The Meet-URO score showed the highest c-index for both OS (0.73) and PFS (0.67). Limitations include the post hoc nature of this analysis and the lack of a comparative arm to assess predictive value. Conclusion: The Meet-URO score appeared to show better prognostic classification than the IMDC alone in patients with mRCC at IMDC intermediate-poor risk treated with first-line nivolumab and ipilimumab.
I.F.^{2021}: 6,883

468. Meirson T, Nardone V, Pentimalli F, Markel G, Bomze D, D'Apolito M, Correale P, Giordano A, Pirtoli L, **Porta C**, Gray SG, Mutti L. Analysis of new treatments proposed for malignant pleural mesothelioma raises concerns about the conduction of clinical trials in oncology. *J Transl Med* 2022;20:593.

ABSTRACT - In this commentary, using existing clinical trial data and FDA approvals we propose that there is currently a critical need for an appropriate balancing between the financial impact of new cancer drugs and their actual benefit for patients. By adopting "pleural mesothelioma" as our clinical model we summarize the most relevant pertinent and available literature on this topic, and use an analysis of the reliability of the trials submitted for registration and/or recently published as a case in point to raise concerns with respect to appropriate trial design, biomarker based stratification and to highlight the ongoing need for balancing the benefit/cost ratio for both patients and healthcare providers.
I.F.^{2021}: 8,44

469. Rizzo M, **Porta C**. Concurrent stereotactic ablative radiotherapy and antiangiogenic targeted agents: redefining strategy. *Eur Urol Oncol* 2022;S2588-9311(22)00179-1 (Editoriale).

If, on one hand, the prognosis for patients with metastatic renal cell carcinoma (mRCC) has greatly improved with immune-based combinations, on the other hand their effectiveness could theoretically lead to a decrease in the use of locoregional treatments, such as cytoreductive nephrectomy, and radiotherapy (RT). However, RT as a whole, and stereotactic ablative body RT (SABR) in particular, should be regarded as a key treatment option within the global strategy for this disease. In cases of oligometastatic disease, SABR is associated with favorable oncological outcomes (high local control rates) and minimal toxicity, while SABR in polymetastatic RCC leads to high long-term local control rates, and possibly improves overall response to systemic therapy. To date, few prospective clinical trials have explored the activity, efficacy, and safety of RT combined with VEGFR-targeted tyrosine kinase inhibitors (TKIs). It is still unclear whether concomitant RT can contribute to prolong survival (either progression-free survival [PFS] or overall survival [OS]) without exacerbating the on-target toxicities of VEGFR TKIs. More recently, combinations of SABR and immune checkpoint inhibitor (ICIs) have been investigated from a mechanistic viewpoint. High-dose RT induced dynamic changes to the T-cell repertoire, thus promoting antitumor immune responses. Unfortunately, only a few prospective single-arm or retrospective studies are available, all with a small sample size and short follow-up. Furthermore, discrepancies between trial results have left several questions concerning the selection of patients and irradiation sites unanswered, and the effective clinical benefit of SABR + ICI combinations thus remains unresolved. However, recent preclinical evidence showed that high-dose RT, beyond killing cancer cells, also destroys the tumor microvasculature and could thus theoretically lead to additive antitumor activity. Liu et al retrospectively evaluated 74 patients treated with non-frontline ICI + VEGFR TKI combinations with or without SABR. Patients who received SABR experienced significantly better PFS (13.2 vs 5.0 mo) and OS (38.5 vs 15.4 mo). The cumulative toxicity of concomitant RT and VEGFR TKI treatment is a further critical issue to be considered. Overall, combinations of SABR and systemic agents have been associated with overall good tolerance, with grade ≥3 toxicity rates ranging from 0% to 13%. In this issue of European Urology Oncology, Gan et al. present results from the largest real-world multicenter retrospective study investigating the toxicity of concurrent use of cabozantinib, a multitargeted antiangiogenic agent, and cranial/extracranial SABR and/or conventional palliative RT (CRT). Of 127 patients, 118 (93%) received cabozantinib after at least one systemic therapy, 77 (60.6%) received

CRT, 39 (30.7%) received SABR, 11 (8.7%) received both CRT and SABR, and 67 (53%) took cabozantinib on RT days. The most common target sites for CRT were bone (84%), brain (9.1%), and lymph nodes (4.5%), while those for SABR were bone (56%), brain (36%), and lung (16%). Overall, the median time to cabozantinib treatment failure was 9.6 mo (95% confidence interval [CI] 8.4–12.0) and median OS was 20.4 mo (95% CI 14.4–26.4). Almost half of the patients treated with CRT (47.7%) and SABR (48%) experienced an adverse event (AEs) of any grade within 3-mo follow-up after completion of RT. Grade 3–4 AEs were observed in 6.3% of the overall population. There was a higher rate of grade 1–2 AEs for SABR + cabozantinib (50%) than for CRT + cabozantinib (31%), and a lower rate of grade 3–4 AEs for SABR + cabozantinib (3.6%) than for CRT + cabozantinib (6.3%). Most of the AEs reported were systemic (fatigue, 16–20%; diarrhea, 4–9%; nausea, 4–9%; and anorexia, 6–7%) and of low grade (grade 1–2). Brain metastases (26 patients overall) were treated more frequently with SABR (69%) than with CRT (31%), and a lower percentage of patients with brain metastases received cabozantinib on RT days (42%) than patients with bone (60%) or other-site metastases (60%). In accordance with the literature, no grade ≥3 AEs were observed in the group that received cranial SABR and TKI treatment simultaneously. In this real-world report, the synergistic toxicity of short-term RT and concurrent cabozantinib was modest, and mainly related to the RT site. In clinical practice, concomitant treatment with SABR and TKIs for sites with a high risk of complications, such as brain and liver, should be assessed by a multidisciplinary team and limited to selected cases. Evasive resistance to VEGF pathway inhibitors is mostly attributable to overexpression of various receptors (including MET, AXL, PDGFR, FGFR, ALK1) and growth factors (including HGF, PDGF, FGF, TGF-β) that modulate several VEGF-independent compensatory proangiogenic signaling pathways. The cumulative effect of SABR-induced intratumor immunogenicity and the broad-spectrum antiangiogenic activity of cabozantinib could overcome the evasive resistance mechanisms triggered by the first-line ICI + VEGFR TKI combination. Emerging data on HIF-2α inhibitors and on ICI rechallenges in the refractory setting are likely to guide the choice of subsequent systemic therapies. Several ongoing studies will help in better defining combinations of SABR with systemic treatments, including the IMMUNOs-SBRT phase 1 trial (ClinicalTrials.gov Identifier: NCT05259319), the SABR-PDL1 phase 2 trial (NCT02992912), and the OligoRARE (NCT04498767), SABRCOMET-3 (NCT03862911), and SABR-COMET-10 (NCT03721341) randomized phase 3 trials. Prospective data are needed to identify eligible patients, preferred systemic treatments, and the sites and timing for implementation of the SABR + VEGFR TKI combination strategy, as well as the appropriate agent(s) for subsequent systemic lines.

I.F.^{2021}: 8,512

470. Buti S, Basso U, Giannarelli D, De Giorgi U, Maruzzo M, Iacovelli R, Galli L, **Porta C**, Carrozza F, Procopio G, Fonarini G, Lo Re G, Santoni M, Sabbatini R, Cusmai A, Zucali PA, Aschele C, Baldini E, Zafarana E, Favaretto A, Leo S, Hamzaj A, Mirabelli R, Nole' F, Zai S, Chini C, Masini C, Fatigoni S, Rocchi A, Tamburini E, Cortellini A, Bersanelli M. Concomitant drugs prognostic score in patients with metastatic renal cell carcinoma receiving Ipilimumab and Nivolumab in the compassionate use program in Italy: brief communication. *J Immunother* 2023;46:22-26.

ABSTRACT - A concomitant drug-based score was developed by our group and externally validated for prognostic and predictive purposes in patients with advanced cancer treated with immune checkpoint inhibitors (ICIs). The model considers the use of three classes of drugs within a month before initiating ICI, assigning score 1 for each between proton pump inhibitor and antibiotic administration until a month before immunotherapy initiation and score 2 in case of corticosteroid intake. In the present analysis, the drug score was validated in a prospective population of 305 patients with metastatic renal cell carcinoma treated with ipilimumab plus nivolumab in the first-line setting. The value of the model in predicting overall survival and progression-free survival was statistically significant and clinically meaningful, with an overall survival rate at 12 months of 73% vs. 44% (P<0.0001), and median progression-free survival of 11.6 (95% CI: 9.1-14.1) months versus 4.8 (95% CI: 2.7-7.0) months (P=0.002), respectively, for patients belonging to the favorable group (score 0-1) versus the unfavorable (score 2-4). Further development will be represented by the gut microbiome analysis according to the drug-based model classification and to the outcome of patients to ICI therapy to demonstrate the link between drug exposure and immune sensitivity.

I.F.^{2021}: 4,912

471. Meza L, McDermott DF, Escudier B, Hutson TE, **Porta C**, Verzoni E, Atkins MB, Kasturi V, Pal SK, Rini B. Tivozanib in patients with advanced renal cell carcinoma previously treated with Axitinib: subgroup analysis from TIVO-3. *Oncologist* 2022 Dec 28:oyac255. Epub ahead of print.

ABSTRACT - Background: In phase III TIVO-3 trial, tivozanib improved progression-free survival (PFS) compared to sorafenib for patients with metastatic renal cell carcinoma (mRCC). However, the effectiveness of this drug after exposure to other selective VEGFR agents has not yet been defined. Herein, we characterize the clinical efficacy of tivozanib in patients with mRCC previously treated with axitinib. Methods: We identified patients from the intention to treat (ITT) population, in the TIVO-3 trial, who received treatment with axitinib before enrolment in the study and evaluated PFS, response rate (RR), and safety. Results: Out of 350 patients, 172 (83:89, tivozanib:sorafenib) had received prior treatment with axitinib in TIVO-3. In this subgroup, PFS was 5.5 months with tivozanib and 3.7 months with sorafenib (HR 0.68). RR was 13% and 8% favoring tivozanib. Conclusions: Tivozanib is active in the treatment of patients with mRCC who have progressed on prior therapies, including axitinib.

I.F.^{2021}: 5,837

472. Grünwald V, Powles T, Kopyltsov E, Kozlov V, Alonso-Gordoa T, Eto M, Hutson T, Motzer R, Winquist E, Maroto P, Keam B, Procopio G, Wong S, Melichar B, Rolland F, Oya M, Rodriguez-Lopez K, Saito K, McKenzie J, **Porta C**. Survival by depth of response and efficacy by International Metastatic Renal Cell Carcinoma Database Consortium subgroup with Lenvatinib plus Pembrolizumab versus Sunitinib in advanced Renal Cell Carcinoma: analysis of the phase 3 randomized CLEAR study. *Eur Urol Oncol* 2023 Jan 29:S2588-9311(23)00028-7. Epub ahead of print.

