4500 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Cardiac safety analysis for a phase III trial of sunitinib (SU) or sorafenib (SO) or placebo (PLC) in patients (pts) with resected renal cell carcinoma (RCC).

Naomi B. Haas, Judith Manola, Bonnie Ky, Keith T. Flaherty, Robert G. Uzzo, Christopher G. Wood, Christopher J Kane, Michael A. S. Jewett, Michael B. Atkins, Janice P. Dutcher, Robert S. DiPaola, Eastern Cooperative Oncology Group; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; Dana-Farber Cancer Institute, Boston, MA; University of Pennsylvania, Philadelphia, PA; Massachusetts General Hospital, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; University of Texas M. D. Anderson Cancer Center, Houston, TX; Moores Cancer Center, University of California, San Diego, La Jolla, CA; Department of Urology, Princess Margaret Hospital and University of Toronto, Toronto, ON, Canada; Beth Israel Deaconess Medical Center, Boston, MA; St. Luke's-Roosevelt Hospital Center, New York, NY; Cancer Institute of New Jersey, New Brunswick, NJ

Background: We performed a cardiac analysis of E2805, a well population of pts with resected high risk RCC. The objectives were to determine if pts treated with SU or SO had clinically significant decreases in left ventricular (LV) ejection fraction (EF) and to describe the frequency of clinically significant heart failure (HF). We also report the frequency of other events including (un)stable angina or myocardial infarction. **Methods:** EF was measured by multiple gated acquisition scan (MUGA) at baseline, 3, 6, and 12 months (mo), and end of treatment, if symptoms developed, and 3 mo after the last abnormal assessment. The primary cardiac endpoint was defined as an EF decline $<$ the institutional lower limit of normal (ILN) that was a $\geq$ 16% decline from baseline, and that occurred $\leq$ 6 mo into therapy. Clinically significant HF was $\geq$ Grade 3 LV systolic or diastolic dysfunction (severe symptoms with any activity or from drop in EF responsive (Grade 3) or refractory (Grade 4) to therapy. Late LVEF events were a drop in LVEF of $\geq$ 16% occurring after 6 mo of therapy. Event rates on each treatment arm were calculated, with 90% exact binomial confidence intervals (CI). **Results:** Post-baseline MUGAs are available for 1589 of 1943 total pts accrued. 1293 pts had MUGA assessment $\geq$ 6 mo. 21 pts had primary events (Table). 71 pts had worst LVEF declines of $\geq$16% from baseline, including 52 of which occurred $\leq$ 6 mo from baseline, with the majority not meeting full primary event criteria. There were 11 reported grade 3 LV systolic events (5 SU, 4 SO and 2 PLC). 8 pts had cardiac ischemia possibly or probably from agent. Only one grade 4 event followed a primary LVEF event. 4 of 7 pts who began treatment with LVEF $<$ILN had primary LVEF events. **Conclusions:** In detailed followup of SU and SO use, cardiac function in pts starting with normal EF, was not impaired significantly over placebo. Ischemic events were uncommon and not clearly associated with treatment. The data demonstrate that SU or SO for adjuvant therapy will likely not cause significant cardiac toxicity.

Arm	Pts assessed	1° Cardiac endpt	Rate	90% CI
SU	397	9	2.3%	1.2-3.9%
SO	394	7	1.8%	0.8-3.3%
PLC	502	5	1.0%	0.4-2.1%

4501 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: Results from a phase III randomized, open-label, multicenter trial.

Robert John Motzer, Dmitry Nosov, Tim Eisen, Igor N. Bondarenko, Vladmir Lesovoy, Oleg N. Lipatov, Piotr Tomczak, Alexey A. Lyulko, Anna Alyasova, Mihai Harza, Mikhail Kogan, Boris Y. Alexeev, Cora N. Sternberg, Cezary Szczylik, Joshua Zhang, Andrew Louis Strahs, Brooke Esteves, William J. Slichenmyer, Anna Berkenblit, Thomas E. Hutson; Memorial Sloan-Kettering Cancer Center, New York, NY; N. N. Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia; Cambridge University Health Partners, Cambridge, United Kingdom; Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine; V.I. Shapoval Regional Clinical Center for Urology and Nephrology, Kharkiv, Ukraine; State Budget Medical Institution, Republican Clinical Oncological Center, under the Healthcare Ministry of Bashkortostan Republic, Ufa, Russia; Clinical Hospital No. 1 of the Poznan University of Medical Sciences, Poznan, Poland; Zaporizhya Medical Academy of Postgraduate Education, Zaporizhya, Ukraine; Federal State Institution, Privolzhsky District Medical Center, under the Federal Medical-Biological Agency of Russia, Nizhny Novgorod, Russia; Fundeni Clinical Institute, Bucharest, Romania; State-Funded Higher Educational Institution, Rostov State Medical University, under the Federal Agency for Healthcare and Social Development of Russia, Rostov-on-Don, Russia; Federal State Institution, Moscow Research Oncological Institute, Moscow, Russia; San Camillo and Forlanini Hospitals, Rome, Italy; Military Institute of Health Services, Warsaw, Poland; AVEO Pharmaceuticals, Cambridge, MA; Texas Oncology–Baylor Charles A. Sammons Cancer Center, Dallas, TX