ABSTRACT - Background: The extent of tumor shrinkage has been deemed a predictor of survival for advanced/metastatic renal cell carcinoma (RCC), a disease with historically poor survival. Objective: To perform an exploratory analysis of overall survival (OS) by tumor response by 6 mo,

and to assess the efficacy and survival outcomes in specific subgroups. Design, setting, and participants: CLEAR was an open-label, multicenter, randomized, phase 3 trial of first-line treatment of advanced clear cell RCC. Intervention: Patients were randomized 1:1:1 to lenvatinib 20 mg orally daily with pembrolizumab 200 mg intravenously once every 3 wk, lenvatinib plus everolimus (not included in this analysis), or sunitinib 50 mg orally daily for 4 wk on treatment/2 wk of no treatment. Outcome measurements and statistical analysis: Landmark analyses were conducted to assess the association of OS with tumor shrinkage and progressive disease status by 6 mo. Progression-free survival, duration of response, and objective response rate (ORR) were analyzed by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk subgroup and by the presence of target kidney lesions. Efficacy was assessed by an independent review committee as per Response Evaluation Criteria in Solid Tumors version 1.1. Results and limitations: Landmark analyses by tumor shrinkage showed that patients enrolled to lenvatinib plus pembrolizumab arm with a confirmed complete response or >75% target-lesion reduction by 6 mo had a 24-mo OS probability of ≥91.7%. A landmark analysis by disease progression showed that patients with no progression by 6 mo had lower probabilities of death in both arms. Patients with an IMDC risk classification of intermediate/poor had longer median progression-free survival (22.1 vs 5.9 mo) and a higher ORR (72.4% vs 28.8%) with lenvatinib plus pembrolizumab versus sunitinib. Similarly, results favored lenvatinib plus pembrolizumab in IMDC-favorable patients and those with/without target kidney lesions. Limitations of the study are that results were exploratory and not powered/stratified. Conclusions: Lenvatinib plus pembrolizumab showed improved efficacy versus sunitinib for patients with advanced RCC; landmark analyses showed that tumor response by 6 mo correlated with longer OS.

I.F.^{2021}: 8,512

473. Choueiri TK, Eto M, Motzer RJ, De Giorgi U, Buchler T, Basappa NS, Méndez-Vidal MJ, Tjulandin S, Park SH, Melichar B, Hutson T, Alemany C, McGregor B, Powles T, Grunwald V, Alekseev B, Rha SY, Kopyltsov E, Kappor A, Gordoa TA, Goh JC, Staehler M, Merchan JR, Xie R, Perini RF, Mody K, McKenzie J, **Porta C**. Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma: extended follow-up from the phase 3 randomized, open-label CLEAR study. *Lancet Oncol* 2023;24:228-38.

ABSTRACT - Background: In the primary analysis of the CLEAR study, lenvatinib plus pembrolizumab significantly improved progression-free survival and overall survival versus sunitinib in patients with advanced renal cell carcinoma (data cutoff Aug 28, 2020). We aimed to assess overall survival based on 7 months of additional follow-up. Methods: This is a protocol-prespecified updated overall survival analysis (data cutoff March 31, 2021) of the open-label, phase 3, randomised CLEAR trial. Patients with clear-cell advanced renal cell carcinoma who had not received any systemic anticancer therapy for renal cell carcinoma, including anti-vascular endothelial growth factor therapy, or any systemic investigational anticancer drug, were eligible for inclusion from 200 sites (hospitals and cancer centres) across 20 countries. Patients were randomly assigned (1:1:1) to receive lenvatinib (20 mg per day orally in 21-day cycles) plus pembrolizumab (200 mg intravenously every 21 days; lenvatinib plus pembrolizumab group), lenvatinib (18 mg per day orally) plus everolimus (5 mg per day orally; lenvatinib plus everolimus group [not reported in this updated analysis]) in 21-day cycles, or sunitinib (50 mg per day orally, 4 weeks on and 2 weeks off; sunitinib group). Eligible patients were at least 18 years old with a Karnofsky performance status of 70 or higher. A computer-generated randomisation scheme was used, and stratification factors were geographical region and Memorial Sloan Kettering Cancer Center prognostic groups. The primary endpoint was progression-free survival assessed by independent imaging review according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). In this Article, extended follow-up analyses for progression-free survival and protocol-specified updated overall survival data are reported for the intention-to-treat population. No safety analyses were done at this follow-up. This study is closed to new participants and is registered with ClinicalTrials.gov, NCT02811861. Findings: Between Oct 13, 2016, and July 24, 2019, 1417 patients were screened for inclusion in the CLEAR trial, of whom 1069 (75%; 273 [26%] female, 796 [74%] male; median age 62 years [IQR 55-69]) were randomly assigned: 355 (33%) patients (255 [72%] male and 100 [28%] female) to the lenvatinib plus pembrolizumab group, 357 (33%) patients (275 [77%] male and 82 [23%] female) to the sunitinib group, and 357 (33%) patients to the lenvatinib plus everolimus group (not reported in this updated analysis). Median follow-up for progression-free survival was 27·8 months (IQR 20·3-33·8) in the lenvatinib plus pembrolizumab group and 19·4 months (5·5-32·5) in the sunitinib group. Median progression-free survival was 23·3 months (95% CI 20·8-27·7) in the lenvatinib plus pembrolizumab group and 9·2 months (6·0-11·0) in the sunitinib group (stratified hazard ratio [HR] 0·42 [95% CI 0·34-0·52]). Median overall survival follow-up was 33·7 months (IQR 27·4-36·9) in the lenvatinib plus pembrolizumab group and 33·4 months (26·7-36·8) in the sunitinib group. Overall survival was improved with lenvatinib plus pembrolizumab (median not reached [95% CI 41·5-not estimable]) versus sunitinib (median not reached [38·4-not estimable]; HR 0·72 [95% CI 0·55-0·93]). Interpretation: Efficacy benefits of lenvatinib plus pembrolizumab over sunitinib were durable and clinically meaningful with extended follow-up. These results support the use of lenvatinib plus pembrolizumab as a first-line therapy for patients with advanced renal cell carcinoma.

I.F.^{2021}: 54,433

474. McGregor B, Geynisman DM, Burotto M, Suarez C, Bourlon MT, Barata PC, Gulati S, Huo S, Ejzykowicz F, Blum SI, Del Tejo V, Hamilton M, May JR, Du EX, Wu A, Kral P, Ivanescu C, Chin A, Betts KA, Lee C-H, Choueiri TK, Cella D, **Porta C**. A matching-adjusted indirect comparison of Nivolumab plus Cabozantinib vs Pembrolizumab plus Axitinib in patients with advanced renal cell carcinoma. *Eur Urol Oncol* 2023 Feb 24;S2588-9311(23)00031-7. Epub ahead of print.

ABSTRACT - Background: The comparative efficacy and health-related quality of life (HRQoL) outcomes of nivolumab plus cabozantinib versus pembrolizumab plus axitinib as first-line treatments for advanced renal cell carcinoma (aRCC) have not been assessed in head-to-head trials. Objective: To assess the efficacy and HRQoL outcomes of nivolumab plus cabozantinib versus pembrolizumab plus axitinib. Design, setting, and participants: Patient-level data for nivolumab plus cabozantinib from the CheckMate 9ER trial and published data for pembrolizumab plus axitinib from the KEYNOTE-426 trial were used. CheckMate 9ER data were reweighted to match the key baseline characteristics as reported in KEYNOTE-426. Intervention: Nivolumab (240 mg every 2 wk) plus cabozantinib (40 mg once daily) and pembrolizumab (200 mg every 3 wk) plus axitinib (5 mg twice daily, initially). Outcome measurements and statistical analysis: Hazard ratios (HRs) for progression-free survival (PFS),

duration of response, overall survival (OS), and deterioration in HRQoL were assessed using weighted Cox proportional-hazard models, with sunitinib as a common anchor. Objective response rates (ORRs) and changes in HRQoL scores from baseline were assessed as difference-in-differences for the two treatments relative to sunitinib. Results and limitations: After balancing patient characteristics between the trials, nivolumab plus cabozantinib was associated with significantly improved PFS (HR [95% confidence interval {CI}] 0.70 [0.53-0.93]; p = 0.01) and a significantly decreased risk of confirmed deterioration in HRQoL (Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease-related Symptoms: HR [95% CI] 0.48 [0.34-0.69]) versus pembrolizumab plus axitinib. OS was similar between treatments (HR [95% CI] 0.99 [0.67-1.44]; p = 0.94). Nivolumab plus cabozantinib was associated with numerically greater ORRs (difference-in-difference [95% CI] 8.4% [-1.7 to 18.4]; p = 0.10) and longer duration of response (HR [95% CI] 0.79 [0.47-1.31]; p = 0.36) than pembrolizumab plus axitinib. Comparative studies using data with a longer duration of follow-up are warranted. Conclusions: Nivolumab plus cabozantinib significantly improved PFS and HRQoL compared with pembrolizumab plus axitinib as first-line treatment for aRCC.

I.F.^{2021}: 8,512

475. Barkan E, **Porta C**, Rabinovici-Cohen S, Tibollo V, Quaglini S, Rizzo M. Artificial intelligence-based prediction of overall survival in metastatic renal cell carcinoma. *Front Oncol* 2023;13:1021684.

ABSTRACT - Background and objectives: Investigations of the prognosis are vital for better patient management and decision-making in patients with advanced metastatic renal cell carcinoma (mRCC). The purpose of this study is to evaluate the capacity of emerging Artificial Intelligence (AI) technologies to predict three- and five-year overall survival (OS) for mRCC patients starting their first-line of systemic treatment. Patients and methods: The retrospective study included 322 Italian patients with mRCC who underwent systemic treatment between 2004 and 2019. Statistical analysis included the univariate and multivariate Cox proportional-hazard model and the Kaplan-Meier analysis for the prognostic factors' investigation. The patients were split into a training cohort to establish the predictive models and a hold-out cohort to validate the results. The models were evaluated by the area under the receiver operating characteristic curve (AUC), sensitivity, and specificity. We assessed the clinical benefit of the models using decision curve analysis (DCA). Then, the proposed AI models were compared with well-known pre-existing prognostic systems. Results: The median age of patients in the study was 56.7 years at RCC diagnosis and 78% of participants were male. The median survival time from the start of systemic treatment was 29.2 months; 95% of the patients died during the follow-up that finished by the end of 2019. The proposed predictive model, which was constructed as an ensemble of three individual predictive models, outperformed all well-known prognostic models to which it was compared. It also demonstrated better usability in supporting clinical decisions for 3- and 5-year OS. The model achieved (0.786 and 0.771) AUC and (0.675 and 0.558) specificity at sensitivity 0.90 for 3 and 5 years, respectively. We also applied explainability methods to identify the important clinical features that were found to be partially matched with the prognostic factors identified in the Kaplan-Meier and Cox analyses. Conclusions: Our AI models provide best predictive accuracy and clinical net benefits over well-known prognostic models. As a result, they can potentially be used in clinical practice for providing better management for mRCC patients starting their first-line of systemic treatment. Larger studies would be needed to validate the developed model.