Background: Tivozanib, a potent, selective, long half-life tyrosine kinase inhibitor targeting all three VEGF receptors, showed activity and tolerability in a Phase II trial (*JCO* 2011;29[18S]:4550). **Methods:** Patients (pts) with clear cell advanced renal cell carcinoma (RCC), prior nephrectomy, RECIST-defined measurable disease, and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 were randomized 1:1 to tivozanib (T) 1.5 mg once daily for 3 weeks (wks) followed by 1 wk rest, or sorafenib (S) 400 mg twice daily continuously in a 4-wk cycle. Pts were treatment naïve or received no more than 1 prior systemic therapy for metastatic disease; pts receiving prior VEGF- or mTOR-targeted therapy were excluded. The primary endpoint was progression-free survival (PFS) per blinded, independent radiological review. 500 pts were to be enrolled to observe 310 events, yielding 90% power to detect medians of 9.7 and 6.7 months (m) with 5% type I error (2-sided). **Results:** A total of 517 pts were randomized to T (n=260) or S (n=257). Demographics were well balanced between the 2 groups, except ECOG 0 (T: 45% vs S: 54%, p=0.035). Median PFS was 11.9 m for T vs 9.1 m for S (HR=0.797, 95% CI 0.639–0.993; p=0.042). In the treatment-naïve stratum (70% of pts enrolled in each arm), the median PFS was 12.7 m for T vs 9.1 m for S (HR 0.756, 95% CI 0.580–0.985; p=0.037). In all pts, objective response rate (ORR) for T was 33% vs 23% for S (p=0.014). The most common adverse event (AE; all grades/≥grade 3) for T was hypertension (T: 46%/26% vs S: 36%/18%) and for S was hand-foot syndrome (T: 13%/2% vs S: 54%/17%). Other important AEs included diarrhea (T: 22%/2% vs S: 32%/6%), fatigue (T: 18%/5% vs S: 16%/4%), and neutropenia (T: 10%/2% vs S: 9%/2%). Patient-reported outcome data are being analyzed. Overall survival data are not mature. **Conclusions:** Tivozanib demonstrated significant improvement in PFS and ORR compared with sorafenib as initial targeted treatment for advanced RCC. The safety profile of tivozanib is favorable, and includes a low incidence of fatigue, diarrhea, myelosuppression, and hand-foot syndrome.

CRA4502 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Patient preference between pazopanib (Paz) and sunitinib (Sun): Results of a randomized double-blind, placebo-controlled, cross-over study in patients with metastatic renal cell carcinoma (mRCC)—PISCES study, NCT 01064310.

Bernard J. Escudier, Camillo Porta, Petri Bono, Ugo De Giorgi, Omi Parikh, Robert E. Hawkins, Emmanuel Sevin, Sylvie Negrier, Sadya Khan, Lauren McCann, Faisal Mehmud, David Cella; Institut Gustave Roussy, Villejuif, France; Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; Helsinki University Hospital, Helsinki, Finland; Istituto Tumori Romagna, Meldola, Italy; Royal Preston Hospital, Lancashire, United Kingdom; Christie Cancer Research UK, Manchester, United Kingdom; Centre François Baclesse, Caen, France; Léon-Bérard Cancer Centre, Lyon, France; GlaxoSmithKline, Uxbridge, United Kingdom; GlaxoSmithKline, Collegeville, PA; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL

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4503 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Axitinib for first-line metastatic renal cell carcinoma (mRCC): Overall efficacy and pharmacokinetic (PK) analyses from a randomized phase II study.