I.F.^{2021}: 5,738

476. Internò V, Sergi MC, Metta ME, Guida M, Trerotoli P, Strippoli S, Circelli S, **Porta C***, Tucci M* (*co-Senior Authors). Melanoma brain metastases: a retrospective analysis of prognostic factors and efficacy of multimodal treatments. *Cancer (Basel)* 2023;15:1542.

ABSTRACT - Brain metastasis in cutaneous melanoma (CM) has historically been considered to be a dismal prognostic feature, although recent evidence has highlighted the intracranial activity of combined immunotherapy (IT). Herein, we completed a retrospective study to investigate the impact of clinical–pathological features and multimodal therapies on the overall survival (OS) of CM patients with brain metastases. A total of 105 patients were evaluated. Nearly half of the patients developed neurological symptoms leading to a negative prognosis (p = 0.0374). Both symptomatic and asymptomatic patients benefited from encephalic radiotherapy (eRT) (p = 0.0234 and p = 0.011). Lactate dehydrogenase (LDH) levels two times higher than the upper limit normal (ULN) at the time of brain metastasis onset was associated with poor prognosis (p = 0.0452) and identified those patients who did not benefit from eRT. Additionally, the poor prognostic role of LDH levels was confirmed in patients treated with targeted therapy (TT) (p = 0.0015) concerning those who received immunotherapy (IT) (p = 0.16). Based on these results, LDH levels higher than two times the ULN at the time of the encephalic progression identify those patients with a poor prognosis who did not benefit from eRT. The negative prognostic role of LDH levels on eRT observed in our study will require prospective evaluations.

I.F.^{2021}: 6,575

477. Sergi MC, Lauricella E, **Porta C**, Tucci M, Cives M. An update on Merkel cell carcinoma. *Biochim Biophys Acta Rev Cancer* 2023;1878:188880.

ABSTRACT - Merkel cell carcinoma (MCC) is a rare cancer of the skin characterized by a neuroendocrine phenotype and an aggressive clinical behavior. It frequently originates in sun-exposed body areas, and its incidence has steadily increased in the last three decades. Merkel cell polyomavirus (MCPyV) and ultraviolet (UV) radiation exposure are the main causative agents of MCC, and distinct molecular features have been documented in virus-positive and virus-negative malignancies. Surgery remains the cornerstone of treatment for localized tumors, but even when integrated with adjuvant radiotherapy is able to definitively cure only a fraction of MCC patients. While characterized by a high objective response rate, chemotherapy is associated with a short-lasting benefit of approximately 3 months. On the other hand, immune checkpoint inhibitors including avelumab and pembrolizumab have demonstrated durable antitumor activity in patients with stage IV MCC, and investigations on their use in the neoadjuvant or adjuvant setting are currently underway. Addressing the needs of those patients who do not persistently benefit from immunotherapy is currently one of the most compelling unmet needs in the field, and multiple clinical trials of new tyrosine kinase inhibitors (TKIs), peptide receptor radionuclide therapy (PRRT), therapeutic vaccines, immunocytokines as well as innovative forms of adoptive cellular immunotherapies are under clinical scrutiny at present.

I.F.^{2021}: 11,414

478. Belli C, Repetto M, Anand S, **Porta C**, Subbiah V, Curigliano G. The emerging role of PI3K inhibitors for solid

tumour treatment and beyond. *Br J Cancer* 2023 doi: 10.1038/s41416-023-02221-1. Epub ahead of print.

ABSTRACT - Phosphoinositide 3-kinases (PI3Ks) play a central role in tumourigenesis with recurrent activating mutations of its p110α subunit (PIK3CA) identified in several tumours. Although several PI3K inhibitors are approved for haematological malignancies, only alpelisib was approved in solid tumours and for the treatment of PIK3CA-related overgrowth spectrum (PROS) syndrome. Traditional PI3K inhibitors inhibit both wild-type and mutant PI3K with almost equal potency, thus limiting their efficacy due to on-target toxicity. Since the initiation of phase I clinical trials investigating next generation allosteric mutant and isoform selective PIK3CA inhibitors, there has been a surge in interest in PIK3CA targeting in solid tumours. Preclinical characterisation of these compounds showed that maximal mutant protein inhibition fails to elicit metabolic and glucose homoeostasis dysregulation, one of the dose limiting toxicities of both selective and pan PI3K inhibitors. While extreme selectivity can be hypothesised to grant activity and safety advantage to these novel agents, on the other hand reduced benefit can be speculated for patients harbouring multiple or rare PIK3CA mutations. This review summarises the current understanding of PI3K alterations and the state-of-the-art treatment strategies in PI3K driven solid tumours, while also exploring the potential intrinsic and acquired resistance mechanisms to these agents, and the emerging role of mutant selective PIK3CA inhibitors.
I.F.^{2021}: 9,075

479. Santoni M, Massari F, Myint ZW, Iacovelli R, Pichler M, Basso U, Kopecky J, Kucharz J, Buti S, Salfi A, Büttner T, De Giorgi U, Kanesvaran R, Fiala O, Grande E, Zucali PA, Fornarini G, Bourlon MT, Scagliarini S, Molina-Cerrillo J, Aurilio G, Matrana MR, Pichler R, Cattrini C, Büchler T, Seront E, Calabrò F, Pinto A, Berardi R, Zgura A, Mammone G, Ansari J, Atzori F, Chiari R, Zakopoulou R, Caffo O, Procopio G, Bassanelli M, Zampiva I, Messina C, Küronya Z, Mosca A, Bhuva D, Vau N, Incorvaia L, Rebuzzi SE, Roviello G, Zabalza IO, Rizzo A, Mollica V, Catalini I, Monteiro FSM, Montironi R, Battelli N, Rizzo M, **Porta C**. Clinico-Pathological Features Influencing the Prognostic Role of Body Mass Index in Patients With Advanced Renal Cell Carcinoma Treated by Immuno-Oncology Combinations (ARON-1). *Clin Genitourin Cancer* 2023:S1558-7673(23)00065-4. doi: 10.1016/j.clgc.2023.03.006. Epub ahead of print.

ABSTRACT - Background: Obesity has been associated with improved response to immunotherapy in cancer patients. We investigated the role of body mass index (BMI) in patients from the ARON-1 study (NCT05287464) treated by dual immuno-oncology agents (IO+IO) or a combination of immuno-oncology drug and a tyrosine kinase inhibitors (TKI) as first-line therapy for metastatic renal cell carcinoma (mRCC). Patients and methods: Medical records of patients with documented mRCC treated by immuno-oncology combinations were reviewed at 47 institutions from 16 countries. Patients were assessed for overall survival (OS), progression-free survival (OS), and overall clinical benefit (OCB), defined as the sum of the rate of partial/complete responses and stable disease. Univariate and multivariate analyses were used to explore the association of variables of interest with survival. Results: A total of 675 patients were included; BMI was >25 kg/m2 in 345 patients (51%) and was associated with improved OS (55.7 vs. 28.4 months, P < .001). The OCB of patients with BMI >25 kg/m2 versus those with BMI ≤25 kg/m2 was significantly higher only in patients with nonclear cell histology (81% vs. 65%, P = .011), and patients with liver metastases (76% vs. 58%, P = .007), Neutrophil to lymphocyte ratio >4 (77% vs 62%, P = .022) or treated by nivolumab plus ipilimumab (77% vs. 64%, P = .044). In the BMI ≤25 kg/m2 subgroup, significant differences were found between patients with NLR >4 versus ≤4 (62% vs. 82%, P = .002) and patients treated by IO+IO versus IO+TKIs combinations (64% vs. 83%, P = .002). Conclusion: Our study suggests that the prognostic significance and the association of BMI with treatment outcome varies across clinico-pathological mRCC subgroups.
I.F.^{2021}: 3,121

480. Lauricella E, Manicone A, Cavallo F, Dagrada GP, Centonze G, Bertulli R, Quattrone P, **Porta C***, Cives M* (*co-Senior Authors). Adamantinoma-like Ewing sarcoma of the salivary glands: a case report and systematic literature review. *Ther Adv Med Oncol* 2023;15:17588359231165979.

ABSTRACT - Adamantinoma-like Ewing sarcoma (ALES) of the salivary glands is an exceedingly rare malignancy defined by the t(11,22) EWSR1::FLI1 fusion, with complex epithelial differentiation. To identify features that can allow for better recognition of this disease entity, we reviewed all published reports of molecularly confirmed ALES of the salivary glands and explored epidemiological, clinical, radiological, pathological, and therapeutic characteristics of a population of 21 patients including a single newly reported patient from our group. We searched the English-language literature indexed in PubMed, Medline, Scopus, and Web of Science using the keyword 'Adamantinoma-like Ewing sarcoma' published up to June 2022. The median age at diagnosis was 46 years, and a slight female sex predilection was observed. Most tumors originated in the parotid gland (86%) and presented as a painless palpable mass with a median diameter of 3.6 cm. Metastatic dissemination was reported only in one patient (5%), and after a median follow-up of 13 months the 1-year overall survival rate was 92%. Salivary gland ALES were frequently misdiagnosed at presentation (62% of cases) and were pathologically characterized by the presence of highly monomorphic small round blue cells with infiltrative pattern and positive immunostaining for CD99 and high- and low-molecular weight cytokeratins. Epidemiological and clinical features of salivary gland ALES raise questions on the incorporation of this malignancy in the Ewing sarcoma family tumor group.
I.F.^{2021}: 5,485

481. Marletta S, Caliò A, Bogina G, Rizzo M, Brunelli M, Pedron S, Marcolini L, Stefanizzi L, Gobbo S, Princiotta A, **Porta C**, Pecoraro A, Antonelli A, Martignoni G. STING is a prognostic factor related to tumor necrosis, sarcomatoid dedifferentiation, and distant metastasis in clear cell renal cell carcinoma. *Virchows Arch* 2023. doi: 10.1007/s00428-023-03549-y. Epub ahead of print.