Brian I. Rini, Viktor Grünwald, Mayer N. Fishman, Bohuslav Melichar, Takeshi Ueda, Petr A Karlov, A H. Bair, Ying Chen, Sinil Kim, Eric Jonasch; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Hannover Medical School, Hannover, Germany; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; University Hospital, Olomouc, Czech Republic; Division of Urology, Chiba Cancer Center, Chiba, Japan; City Clinical Oncology Dispensary, St. Petersburg, Russia; Pfizer Oncology, San Diego, CA; University of Texas M. D. Anderson Cancer Center, Houston, TX

Background: Axitinib is a potent, selective, second-generation inhibitor of vascular endothelial growth factor receptors with efficacy in mRCC. Due to PK and pharmacodynamic variability, some patients have sub-optimal drug exposures at the standard 5-mg twice daily (BID) dose. Prior analyses indicated higher drug exposure enhanced efficacy; thus, dose titration based on individual tolerability may optimize exposure and improve outcomes. A randomized phase II trial evaluated the efficacy and safety of axitinib dose titration from 5 mg BID to a maximum of 10 mg BID in first-line mRCC. **Methods:** Patients with treatment-naïve mRCC received axitinib 5 mg BID for a 4-week lead-in period (cycle 1). Then, patients with 2 consecutive weeks of blood pressure (BP) $\leq$150/90 mmHg, no axitinib-related toxicities $>$grade 2, no dose reductions, and $\leq$2 antihypertensive medications were randomized in a double-blind fashion to axitinib 5 mg BID + dose titration with either axitinib (arm A) or placebo (arm B); those ineligible for randomization continued with same dose (arm C). Primary endpoint is objective response rate (ORR). Serial 6-hr PK sampling and 24-hr ambulatory BP monitoring (ABPM) were performed on cycle 1 day 15 in a subset of patients. **Results:** In all, 203 patients were accrued; 112 randomized to arms A or B, and 91 in arm C. As of July 1, 2011, ORR (95% confidence interval [CI]) was 40.2% (31.0, 49.9) in A+B (blinded pooled analysis) and 56.0% (45.2, 66.4) in C. Median progression-free survival (mPFS) (95% CI) was 13.7 mo (9.2, not estimable [NE]) in A+B and 12.2 mo (8.6, 16.7) in C. Patients with drug exposure above therapeutic threshold (AUC_{24} $\geq$300 ng·h/mL; n=27) on cycle 1 day 15 had longer mPFS and higher ORR than those with sub-therapeutic exposure (n=25) (mPFS [95% CI]: 13.9 mo [12.2, NE] vs 8.3 mo [5.5, NE]; ORR: 59% vs 48%). Patients with mean increases of diastolic BP (ΔdBP) $\geq$15 mmHg (n=18) per ABPM had higher ORR than those with ΔdBP $<$15 mmHg (n=36) (61% vs 53%). **Conclusions:** Axitinib is effective in first-line treatment of mRCC, with high ORR and mPFS $>$1 yr. Preliminary results suggest therapeutic drug exposure and ΔdBP $\geq$15 mmHg on cycle 1 day 15 may be associated with better outcomes.

4504 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Efficacy of cabozantinib (XL184) in patients (pts) with metastatic, refractory renal cell carcinoma (RCC).

Toni K. Choueiri, Sumanta Kumar Pal, David F. McDermott, David A. Ramies, Stephanie Morrissey, Yihua Lee, Dale Miles, Jaymes Holland, Janice P. Dutcher; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, MA; City of Hope, Duarte, CA; Beth Israel Deaconess Medical Center, Boston, MA; Exelixis, South San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA; St. Luke's-Roosevelt Hospital Center, New York, NY

Background: Cabozantinib (cabo) is an oral, potent inhibitor of MET and VEGFR2 that is currently undergoing evaluation in several oncology indications. Renal cell carcinoma (RCC) was chosen as an indication in this drug-drug interaction (DDI) study based on involvement of the MET and VEGFR signaling pathways in this disease. The primary objective of this study is to determine the effect of cabo on single dose PK of the CYP2C8 substrate rosiglitazone (rosi). Anti-tumor activity was also evaluated. **Methods:** Eligible pts were required to have RCC with clear cell components with metastases, Karnofsky performance status of ≥70 and measurable disease by RECIST. Pts needed to have experienced PD following standard therapies. Cabo was given daily at a dose of 140 mg free base (equivalent to 175 mg salt form) starting at Day 2. Rosi (4 mg) was given Day 1 and Day 22 to complete PK assessment for DDI. Cabo was continued until PD. On Day 57 and every 8 weeks thereafter subjects underwent tumor assessments by mRECIST. **Results:** Enrollment is complete at 25 RCC pts; 17/25 (64%) RCC pts had received ≥ 2 prior agents; 13/25 (52%) with at least 1 VEGF pathway inhibitor and 1 mTOR inhibitor. The majority of pts were in an intermediate (21/25) or poor (3/25) prognostic category (1/25 in favorable category) per Heng et al (JCO, 2009, v27, p5794). ORR by mRECIST: 7/25 (28%). Disease control rate (PR + SD): 72% at 16 weeks; 19/21 (90%) pts with ≥1 post-baseline scan experienced tumor regression (range: 4 - 63% reduction in measurements). 10/25 (36%) pts remain on cabo. Median PFS is 14.7 months (95% CI: 7.3, upper limit not reached) with a median follow-up of 7.7 months. AEs ≥ Grade 3 severity: hypophosphatemia (36%), hyponatremia (20%), and fatigue (16%). PK data suggest that clinically relevant doses of cabo do not alter the C_{max} or $AUC_{0\text{-}24h}$ of rosi, consistent with no inhibition of CYP2C8. **Conclusions:** Cabo demonstrates encouraging anti-tumor activity in heavily pretreated RCC pts with a toxicity profile similar to that of other VEGFR TKIs. PK data suggest no DDI between cabo and rosi (CYP2C8 substrate).

4505 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Clinical activity and safety of anti-PD-1 (BMS-936558, MDX-1106) in patients with previously treated metastatic renal cell carcinoma (mRCC).

David F. McDermott, Charles G. Drake, Mario Sznol, Toni K. Choueiri, John Powderly, David C. Smith, Jon Wigginton, Dan McDonald, Georgia Kollia, Ashok Kumar Gupta, Michael B. Atkins; Beth Israel Deaconess Medical Center, Boston, MA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Yale Cancer Center, New Haven, CT; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Carolina Bio-Oncology Institute, Huntersville, NC; University of Michigan, Ann Arbor, MI; Bristol-Myers Squibb, Princeton, NJ

Background: BMS-936558 is a fully human monoclonal antibody that blocks the programmed death-1 co-inhibitory receptor (PD-1) expressed by activated T cells. In the initial portion of a phase I study, BMS-936558 showed promising activity in patients (pts) with various solid tumors, including mRCC. We expanded accrual in order to better characterize antitumor and dose effects. **Methods:** RCC pts were treated with BMS-936558 administered IV Q2WK at 10 mg/kg initially, followed by additional pts at 1 mg/kg. Pts received up to 12 cycles (4 doses/cycle) of treatment or until PD or CR. Clinical activity was assessed by RECIST 1.0. **Results:** Of 240 pts treated as of July 1 2011, 33 had mRCC and were treated at 1 (n=17) or 10 mg/kg (n=16). ECOG performance status was 0/1 in 13/19 pts. The number of prior therapies was 1 (n=10), 2 (n=9), or ≥3 (n=14), and included prior immunotherapy (n=20) or antiangiogenic therapy (n=24); 31 pts had prior nephrectomy. Sites of metastatic disease included lymph node (n=26), liver (n=7), lung (n=28), and bone (n=10). Median duration of therapy was 19 wk (max 96 wk). The incidence of grade 3-4 related AEs was 12% and included hypophosphatemia (6%), elevated ALT (3%), and cough (3%). Clinical activity was observed at both dose levels (Table). Some pts had a persistent reduction in overall tumor burden in the presence of new lesions and were not categorized as responders. Responses were noted in pts with visceral and bone metastases. Among the responders who were first treated ≥1 yr prior to data lock, 4 of 5 pts treated at 10 mg/kg had OR duration ≥1 yr, and 1 of 2 pts treated at 1 mg/kg was still on study with OR duration of 17.5 mo. Although the data for pts treated at 1mg/kg are not mature, the estimated progression-free survival (PFS) rate at 24 wk in pts receiving 10 mg/kg was 67% (Table). **Conclusions:** BMS-936558 is well tolerated and has durable clinical activity in pts with previously treated mRCC. Further development of BMS-936558 in pts with mRCC is ongoing.