ABSTRACT - STING is a molecule involved in immune reactions against double-stranded DNA fragments, released in infective and neoplastic diseases, whose role in the interactions between immune and neoplastic cells in clear cell renal cell carcinoma has not been studied yet. We investigated the immunohistochemical expression of STING in a series of 146 clear-cell renal cell carcinomas and correlated it with the main patho-

logical prognostic factors. Furthermore, tumoral inflammatory infiltrate was evaluated and studied for the subpopulations of lymphocytes. Expression of STING was observed in 36% (53/146) of the samples, more frequently in high-grade (G3-G4) tumors (48%,43/90) and recurrent/metastatic ones (75%, 24/32) than in low grade (G1-G2) and indolent neoplasms (16%, 9/55). STING staining correlated with parameters of aggressive behavior, including coagulative granular necrosis ($p = 0.001$), stage ($p < 0.001$), and development of metastases ($p < 0.001$). Among prognostic parameters, STING immune expression reached an independent statistical significance ($p = 0.029$) in multivariable analysis, along with the stage and the presence of coagulative granular necrosis. About tumor immune-environment, no significant statistical association has been demonstrated between tumor-infiltrating lymphocytes and STING. Our results provide novel insights regarding the role of STING in aggressive clear cell renal cell carcinomas, suggesting its adoption as a prognostic marker and a potentially targetable molecule for specific immunotherapies.

I.F.^{2021}: 4,548

IMPACT FACTORS & H-Index

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H-index: **61**

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1. Galbusera M, Noris M, Rossi C, Orisio S, Caprioli J, Ruggeri ZM, Amadei B, Ruggenenti P, Vasile B, Casari G, Remuzzi G on behalf of the Italian Registry of familial and recurrent HUS/TTP (including **Porta C**). Increased fragmentation of von Willebrand factor, due to abnormal cleavage of the subunit, parallels disease activity in recurrent hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and discloses predisposition in families. *Blood* 1999;94:610-20.

ABSTRACT - We investigated here the changes in von Willebrand factor (vWF) multimers in recurrent, sporadic and familial forms of hemolytic uremic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP) to see whether they are actually proteolyzed in vivo in these patients. Molecular determinants of fragments in vWF were also characterized to identify possible sites of cleavage of the subunit. Unusually large vWF multimers were found in blood of 8 of 10 patients with reccurrent HUS/TTP, both in the acute phase and in remission, but never in familial and sporadic cases. Instead, all of the groups showed evidence of enhanced fragmentation of vWF multimers during the acute phase. Increased fragmentation was also shown by decrease in native 225-kD vWF subunit. In recurrent and sporadic HUS/TTP, enhanced fragmentation normalized at remission, but the abnormality persisted in familial HUS/TTP patients. The latter findings suggest that patients with familial HUS/TTP may have a congenital abnormality in vWF processing. Analysis with specific monoclonal antibodies showed the presence of the normal vWF fragments with apparent molecular mass of 189, 176, and 140 kD in all patients; however, in 6 recurrent and in 5 familial cases. novel fragments that differed in size from normal ones were found. The size of these abnormal fragments differed from one patient to another and none of them was ever found in normal plasma. These results documented, for the first time in HUS/TTP, an abnormal cleavage of the vWF subunit that might account for the increased fragmentation observed in these patients.
I.F. = 8,782
N. citazioni = 4

2. Noris M, Ruggenenti P, Perna A, Orisio S, Caprioli J, Skerka C, Vasile B, Zipfel PF, Remuzzi G on behalf of the Italian Registry of familial and recurrent HUS/TTP (including **Porta C**). Hypocomplementemia discloses genetic predisposition to hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: role of factor H abnormalities. *J Am Soc Nephrol* 1999;10:281-93.

ABSTRACT - Familial hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) carry a very poor outcome and have been reported in association with decreased serum levels of the third complement component (C3). Uncontrolled consumption in the microcirculation, possibly related to genetically determined deficiency in factor H - a modulator of the alternative pathway of complement activation - may account for decreased C3 serum levels even during disease remission and may predispose to intravascular thrombosis. In a case-control study by multivariate analysis, we correlated putative predisposing conditions, including low C3 serum levels, with history of disease in 15 cases reporting one or more episodes of familial HUS and TTP, in 25 age- and gender-matched healthy controls and in 63 case-relatives and 56 control-relatives, respectively. The relationship between history of disease, low C3, and factor H abnormalities was investigated in all affected families and in 17 controls. Seventy-three percent of cases compared with 16% of controls ($p < 0.001$), and 24% of case-relatives compared with 5% of control-relatives ($p = 0.005$) had decreased C3 serum levels. At multivariate analysis, C3 serum level was the only parameter associated with the disease within affected families ($p = 0.02$) and in the overall study population ($p = 0.01$). Thus, subjects with decreased C3 serum levels had a relative risk of HUS or TTP of 16.56% (95% confidence interval [CI], 1.66 to 162.39) within families and of 27.77 (95% confidence interval [CI], 2.44 to 314.19) in the overall population, compared to subjects with normal serum levels. Factor H abnormalities were found in four of the cases, compared with three of the healthy family members ($p = 0.02$) and none of the controls ($p = 0.04$) and, within families, factor H abnormalities were correlated with C3 reduction ($p < 0.05$). Reduced C3 clusters in familial HUS and TTP is likely related to a genetically determined deficiency in factor H and may predispose to the disease. Its demonstration may help identify subjects at risk in affected families.
I.F. = 6,182
N. citazioni = 135

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ABSTRACT - <u>Purpose</u>: The modulation of fluorouracil (FU) by folinic acid (leucovorin [LV]) has been shown to be effective in terms of tumor response rate in patients with advanced colorectal cancer, but a meta-analysis of nine trials previously published by our group failed to demonstrate a statistically significant survival difference between FU and FU-LV. We present an update of the meta-analysis, with a longer follow-up and the inclusion of 10 newer trials. <u>Patients and Methods</u>: Analyses are based on individual data from 3,300 patients randomized in 19 trials on an intent-to-treat basis. Two trials had multiple comparisons, leading to a total of 21 pair-wise comparisons. FU doses were similar in both arms in 10 pair-wise comparisons, 15% to 33% higher in the FU-alone arm in six comparisons, and more than 66% higher in five comparisons. <u>Results</u>: Overall analysis showed a two-fold increase in tumor response rates (11% for FU-LV v 21% for FU alone; odds ratio, 0.53; 95% CI, 0.44 to 0.63; p <.0001) and a small but statistically significant overall survival benefit for FU-LV over FU alone (median survival, 11.7 v 10.5 months, respectively; hazards ratio, 0.90; 95% CI, 0.87 to 0.94; p =.004), which were primarily seen in the first year. We observed a significant interaction between treatment benefit and dose of FU, with tumor response and overall survival advantages of FU-LV over FU-alone being restricted to trials in which a similar dose of FU was prescribed in both arms. <u>Conclusion</u>: This updated analysis demonstrates, on a large data set, that FU-LV improves both response rate and overall survival compared with FU alone and that this benefit is consistent across various prognostic factors.
I.F. = 9,835
N. citazioni = 321

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ABSTRACT - Purpose: Studies in cancer patients with venous thromboembolism suggested that low molecular weight heparin may prolong survival. In a double-blind study, we evaluated the effect of low molecular weight heparin on survival in patients with advanced malignancy without venous thromboembolism. Methods: Patients with metastasized or locally advanced solid tumors were randomly assigned to receive a 6-week course of subcutaneous nadroparin or placebo. The primary efficacy analysis was based on time from random assignment to death. The primary safety outcome was major bleeding. Results: In total, 148 patients were allocated to nadroparin and 154 patients were allocated to placebo. Mean follow-up was 1 year. In the intention-to-treat analysis the overall hazard ratio of mortality was 0.75 (95% CI, 0.59 to 0.96) with a median survival of 8.0 months in the nadroparin recipients versus 6.6 months in the placebo group. After adjustment for potential confounders, the treatment effect remained statistically significant. Major bleeding occurred in five (3%) of nadroparin-treated patients and in one (1%) of the placebo recipients (p = .12). In the a priori specified subgroup of patients with a life expectancy of 6 months or more at enrollment, the hazard ratio was 0.64 (95% CI, 0.45 to 0.90) with a median survival of 15.4 and 9.4 months, respectively. For patients with a shorter life expectancy, the hazard ratio was 0.88 (95% CI, 0.62 to 1.25). Conclusion: A brief course of subcutaneous low molecular weight heparin favorably influences the survival in patients with advanced malignancy and deserves additional clinical evaluation.
I.F. = 9,835
N. citazioni = 135

5. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA and others (including **Porta C**). Sunitinib versus Interferon alpha in metastatic renal cell carcinoma. *N Engl J Med* 2007;356:115-24.

ABSTRACT - Background: Since sunitinib malate has shown activity in two uncontrolled studies in patients with metastatic renal-cell carcinoma, a comparison of the drug with interferon alfa in a phase 3 trial is warranted. Methods: We enrolled 750 patients with previously untreated, metastatic renal-cell carcinoma in a multicenter, randomized, phase 3 trial to receive either repeated 6-week cycles of sunitinib (at a dose of 50 mg given orally once daily for 4 weeks, followed by 2 weeks without treatment) or interferon alfa (at a dose of 9 MU given subcutaneously three times weekly). The primary end point was progression-free survival. Secondary end points included the objective response rate, overall survival, patient-reported outcomes, and safety. Results: The median progression-free survival was significantly longer in the sunitinib group (11 months) than in the interferon alfa group (5 months), corresponding to a hazard ratio of 0.42 (95% confidence interval, 0.32 to 0.54; p<0.001). Sunitinib was also associated with a higher objective response rate than was interferon alfa (31% vs. 6%, p<0.001). The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the group treated with interferon alfa, whereas diarrhea was more frequent in the sunitinib group (p<0.05). Patients in the sunitinib group reported a significantly better quality of life than did patients in the interferon alfa group (p<0.001). Conclusions: Progression-free survival was longer and response rates were higher in patients with metastatic renal-cell cancer who received sunitinib than in those receiving interferon alfa.
I.F. = 44,016

6. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevrau C, Solska E, Desai AA, Rolland F, Demkov T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM for the TARGET Study Group (including **Porta C**). Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125-34.