Dose (mg/kg)	n[a]	OR[b]	uPR[c]	RR[d] (%)	PFS rate at 24 wk (%)
1	16	3	2	31	TBD[e]
10	16	5	-	31	67

[a]Response evaluable pts.
[b]CR or PR.
[c]Unconfirmed PR.
[d]Response rate [(OR + uPR) ÷ n].
[e]To be determined (follow up ongoing).

LBA4512 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA).

Chris Parker, Sten Nilsson, Daniel Heinrich, Joe M. O'Sullivan, Sophie D. Fossa, Ales Chodacki, Pawel J. Wiechno, John P. Logue, Mihalj Seke, Anders Widmark, Dag Clement Johannessen, Peter Hoskin, David Bottomley, Robert Edward Coleman, Nicholas J. Vogelzang, C. Gillies O'Bryan-Tear, Jose E. Garcia-Vargas, Minghua Shan, A. Oliver Sartor; The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Karolinska University Hospital, Stockholm, Sweden; Akershus University Hospital, Lørenskog, Norway; Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Ireland; Radiumhospitalet, Oslo, Norway; Hospital Kochova, Chomutov, Czech Republic; Centrum Onkologii – Instytut im Sklodowskiej-Curie, Warsaw, Poland; Christie Hospital, Manchester, United Kingdom; Centrallasarettet Växjö, Växjö, Sweden; Umea University, Umea, Sweden; Ullevål University Hospital, Oslo, Norway; Mount Vernon Hospital Cancer Centre, Middlesex, United Kingdom; St. James's Hospital, Leeds, United Kingdom; Weston Park Hospital, Sheffield, United Kingdom; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Algeta ASA, Oslo, Norway; Bayer HealthCare Pharmaceuticals, Montville, NJ; Tulane Cancer Center, New Orleans, LA

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4536 Poster Discussion Session (Board #15), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

An in-depth multicentered population-based analysis of outcomes of patients with metastatic renal cell carcinoma (mRCC) that do not meet eligibility criteria for clinical trials.

Daniel Yick Chin Heng, Toni K. Choueiri, Jae-Lyun Lee, Lauren Christine Harshman, Georg A. Bjarnason, Jennifer J. Knox, Mary J. MacKenzie, Ulka N. Vaishampayan, Takeshi Yuasa, Min-Han Tan, Sun Young Rha, Frede Donskov, Neeraj Agarwal, Sumanta Kumar Pal, Christian K. Kollmannsberger, Scott A. North, Brian I. Rini, Lori Wood; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Stanford University School of Medicine, Stanford, CA; Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; London Regional Cancer Program, London, ON, Canada; Karmanos Cancer Institute, Wayne State University, Detroit, MI; The Cancer Institute Hospital of JFCR, Tokyo, Japan; National Cancer Centre, Singapore, Singapore; Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Aarhus University Hospital, Aarhus, Denmark; University of Utah Huntsman Cancer Institute, Salt Lake City, UT; City of Hope, Duarte, CA; British Columbia Cancer Agency, Vancouver, BC, Canada; Cross Cancer Institute, Edmonton, AB, Canada; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada

Background: Clinical trials have strict eligibility criteria that exclude many patients to whom the trial results are later extrapolated to in clinical practice. **Methods:** mRCC patients treated with VEGF targeted therapy were retrospectively deemed ineligible for clinical trials (according to commonly used inclusion/exclusion criteria) if they had a Karnofsky Performance Status (KPS) <70%, brain metastases, non-clear cell histology, hemoglobin<=9 g/dL, creatinine >2x the upper limit of normal, platelet count of $<100x10^3$/uL, neutrophil count $<1500/mm^3$ or corrected calcium>=12 mg/dL. **Results:** 894/2076 (43%) patients were deemed ineligible for clinical trials by the above criteria. Between ineligible versus eligible patients, the response rate, median progression free survival (PFS) and median overall survival of first-line targeted therapy were 21% vs 29%, 5.2 vs 8.8 months and 14.5 vs 28.8 months (all p<0.0001), respectively. Second-line PFS (if applicable) was 3.2 months in the trial ineligible vs 4.4 months in the trial eligible patients (p=0.0074). Patients who were excluded due to KPS<70, hemoglobin<=9 g/dL, calcium >=12, brain metastases, and non-clear cell histology, had a hazard ratio (HR) for death of 2.8 (95%CI 2.4-3.4), 1.8 (95%CI 1.4-2.2), 1.8 (95%CI 1.2-2.7), 1.4 (95%CI 1.1-1.8), and 1.4 (95%CI 1.1-1.7), respectively (all p<0.01). When adjusted by the Heng et al prognostic categories, the HR for death between trial ineligible vs trial eligible patients was 1.511 (95%CI=1.335-1.710, p<0.0001). **Conclusions:** The number of patients that are ineligible for clinical trials is high and their outcomes are inferior. Specific trials addressing the needs of protocol ineligible patients and assessing OS are required.