ABSTRACT - Background: We conducted a phase 3, randomized, double-blind, placebo-controlled trial of sorafenib, a multikinase inhibitor of tumor-cell proliferation and angiogenesis, in patients with advanced clear-cell renal-cell carcinoma. Methods: From November 2003 to March 2005, we randomly assigned 903 patients with renal-cell carcinoma that was resistant to standard therapy to receive either continuous treatment with oral sorafenib (at a dose of 400 mg twice daily) or placebo; 451 patients received sorafenib and 452 received placebo. The primary end point was overall survival. A single planned analysis of progression-free survival in January 2005 showed a statistically significant benefit of sorafenib over placebo. Consequently, crossover was permitted from placebo to sorafenib, beginning in May 2005. Results: At the January 2005 cutoff, the median progression-free survival was 5.5 months in the sorafenib group and 2.8 months in the placebo group (hazard ratio for disease progression in the sorafenib group, 0.44; 95% confidence interval [CI], 0.35 to 0.55; P<0.01). The first interim analysis of overall survival in May 2005 showed that sorafenib reduced the risk of death, as compared with placebo (hazard ratio, 0.72; 95% CI, 0.54 to 0.94; P=0.02), although this benefit was not statistically significant according to the O'Brien-Fleming threshold. Partial responses were reported as the best response in 10% of patients receiving sorafenib and in 2% of those receiving placebo (P<0.001). Diarrhea, rash, fatigue, and hand-foot skin reactions were the most common adverse events associated with sorafenib. Hypertension and cardiac ischemia were rare serious adverse events that were more common in patients receiving sorafenib than in those receiving placebo. Conclusions: As compared with placebo, treatment with sorafenib prolongs progression-free survival in patients with advanced clear-cell renal-cell carcinoma in whom previous therapy has failed; however, treatment is associated with increased toxic effects.
I.F. = 44,016
N. citazioni = 4779

7. Eisen T, Oudard S, Szczylik C, Gravis G, Heinzer H, Middleton R, Cihon F, Anderson S, Shah S, Bukowski R, Escudier B for the TARGET Study Group (including **Porta C**). Sorafenib for older patients with renal cell carcinoma: subset analysis from a randomized trial. *J Natl Cancer Inst* 2008;100:1454-63.

ABSTRACT - Background: The perception that older cancer patients may be at higher risk than younger patients of toxic effects from cancer therapy but may obtain less clinical benefit from it may be based on the underrepresentation of older patients in clinical trials and the known toxic effects of cytotoxic chemotherapy. It is not known how older patients respond to targeted therapy. Methods: This retrospective subgroup analysis of data from the phase 3, randomized Treatment Approach in Renal Cancer Global Evaluation Trial examined the safety and efficacy of sorafenib in older (age ≥ 70 years, n = 115) and younger patients (age <70 years, n = 787) who received treatment for advanced renal cell carcinoma. Patient demographics and progression-free survival were recorded. Best tumor response, clinical benefit rate (defined as complete response plus partial response plus stable disease), time to self-reported health status deterioration, and toxic effects were assessed by descriptive statistics. Health-related quality of life was assessed with a Cox proportional hazards model. Kaplan–Meier analyses were used to summarize time-to-event data. Results: Median progression-free survival was similar in sorafenib-treated younger patients (23.9 weeks; hazard ratio [HR] for pro-

gression compared with placebo = 0.55, 95% confidence interval [CI] = 0.47 to 0.66) and older patients (26.3 weeks; HR = 0.43, 95% CI = 0.26 to 0.69). Clinical benefit rates among younger and older sorafenib-treated patients were also similar (83.5% and 84.3%, respectively) and were superior to those of younger and older placebo-treated patients (53.8% and 62.2%, respectively). Adverse events were predictable and manageable regardless of age. Sorafenib treatment delayed the time to self-reported health status deterioration among both older patients (121 days with sorafenib vs 85 days with placebo; HR = 0.66, 95% CI = 0.43 to 1.03) and younger patients (90 days with sorafenib vs 52 days with placebo; HR = 0.69, 95% CI = 0.59 to 0.81) and improved quality of life over that time. Conclusions: Among patients with advanced renal cell carcinoma receiving sorafenib treatment, outcomes of older (≥ 70 years) and younger (<70 years) patients were similar.
I.F. = 15,271
N. citazioni = 120

8. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, Negrier S, Chevreau C, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Anderson S, Hofilena G, Shan M, Pena C, Lathia C, Bukowski RM for the TARGET Study Group (including **Porta C**). Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III Treatment Approaches in Renal Cancer Global Evaluation Trial. *J Clin Oncol* 2009;27:3312-8.

ABSTRACT - Purpose: Mature survival data and evaluation of vascular endothelial growth factor (VEGF) as a prognostic biomarker from the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) study in patients with renal cell carcinoma (RCC) are reported. Patients and Methods: Nine hundred three previously treated patients were randomly assigned to receive sorafenib versus placebo. On demonstration of progression-free survival (PFS) benefit with sorafenib, patients assigned to placebo were offered sorafenib. Overall survival (OS) was determined at two planned interim analyses and one final analysis, with a secondary OS analysis conducted by censoring placebo patients who crossed over to sorafenib. The relationships between baseline VEGF level and prognosis and efficacy were evaluated. Results: The final OS of patients receiving sorafenib was comparable with that of patients receiving placebo (17.8 v 15.2 months, respectively; hazard ratio [HR] = 0.88; P = .146); however, when post–cross-over placebo survival data were censored, the difference became significant (17.8 v 14.3 months, respectively; HR = 0.78; P = .029). Adverse events at 16 months after cross over were similar to those previously reported. Baseline VEGF levels correlated with Eastern Cooperative Oncology Group performance status (P < .0001), Memorial Sloan-Kettering Cancer Center score (P < .0001), and PFS and OS in univariate (PFS, P = .0013; OS, P = .0009) and multivariate (PFS, P = .0231; OS, P = .0416) analyses of placebo patients and with short OS by multivariate analysis of patients receiving sorafenib (P = .0145). Both high-VEGF (P < .01) and low-VEGF (P < .01) groups benefited from sorafenib. Conclusion: Although an OS benefit was not seen on a primary intent-to-treat analysis, results of a secondary OS analysis censoring placebo patients demonstrated a survival advantage for those receiving sorafenib, suggesting an important cross-over effect. VEGF levels are prognostic for PFS and OS in RCC. The results of TARGET establish the efficacy and safety of sorafenib in advanced RCC.
I.F. = 17,157
N. citazioni = 926

9. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, Garcia-del-Muro X, Sosman JA, Solska E, Wilding G, Thompson JA, Kim ST, Chen I, Huang X, Figlin RA for the Sunitinib study group (including **Porta C**). Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:3584-90.

ABSTRACT - Purpose: A randomized, phase III trial demonstrated superiority of sunitinib over interferon alfa (IFN-alpha) in progression-free survival (primary end point) as first-line treatment for metastatic renal cell carcinoma (RCC). Final survival analyses and updated results are reported. Patients and Methods: Seven hundred fifty treatment-naïve patients with metastatic clear cell RCC were randomly assigned to sunitinib 50 mg orally once daily on a 4 weeks on, 2 weeks off dosing schedule or to IFN-alpha 9 MU subcutaneously thrice weekly. Overall survival was compared by two-sided log-rank and Wilcoxon tests. Progression-free survival, response, and safety end points were assessed with updated follow-up. Results: Median overall survival was greater in the sunitinib group than in the IFN-alpha group (26.4 v 21.8 months, respectively; hazard ratio [HR] = 0.821; 95% CI, 0.673 to 1.001; P = .051) per the primary analysis of unstratified log-rank test (P = .013 per unstratified Wilcoxon test). By stratified log-rank test, the HR was 0.818 (95% CI, 0.669 to 0.999; P = .049). Within the IFN-alpha group, 33% of patients received sunitinib, and 32% received other vascular endothelial growth factor-signaling inhibitors after discontinuation from the trial. Median progression-free survival was 11 months for sunitinib compared with 5 months for IFN-alpha (P < .001). Objective response rate was 47% for sunitinib compared with 12% for IFN-alpha (P < .001). The most commonly reported sunitinib-related grade 3 adverse events included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%). Conclusion: Sunitinib demonstrates longer overall survival compared with IFN-alpha plus improvement in response and progression-free survival in the first-line treatment of patients with metastatic RCC. The overall survival highlights an improved prognosis in patients with RCC in the era of targeted therapy.
I.F. = 17,157
N. citazioni = 1812

10. Scagliotti G, Novello S, Von Pawel J, Reck M, Rodrigues-Pereira J, Thomas M, Abrao-Miziara JE, Balint B, De Marinis F, Keller A, Aren O, Csollak M, Albert I, Barriso CH, Grossi F, Krzakowski M, Cupit L, Cihon F, Di Matteo S, Hanna N for the ESCAPE study group (including **Porta C**). Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:3584-90.

ABSTRACT - Purpose: This phase III, multicenter, randomized, placebo-controlled trial assessed the efficacy and safety of sorafenib, an oral multikinase inhibitor, in combination with carboplatin and paclitaxel in chemotherapy-naïve patients with unresectable stage IIIB or IV non-small-cell lung cancer (NSCLC). Patients and Methods: Nine hundred twenty-six patients were randomly assigned to receive up to six 21-day cycles of carboplatin area under the curve 6 and paclitaxel 200 mg/m(2) (CP) on day 1, followed by either sorafenib 400 mg twice a day (n = 464, arm A) or placebo (n = 462, arm B) on days 2 to 19. The maintenance phase after CP consisted of sorafenib 400 mg or placebo twice a day. The primary end point was overall survival (OS); secondary end points included progression-free survival and tumor response. Results: Overall demographics were balanced between arms; 223 patients (24%) had squamous cell histology. On the basis of a planned interim analysis, median OS was 10.7 months in arm A and 10.6 months in arm B (hazard ratio [HR] = 1.15; 95% CI, 0.94 to 1.41; P = .915). The study was terminated after the interim analysis concluded that the study was highly unlikely to meet its primary end point. A prespecified exploratory analysis revealed that patients with squamous cell histology had greater mortality in arm A than in arm B (HR = 1.85; 95% CI, 1.22 to 2.81). Main grade 3 or 4 sorafenib-related toxicities included rash (8.4%), hand-foot skin reaction (7.8%), and diarrhea (3.5%). Conclusion: No clinical benefit was observed from adding sorafenib to CP chemotherapy as first-line treatment for NSCLC.
I.F. = 17,157
N. citazioni = 1812

11. Fagnani D, Bertolini A, Catena L, Tomirotti M, Visini M, Alatri A, De Paoli A, Aondio GM, Milani M, Arpaia G, Cimminiello C on behalf of the POLONORD Group (including **Porta C**). The impact of antithrombotic prophylaxis on infectious complications in cancer patients with central venous catheters: an observational study. *Blood Coagul Fibrinolysis* 2009;20:35-40.