Parameter	Clinical trial ineligible N=894	Clinical trial eligible N=1,182	P value
Heng et al prognosis			<0.0001
Favorable	9%	25%	
Intermediate	48%	59%	
Poor	43%	16%	
Median KPS (%) (range)	80 (20-100)	90 (70-100)	<0.0001
Anemia (below LLN)	68.7%	51.4%	<0.0001
Hypercalcemia (above ULN)	14.5%	6.8%	<0.0001
Brain metastases present	19%	0%	<0.0001
Non-clear cell histology	26%	0%	<0.0001

LBA4537 Poster Discussion Session (Board #16), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Axitinib versus sorafenib as second-line therapy in Asian patients with metastatic renal cell carcinoma (mRCC): Results from a registrational study.

Shukui Qin, Feng Bi, Ying Cheng, Jun Guo, Xiu Bao Ren, Yiran Huang, Jinwan Wang, Yong Ben, Sinil Kim, Jie Tang, Dingwei Ye; Nanjing Bayi Hospital, Nanjing, China; Department of Medical Oncology, West China Hospital, Sichuan University, Chengdu, China; Jilin Provincial Cancer Hospital, Changchun, China; Beijing Cancer Hospital, Beijing, China; Tianjin Oncology Hospital, Tianjin, China; Renji Hospital, Shanghai, China; Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing, China; Pfizer Oncology, San Diego, CA; Cancer Hospital, Fudan University, Shanghai, China

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4538 Poster Discussion Session (Board #17), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Characteristics of long-term and short-term survivors of metastatic renal cell carcinoma (mRCC) treated with targeted therapy: Results from the International mRCC Database Consortium.

Wanling Xie, Toni K. Choueiri, Jae-Lyun Lee, Lauren Christine Harshman, Georg A. Bjarnason, Jennifer J. Knox, Mary J. MacKenzie, Lori Wood, Ulka N. Vaishampayan, Takeshi Yuasa, Min-Han Tan, Sun Young Rha, Frede Donskov, Neeraj Agarwal, Christian K. Kollmannsberger, Scott A. North, Brian I. Rini, Daniel Yick Chin Heng; Dana-Farber Cancer Institute, Boston, MA; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Stanford University School of Medicine, Stanford, CA; Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; London Regional Cancer Program, London, ON, Canada; Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; Karmanos Cancer Institute, Wayne State University, Detroit, MI; The Cancer Institute Hospital of JFCR, Tokyo, Japan; National Cancer Centre, Singapore, Singapore; Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea; Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; University of Utah Huntsman Cancer Institute, Salt Lake City, UT; British Columbia Cancer Agency, Vancouver, BC, Canada; Cross Cancer Institute, Edmonton, AB, Canada; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada

Background: Patients with mRCC have variable courses in terms of survival and response to targeted therapy. The patients at the two extremes of the survival spectrum need to be characterized. **Methods:** 2,161 patients with mRCC treated with targeted therapy were examined. 152 patients who survived 4 years or more after the initiation of targeted therapy (long-term) were compared with 218 patients who survived 6 months or less (short-term) over the same time period (2004-2007). **Results:** Long-term survivors had fewer poor prognostic factors (PFs) such as Karnofsky performance status (KPS) $<80\%$, diagnosis to treatment interval<1 yr, hypercalcemia, anemia, thrombocytosis and neutrophilia (all $p<0.0001$). Patients with favorable prognosis who responded to targeted therapy were more likely to be long term survivors. For those in the intermediate risk group, patients who were long-term survivors were more likely to have only 1 poor prognostic factor (73% vs. 28%, $p<0.0001$) and KPS$\geq$80% (88% vs. 69%, $p=0.009$) compared to those in the short term survivor group. On multivariable analysis adjusting for PFs, response to targeted therapy (PR or better) significantly predicted long term survivor status (odds ratio=6.3, 95% CI: 2.3,17.4, $p=0.0004$). **Conclusions:** Long term survivors had a higher response rate to targeted therapy, a longer treatment duration and more use of second-line targeted therapy. Baseline prognostic criteria may be able to discriminate between long- and short- term survivors.