ABSTRACT - Infections in cancer patients after implantation of a central venous device (CVD) are not infrequent and are potentially serious. The possibility of limiting this complication with antithrombotic drugs is still debated. For this observational study, we recorded the routine management of CVD in cancer patients in 18 oncology centers in Lombardy (northern Italy), assessing the effect of antithrombotic prophylaxis on catheter-related infections. Out of 1410 patients enrolled, 451 received antithrombotic prophylaxis continuously after implantation of the central line. During a median follow-up of 30 months, 57 catheter-related infections were reported in the 1390 patients seen at least once at follow-up visits (4.1% of the whole series), giving an overall incidence of 0.10 infections per 1000 catheter days. This complication was significantly more frequent among patients with an indwelling central venous catheter, or peripherally inserted catheter, than among those with a port device, and the group not given antithrombotic prophylaxis had 0.14 infective complications/1000 CVD days compared with 0.05/1000 CVD days (odds ratio 2.4; 95% confidence interval 1.7-5.0) for those treated. Antithrombotic prophylaxis protected against infections at the catheter exit site and track but not against systemic infections. Confirming earlier evidence, this study found a reduction in catheter-related infections in patients given antithrombotic prophylaxis. However, this reduction, reflecting local infections, seems unlikely to be one of the mechanisms explaining the lower mortality among our patients treated with anticoagulants.
I.F. = 1,246
N. citazioni = 3

12. Llovet JM, Peña CE, Lathia CD, Shan M, Meinhardt G, Bruix J and the SHARP Investigators Study Group (including **Porta C**). Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. *Clin Cancer Res* 2012;18:2290-300.

ABSTRACT - Purpose: Validated biomarkers of prognosis and response to drug have not been identified for patients with hepatocellular carcinoma (HCC). One of the objectives of the phase III, randomized, controlled Sorafenib HCC Assessment Randomized Protocol (SHARP) trial was to explore the ability of plasma biomarkers to predict prognosis and therapeutic efficacy. Experimental design: In SHARP, 602 patients with advanced HCC were randomized to receive either oral sorafenib 400 mg twice a day per os or matching placebo daily on a continuous basis. Ten plasma biomarkers implicated in the pathogenesis of HCC were measured in 491 patients at baseline and in 305 after 12 weeks of treatment. The candidate biomarkers were analyzed to identify correlates of prognosis or predictors of response to sorafenib. Results: In both the entire patient population and the placebo cohort, baseline angiopoietin 2 (Ang2) and VEGF concentrations independently predicted survival. Clinical variables such as macroscopic vascular invasion, Eastern Cooperative Oncology Group (ECOG) performance status, and baseline α-fetoprotein and alkaline phosphatase concentrations also independently predicted survival in these groups. In the sorafenib cohort, trends toward enhanced survival benefit from sorafenib were observed in patients with high s-c-KIT or low hepatocyte growth factor concentration at baseline (P of interaction = 0.081 and 0.073, respectively). Conclusions: The angiogenesis biomarkers Ang2 and VEGF were independent predictors of survival in patients with advanced HCC. In contrast, none of the biomarkers tested significantly predicted response to sorafenib.
I.F. = 7,742
N. citazioni = 382

13. Grünwald V, Karakiewicz PI, Bavbek SE, Miller K, Machiels JP, Lee SH, Larkin J, Bono P, Rha SY, Castellano D, Blank CU, Knox JJ, Hawkins R, Anak O, Rosamilia M, Booth J, Pirotta N, Bodrogi I and the REACT Study Group (including **Porta C**). An international expanded-access programme of everolimus: addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy. *Eur J Cancer* 2012;48:324-32.

ABSTRACT - Background and objectives: The RECORD-1 trial established the clinical benefit of everolimus in patients with metastatic renal cell carcinoma (mRCC) after failure of initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) therapy. The REACT (RAD001 Expanded Access Clinical Trial in RCC) study was initiated to address an unmet medical need by providing everolimus prior to commercial availability, and also to further assess the safety and efficacy of everolimus in patients with VEGFr-TKI-refractory mRCC. Patients and methods: REACT (Clinicaltrials.gov: NCT00655252) was a global, open-label, expanded-access programme in patients with mRCC who were intolerant of, or who had progressed on or after stopping treatment with, any available VEGFr-TKI therapy. Patients received everolimus 10 mg once daily, with dose and schedule modifications allowed for toxicity. Patients were closely monitored for the development of serious and grades 3/4 adverse events (AEs). Response was assessed by RECIST every 3 months for the first year and every 6 months thereafter. Results: A total of 1367 patients were enroled. Safety findings and tumour responses were consistent with those observed in RECORD-1, with no new safety issues identified. The most commonly reported serious AEs were dyspnoea (5.0%), pneumonia (4.7%) and anaemia (4.1%), and the most commonly reported grades 3/4 AEs were anaemia (13.4%), fatigue (6.7%) and dyspnoea (6.5%). Best overall response was stable disease in 51.6% and partial response in 1.7% of patients. Median everolimus treatment duration was 14 weeks. Conclusion: Everolimus is well tolerated in patients with mRCC and demonstrates a favourable risk-benefit ratio.
I.F. = 4,944
N. citazioni = 81

14. Stein A, Bellmunt J, Escudier B, Kim D, Stergiopoulos SG, Mietlowski W, Motzer RJ for the RECORD-1 Trial Study Group (including **Porta C**). Survival prediction in Everolimus-treated patients with metastatic Renal Cell Carcinoma incorporating tumor burden response in the RECORD-1 trial. *Eur Urol* 2013;64:994-1002.

ABSTRACT - Background: The phase 3 RECORD-1 study demonstrated clinical benefit of everolimus over placebo (median progression-free survival: 4.9 mo compared with 1.9 mo, p<0.001) in treatment-resistant patients with metastatic renal cell carcinoma (mRCC). However, the Response Evaluation Criteria in Solid Tumors (RECIST) objective response rate was low. Objective: To explore the potential role of tumor burden response to everolimus in predicting patient survival. Design, setting, and participants: RECORD-1 patients with at least two tumor assessments (baseline and weeks 2-14) were included (n=246). Outcome measurements and statistical analysis: A multivariate Cox proportional hazard model was used to assess the impact of various prognostic factors on overall survival (OS). Components of RECIST progression were explored using univariate Cox regression. Results and limitations: The baseline sum of longest tumor diameters (SLD) and progression at weeks 2-14 were prognostic factors of OS by multivariate analysis. Univariate analysis at weeks 2-14 demonstrated that growth of nontarget lesions and appearance of new lesions were predictive of OS (p<0.001). This retrospective analysis used data from one arm of one trial; patients in the placebo arm were excluded because of confoun-

ding effects when they crossed over to everolimus. Conslusions: This analysis identified baseline SLD as a predictive factor of OS, and the appearance of a new lesion or progression of a nontarget lesion at first assessment after baseline also affects OS in patients with mRCC treated with everolimus. Trial registration: ClinicalTrials.gov: NCT00410124.
I.F. = 8,743
N. citazioni = 29

15. Zhu AX, Kudo M, Assenat E, Cattan S, Kang YK, Lim HY, Poon RT, Blanc JF, Vogel A, Chen CL, Dorval E, Peck-Radosavljevic M, Santoro A, Daniele B, Furuse J, Jappe A, Perraud K, Anak O, Sellami DB, Chen LT for the EVOLVE-1 Trial Study Group (including **Porta C**). Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA* 2014;312:57-67.

ABSTRACT - Importance Aside from the multikinase inhibitor sorafenib, there are no effective systemic therapies for the treatment of advanced hepatocellular carcinoma. Objective: To assess the efficacy of everolimus in patients with advanced hepatocellular carcinoma for whom sorafenib treatment failed. Design, setting and participants: EVOLVE-1 was a randomized, double-blind, phase 3 study conducted among 546 adults with Barcelona Clinic Liver Cancer stage B or C hepatocellular carcinoma and Child-Pugh A liver function whose disease progressed during or after sorafenib or who were intolerant of sorafenib. Patients were enrolled from 17 countries between May 2010 and March 2012. Randomization was stratified by region (Asia vs rest of world) and macrovascular invasion (present vs absent). Interventions: Everolimus, 7.5 mg/d, or matching placebo, both given in combination with best supportive care and continued until disease progression or intolerable toxicity. Per the 2:1 randomization scheme, 362 patients were randomized to the everolimus group and 184 patients to the placebo group. Main outcomes and measures: The primary end point was overall survival. Secondary end points included time to progression and the disease control rate (the percentage of patients with a best overall response of complete or partial response or stable disease). Results: No significant difference in overall survival was seen between treatment groups, with 303 deaths (83.7%) in the everolimus group and 151 deaths (82.1%) in the placebo group (hazard ratio [HR], 1.05; 95% CI, 0.86-1.27; P=.68; median overall survival, 7.6 months with everolimus, 7.3 months with placebo). Median time to progression with everolimus and placebo was 3.0 months and 2.6 months, respectively (HR, 0.93; 95% CI, 0.75-1.15), and disease control rate was 56.1% and 45.1%, respectively (P=.01). The most common grade 3/4 adverse events for everolimus vs placebo were anemia (7.8% vs 3.3%, respectively), asthenia (7.8% vs 5.5%, respectively), and decreased appetite (6.1% vs 0.5%, respectively). No patients experienced hepatitis C viral flare. Based on central laboratory results, hepatitis B viral reactivation was experienced by 39 patients (29 everolimus, 10 placebo); all cases were asymptomatic, but 3 everolimus recipients discontinued therapy. Conclusions and relevance: mus did not improve overall survival in patients with advanced hepatocellular carcinoma whose disease progressed during or after receiving sorafenib or who were intolerant of sorafenib.
I.F. = 30
N. citazioni = 391

16. Zhu AX, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, Chung HC, Baron AD, Pfiffer TE, Okusaka T, Kubackova K, Trojan J, Sastre J, Chau I, Chang SC, Abada PB, Yang L, Schwartz JD, Kudo M for the REACH Trial Investigators (including **Porta C**). Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2015;16:859-70.

ABSTRACT - *Background: VEGF and VEGF receptor-2-mediated angiogenesis contribute to hepatocellular carcinoma pathogenesis. Ramucirumab is a recombinant IgG1 monoclonal antibody and VEGF receptor-2 antagonist. We aimed to assess the safety and efficacy of ramucirumab in advanced hepatocellular carcinoma following first-line therapy with sorafenib. Methods: In this randomised, placebo-controlled, double-blind, multicentre, phase 3 trial (REACH), patients were enrolled from 154 centres in 27 countries. Eligible patients were aged 18 years or older, had hepatocellular carcinoma with Barcelona Clinic Liver Cancer stage C disease or stage B disease that was refractory or not amenable to locoregional therapy, had Child-Pugh A liver disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, had previously received sorafenib (stopped because of progression or intolerance), and had adequate haematological and biochemical parameters. Patients were randomly assigned (1:1) to receive intravenous ramucirumab (8 mg/kg) or placebo every 2 weeks, plus best supportive care, until disease progression, unacceptable toxicity, or death. Randomisation was stratified by geographic region and cause of liver disease with a stratified permuted block method. Patients, medical staff, investigators, and the funder were masked to treatment assignment. The primary endpoint was overall survival in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01140347. Findings: Between Nov 4, 2010, and April 18, 2013, 565 patients were enrolled, of whom 283 were assigned to ramucirumab and 282 were assigned to placebo. Median overall survival for the ramucirumab group was 9·2 months (95% CI 8·0-10·6) versus 7·6 months (6·0-9·3) for the placebo group (HR 0·87 [95% CI 0·72-1·05]; p=0·14). Grade 3 or greater adverse events occurring in 5% or more of patients in either treatment group were ascites (13 [5%] of 277 patients treated with ramucirumab vs 11 [4%] of 276 patients treated with placebo), hypertension (34 [12%] vs ten [4%]), asthenia (14 [5%] vs five [2%]), malignant neoplasm progression (18 [6%] vs 11 [4%]), increased aspartate aminotransferase concentration (15 [5%] vs 23 [8%]), thrombocytopenia (13 [5%] vs one [<1%]), hyperbilirubinaemia (three [1%] vs 13 [5%]), and increased blood bilirubin (five [2%] vs 14 [5%]). The most frequently reported (≥1%) treatment-emergent serious adverse event of any grade or grade 3 or more was malignant neoplasm progression. Interpretation: Second-line treatment with ramucirumab did not significantly improve survival over placebo in patients with advanced hepatocellular carcinoma. No new safety signals were noted in eligible patients and the safety profile is manageable.*
I.F. = 24,690
N. citazioni = 458

17. Del Mastro L, Laghi A, Ronco C; Consensus Statement Group (including **Porta C**). Methods to address computed tomography-related risk factors in Oncology patients: an expert opinion based on current evidence. *Blood Purif* 2018;46:56-69.

ABSTRACT - Background: The present paper is intended to be a practical guide organized by statements describing methods to reduce risks related to CT examinations in cancer patients. Methods: A panel of radiologists, oncologists and nephrologists were selected based on their publication records in the field and expertise. Ten clinical questions, which were derived from clinical needs and an integration of all the committee members' suggestions, were stated. The modified Delphi approach was used; it involved a detailed literature review and the collective judgement of experts, including electronic and face-to-face discussions. Results: Ten statements were derived from expert opinions based on the current literature, recently developed guidelines and technological advancements. Each statement is discussed in a short paragraph reporting the current key evidence. Conclusion: This paper addresses the clinical implications of performing numerous CT examinations in patients with cancer, providing clinicians with information regarding methods to reduce risk factors in this patient population.
I.F. = 2,363
N. citazioni = 3

18. Schmidinger M, Bamias A, Procopio G, Hawkins R, Sanchez AR, Vázquez S, Srihari N, Kalofonos H, Bono P, Pisal CB, Hirschberg Y, Dezzani L, Ahmad Q, Jonasch E for the PRINCIPAL Study Group (including **Porta C**). Prospective Observational Study of Pazopanib in Patients with Advanced Renal Cell Carcinoma (PRINCIPAL Study). *Oncologist* 2019;24:491-7.

ABSTRACT - Background: Real-world data are essential to accurately assessing efficacy and toxicity of approved agents in everyday practice. PRINCIPAL, a prospective, observational study, was designed to confirm the real-world safety and efficacy of pazopanib in patients with advanced renal cell carcinoma (RCC). Subjects, Materials, and Methods: Patients with clear cell advanced/metastatic RCC and a clinical decision to initiate pazopanib treatment within 30 days of enrollment were eligible. Primary objectives included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), relative dose intensity (RDI) and its effect on treatment outcomes, change in health-related quality of life (HRQoL), and safety. We also compared characteristics and outcomes of clinical-trial-eligible (CTE) patients, defined using COMPARZ trial eligibility criteria, with those of non-clinical-trial-eligible (NCTE) patients. Secondary study objectives were to evaluate clinical efficacy, safety, and RDI in patient subgroups. Results: Six hundred fifty-seven patients were enrolled and received ≥1 dose of pazopanib. Median PFS and OS were 10.3 months (95% confidence interval [CI], 9.2-12.0) and 29.9 months (95% CI, 24.7 to not reached), respectively, and the ORR was 30.3%. HRQoL showed no or little deterioration over time. Treatment-related serious adverse events (AEs) and AEs of special interest occurred in 64 (9.7%), and 399 (60.7%) patients, respectively. More patients were classified NCTE than CTE (85.2% vs. 14.8%). Efficacy of pazopanib was similar between the two groups. Conclusion: PRINCIPAL confirms the efficacy and safety of pazopanib in patients with advanced/metastatic RCC in a real-world clinical setting. Implications for Practice: PRINCIPAL is the largest (n = 657) prospective, observational study of pazopanib in patients with advanced/metastatic renal cell carcinoma, to the authors' knowledge. Consistent with clinical trial results that often contain specific patient types, the PRINCIPAL study demonstrated that the effectiveness and safety of pazopanib is similarly safe and effective in patients with advanced kidney cancer in a real-world clinical setting. The PRINCIPAL study showed that patients with advanced kidney cancer who are treated with first-line pazopanib generally do not show disease progression for approximately 10 months and generally survive for nearly 30 months.
I.F. = 5,306
N. citazioni = 17

19. Capasso A, Benigni A, Capitanio U, Danesh FR, Di Marzo V, Gesualdo L, Grandaliano G, Jaimes EA, Malyszko J, Perazella MA, Qian Q, Ronco P, Rosner MH, Trepiccione F, Viggiano D, Zoccali C, Capasso G for the International Conference on Onco-Nephrology Participants. (including **Porta C**). Summary of the International Conference on Onco-Nephrology: an emerging field in medicine. *Kidney Int* 2019;96:555-67.

ABSTRACT - Onco-nephrology is an emerging field in medicine. Patients with cancer may suffer from kidney diseases because of the cancer itself and cancer-related therapy. It is critical for nephrologists to be knowledgeable of cancer biology and therapy in order to be fully integrated in the multidisciplinary team and optimally manage patients with cancer and kidney diseases. In a recent international meeting, the key issues in this challenging clinical interface were addressed, including many unresolved basic science questions, such as the high tumor incidence in kidney transplant recipients. To this end, 70 highly qualified faculty members were gathered from all over the world to discuss these issues in 8 plenary sessions, including 5 keynote lectures. In addition, 48 young nephrologists and oncologists were invited to present their original observations that were highlighted in 2 large poster sessions.
I.F. = 8,306
N. citazioni = 16

20. Powles T, van der Heijden MS, Castellano D, Galsky MD, Loriot Y, Petrylak DP, Ogawa O, Park SH, Lee JL, De Giorgi U, Bögemann M, Bamias A, Eigl BJ, Gurney H, Mukherjee SD, Fradet Y, Skoneczna I, Tsiatas M, Novikov A, Suárez C, Fay AP, Duran I, Necchi A, Wildsmith S, He P, Angra N, Gupta AK, Levin W, Bellmunt J, DANUBE study investigators (including **Porta C**). Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2020 Sep 21:S1470-2045(20)30541-6.

ABSTRACT - Background: Survival outcomes are poor for patients with metastatic urothelial carcinoma who receive standard, first-line, platinum-based chemotherapy. We assessed the overall survival of patients who received durvalumab (a PD-L1 inhibitor), with or without tremelimumab (a CTLA-4 inhibitor), as a first-line treatment for metastatic urothelial carcinoma. Methods: DANUBE is an open-label, randomised, controlled, phase 3 trial in patients with untreated, unresectable, locally advanced or metastatic urothelial carcinoma, conducted at 224 academic research centres, hospitals, and oncology clinics in 23 countries. Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 or 1. We randomly assigned patients (1:1:1) to receive durvalumab monotherapy (1500 mg) administered intravenously every 4 weeks; durvalumab (1500 mg) plus tremelimumab (75 mg) administered intravenously every 4 weeks for up to four doses, followed by durvalumab maintenance (1500 mg) every 4 weeks; or standard-of-care chemotherapy (gemcitabine plus cisplatin or gemcitabine plus carboplatin, depending on cisplatin eligibility) administered intravenously for up to six cycles. Randomisation was done through an interactive voice-web response system, with stratification by cisplatin eligibility, PD-L1 status, and presence or absence of liver metastases, lung metastases, or both. The coprimary endpoints were overall survival compared between the durvalumab monotherapy versus chemotherapy groups in the population of patients with high PD-L1 expression (the high PD-L1 population) and between the durvalumab plus tremelimumab versus chemotherapy groups in the intention-to-treat population (all randomly assigned patients). The study has completed enrolment and the final analysis of overall survival is reported. The trial is registered with ClinicalTrials.gov, NCT02516241, and the EU Clinical Trials Register, EudraCT number 2015-001633-24. Findings: Between Nov 24, 2015, and March 21, 2017, we randomly assigned 1032 patients to receive durvalumab (n=346), durvalumab plus tremelimumab (n=342), or chemotherapy (n=344). At data cutoff (Jan 27, 2020), median follow-up for survival was 41·2 months (IQR 37·9-43·2) for all patients. In the high PD-L1 population, median overall survival was 14·4 months (95% CI 10·4-17·3) in the durvalumab monotherapy group (n=209) versus 12·1 months (10·4-15·0) in the chemotherapy group (n=207; hazard ratio 0·89, 95% CI 0·71-1·11; p=0·30). In the intention-to-treat population, median overall survival was 15·1 months (13·1-18·0) in the durvalumab plus tremelimumab group versus 12·1 months (10·9-14·0) in the chemotherapy group (0·85, 95% CI 0·72-1·02; p=0·075). In the safety population, grade 3 or 4 treatment-related adverse events occurred in 47 (14%) of 345 patients in the durvalumab group, 93 (27%) of 340 patients in the durvalumab plus tremelimumab group, and in 188 (60%) of 313 patients in the chemotherapy group. The most common grade 3 or 4 treatment-related adverse event was increased lipase in the durvalumab group (seven [2%] of 345 patients) and in the durvalumab plus tremelimumab group (16 [5%] of 340 patients), and neutropenia in the chemotherapy group (66 [21%] of 313 patients). Serious treatment-related adverse events occurred in 30 (9%) of 345 patients in the durvalumab group, 78 (23%) of 340 patients in the durvalumab plus tremelimumab

group, and 50 (16%) of 313 patients in the chemotherapy group. Deaths due to study drug toxicity were reported in two (1%) patients in the durvalumab group (acute hepatic failure and hepatitis), two (1%) patients in the durvalumab plus tremelimumab group (septic shock and pneumonitis), and one (<1%) patient in the chemotherapy group (acute kidney injury). Interpretation: This study did not meet either of its coprimary endpoints. Further research to identify the patients with previously untreated metastatic urothelial carcinoma who benefit from treatment with immune checkpoint inhibitors, either alone or in combination regimens, is warranted.
I.F. = 33,752
N. citazioni = 99

21. Campana LG, Farronato S, Hodgetts J, Odili J, Vecchiato A, Bracken A, Baier S, Bechara FG, Borgognoni L, Caracò C, Carvalhal S, Covarelli P, Clover J, Eisendle K, Fantini F, Fierro MT, Farricha V, Gregorelli C, Hafner J, Kunte C, Gerlini G, Hessam S, Mandalà M, Piazzalunga D, Quaglino P, Snoj M, Ross AM, Trigona B, Moreno-Ramirez D, Tauceri F, Peach H, Rutkowski P, Muir T, de Terlizzi F, Patuzzo R, Mühlstädt M, Dietrich KA, Mussack T, Matteucci P, Kis E, Ascierto P, Sersa G, Valpione S; Melanoma Delphi Working Group (including **Porta C**). European e-Delphi process to define expert consensus on electrochemotherapy treatment indications, procedural aspects, and quality indicators in melanoma. *Br J Surg* 2023:znad105. doi: 10.1093/bjs/znad105. Epub ahead of print.

ABSTRACT - Background: Skin metastases are an important co-morbidity in melanoma. Despite broad adoption, electrochemotherapy implementation is hindered by a lack of treatment indications, uncertainty regarding procedural aspects, and the absence of quality indicators. An expert consensus may harmonize the approach among centres and facilitate comparison with other therapies. Methods: An interdisciplinary panel was recruited for a three-round e-Delphi survey. A literature-based 113-item questionnaire was proposed to 160 professionals from 53 European centres. Participants rated each item for relevance and degree of agreement on a five-point Likert scale, and received anonymous controlled feedback to allow revision. The items that reached concordant agreement in two successive iterations were included in the final consensus list. In the third round, quality indicator benchmarks were defined using a real-time Delphi method. Results: The initial working group included 122 respondents, of whom 100 (82 per cent) completed the first round, thus qualifying for inclusion in the expert panel (49 surgeons, 29 dermatologists, 15 medical oncologists, three radiotherapists, two nurse specialists, two clinician scientists). The completion rate was 97 per cent (97 of 100) and 93 per cent (90 of 97) in the second and third rounds respectively. The final consensus list included 54 statements with benchmarks (treatment indications, (37); procedural aspects, (1); quality indicators, (16)). Conclusion: An expert panel achieved consensus on the use of electrochemotherapy in melanoma, with a core set of statements providing general direction to electrochemotherapy users to refine indications, align clinical practices, and promote quality assurance programmes and local audits. The residual controversial topics set future research priorities to improve patient care.
I.F. = 6,939

ABSTRACTS E COMUNICAZIONI A CONGRESSI NAZIONALI ED INTERNAZIONALI

(*comunicazioni orali o relazioni ufficiali effettuate dal Prof. C. Porta)

A1. Bobbio-Pallavicini E, Luliri P, Anselmetti L, Caneparo R, **Porta C**, Invernizzi R, Gorini M. Role of maintenance therapy in the treatment of acute promyelocytic leukemia (APL). Proceedings of the 1st Advanced International Course 'Leukaemia 1988' - *Haematologica* 1988;73(Suppl. 5):123.

A2. Italian Cooperative Group for the study of TTP. Retrospective study of thrombotic thrombocytopenic Purpura treatment. Results of the Italian Cooperative Group. Abs. XXII Congress of the International Society of Hematology (ISH), Milan (Italy), August 28-September 2, 1988; pag. 296.

A3. Anselmetti L, **Porta C**, Bobbio-Pallavicini E, Fratino P. Significato prognostico dello studio della crescita di CFU-GM *in vitro* nelle sindromi mielodisplastiche. Abs. Meeting Internazionale 'Indagini citobiologiche nelle emopatie maligne: implicazioni cliniche', L'Aquila (Italy), 10 Novembre 1988; pag. 195.

A4. Attardo-Parrinello G, Merlini G, Crema F, Federico M, Bobbio-Pallavicini E, **Porta C**, Frassoldati A, Fiorentini ML. Dichloromethylene-diphosphonate therapy of osteolytic lesions in malignancies. Abs. 4th International Conference on Progress in Cancer Research, San Remo (Italy), April 30-May 2, 1989; pag. 35.

A5. Bobbio-Pallavicini E, **Porta C**, Anselmetti L, Viarengo GL, Spaghi A, Notario A. *In vitro* CFU-GM growth in myelodysplastic syndromes (MDS). Abs. X Convegno Nazionale Associazione Italiana Colture Cellulari (AICC), Pisa, 11-12 Maggio 1989; pag. 3.

A6. **Porta C**, Bobbio-Pallavicini E, Anselmetti L, Fornasari PM. Evoluzione terapeutica nel morbo di Moschowitz: dalla splenectomia alla plasma-exchange. Atti del Convegno "Porpora Trombotica Trombocitopenica: attualità e prospettive terapeutiche", Pavia, 26 Maggio 1989; pagg. 9-17.

A7. Bobbio-Pallavicini E, **Porta C**, Anselmetti L, Viarengo GL. Porpora Trombotica Trombocitopenica (PTT): risultati del Gruppo Cooperativo Italiano. Atti del Convegno "Porpora Trombotica Trombocitopenica: attualità e prospettive terapeutiche", Pavia, 26 Maggio 1989; pagg. 31-42.

A8. Bobbio-Pallavicini E, **Porta C**, Viarengo GL, Notario A. Prognostical index and therapeutical problems in acute promyelocytic leukemias. Abs. International ESO Conference: 'New trends in the treatment of acute leukaemia', Dubrovnik (Jugoslavija), September 20-22, 1989; pag. 98.

A9. Bobbio-Pallavicini E, **Porta C**, Anselmetti L, Viarengo GL, Spaghi A, Notario A. *In vitro* CFU-GM growth in myelodysplastic syndromes (MDS). Abs. of the 10th National Meeting of the Italian Cell Culture Association - *Cytotechnology* 1989; Suppl. September:S5.

A10. Gruppo Cooperativo Italiano per lo studio ed il trattamento della PTT. Porpora trombotica trombocitopenica (PTT): studio retrospettivo su 81 casi ed elaborazione di un protocollo nazionale di trattamento. Abs. XXXII Congresso Nazionale della Società Italiana di Ematologia (SIE), Roma, 8-12 Ottobre 1989; pag. 358.

A11. Bobbio-Pallavicini E, **Porta C**, Anselmetti L, Viarengo GL, Invernizzi R, Notario A. Indici prognostici ed indicazioni al trapianto di midollo nei pazienti affetti da leucemia acuta a promielociti (LAP). Abs. XXXII Congresso Nazionale della Società Italiana di Ematologia (SIE), Roma, 8-12 Ottobre 1989; pag. 516.

A12. Anselmetti L, **Porta C**, Viarengo GL, Bobbio-Pallavicini E. Treatment of acute promyelocytic leukaemia (APL): chemotherapy or bone marrow transplant? Abs. International Symposium on Peripheral Blood Stem Cell Autografts, Mulhouse (France), October 15-17, 1989.

A13. Gruppo Cooperativo Italiano per lo studio della PTT. Plasma-exchange (PE) come trattamento elettivo nella porpora trombotica trombocitopenica (PTT). Abs. XXII Congresso Nazionale della Società Italiana della Trasfusione del Sangue (SITS), Pavia, 30-31 Ottobre 1989; pag. 8.

A14*. **Porta C**, Bobbio-Pallavicini E, Nastasi G, Spaghi A, Moroni M. Polichemioterapia con 5-fluorouracile (5-FU), acido folinico e mitomicina C (MMC) nel trattamento dei carcinomi gastrici in stadio avanzato. Abs. Congresso Nazionale 'Nuove prospettive in Oncologia Medica: l'associazione fluorouracile e folati', Terni, 30-31 Marzo 1990; pag. 187.

A15. Fornasari PM, Bobbio-Pallavicini E, **Porta C**, Viarengo GL and the Italian Cooperative Group for TTP. Plasma-exchange (PE) in the treatment of thrombotic thrombocyto-

penic purpura (TTP). Abs. 3rd International Congress of the World Apheresis Association (WAA), Amsterdam (the Netherlands), April 9-12, 1990; pag. 81.

A16*. **Porta C**, Nastasi G, Spaghi A, Moroni M, Qalqili A, Bobbio-Pallavicini E. Neurological compromission, evaluated according to Frithz-Werner's scale, as a prognostic factor in patients affected by thrombotic thrombocytopenic purpura (TTP). Abs. 1st International Conference on Thrombotic Thrombocytopenic Purpura (TTP) Research, Pavia (Italy), June, 14-15, 1990; pagg. 21-22.

A17. Casagranda I, Davio P, Nastasi G, **Porta C**, Moroni M. Infusione di immunoglobuline ad alte dosi (Sandoglobulin®) in un caso di porpora trombocitopenica idiopatica. Abs. Convegno 'Le Piastrinopenie: fisiopatologia, clinica e terapia', Vicenza, 12 Aprile 1991; pag. 88.

A18. **Porta C**, Nastasi G, Moroni M, Paulli M, Casagranda I. Non-Hodgkin lymphomas and secondary central nervous system involvement: a search for predictive indexes. In: 'New insights in lymphoma', abs. 2nd International Workshop on Lymphomas, Vicenza (Italy), May 30-June 1, 1991; pag. 21.

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N.B. - Il Dr. Camillo Porta è co-Autore degli abstracts pubblicati ad opera del 'Gruppo Cooperativo Italiano per lo studio ed il trattamento della Porpora Trombotica Trombocitopenica', inseriti in questo elenco (A2,A8,A11,A28); ciò è attestato, per ciascuno degli abstracts in oggetto, da una dichiarazione redatta dall'allora Responsabile Nazionale del Gruppo, Prof. Enrico Bobbio-Pallavicini.

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