Characteristic	Long-term survivor (N=152)	Short-term survivor (N=218)	P value
Median age (years)	61	61	0.26
Heng et al prognostic category			<0.0001
Favorable	42%	2%	
Intermediate	49%	34%	
Poor	3%	60%	
Unknown	5%	4%	
KPS < 80%	7%	53%	<0.0001
Prior nephrectomy	95%	65%	<0.0001
>1 site of metastases	73%	83%	0.02
Best response			<0.0001
Complete response	4%	0%	
Partial response	34%	4%	
Stable disease	53%	19%	
Progressive disease	3%	43%	
Unknown	6%	34%	
Median duration of targeted therapy (months)	23.6	2.0	-
Median duration of second-line targeted therapy (months)	11.5 (N=90)	0.8 (N=20)	-
Median overall survival (months)	69.3	3.1	-

4539 Poster Discussion Session (Board #18), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Phase III randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO) followed by sunitinib (SU) versus sunitinib followed by sorafenib in patients with advanced/metastatic renal cell carcinoma without prior systemic therapy (SWITCH Study): Safety interim analysis results.

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Background: Several retrospective studies have investigated the sequential use of SO and SU. Some smaller trials support the use of SO followed by SU forming the rationale for this study. **Methods:** Pts with metastatic RCC unsuitable for cytokines without prior systemic therapy, ECOG PS 0/1, MSKCC score low or intermediate, and ≥1 measurable lesion (CT/MRI every 12 weeks) were randomized to SO->SU or SU->SO in standard dosage (primary endpoint total PFS from randomization to event during 2nd line therapy). Treatment continues until progression or intolerability. Monitoring includes echocardiography and NT pro-BNP. **Results:** Baseline characteristics of 361 randomized pts (116 completed) are balanced between arms. Safety data of 333 pts are evaluable. AE occurring in >10% of pts are listed in tab. 1. Left-ventricular ejection fraction (LVEF) at screening, switch of treatment, and end of study are given in tab. 1. AE occurred in 93.4% and 92.8%; grade 3/4 AE in 59.9% and 50%; and SAE in 46.7% and 42.2% in the SO->SU and SU->SO arm, respectively. Updated results will be presented. **Conclusions:** AE frequencies are higher in 1st than in 2nd line treatments. Typical AE profiles for SO and SU are observed. LVEF values are in a similar range.

	SO 1st		SU 2nd		SU 1st		SO 2nd	
	(n=167) %	%	(n=71) %	%	(n=166) %	%	(n=47) %	%
CTCAE	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4
Hematotoxicity	6.6	1.2	19.7	5.6	16.9	9.0	0	0
Hypertension	26.9	7.2	7.0	1.4	29.5	9.0	4.3	2.1
Fatigue	28.1	5.4	22.5	2.8	31.3	5.4	17.0	0
Weight loss	12.6	0.6	4.2	0	4.2	0.6	4.3	0
Hair loss	28.1	0	1.4	0	3.0	0	4.3	0
Rash	10.8	1.2	4.2	0	3.0	0	6.4	0
Hand-Foot Skin Rct.	41.3	13.8	7.0	1.4	15.1	4.2	21.3	8.5
Diarrhea	45.5	4.8	14.1	2.8	30.1	1.2	29.8	4.3
Mucositis	4.8	0	4.2	0	13.8	2.4	2.1	0
Nausea	18.6	1.2	15.5	1.4	22.9	0.6	4.3	0
Vomiting	6.6	0	12.7	2.8	14.5	1.8	4.3	0
SO->SU				**N**			**Mean LVEF % ±SD**	
Screening				151			63.0 ± 7.6	
Day of stopping 1st-line treatment				46			62.7 ± 8.9	
End of study				23			60.3 ± 10.5	
SU->SO								
Screening				149			64.1 ± 8.2	
Day of stopping 1st-line treatment				28			62.6 ± 10.1	

4540 Poster Discussion Session (Board #19), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

The use of tumor growth rate (TGR) in evaluating sorafenib and everolimus treatment in mRCC patients: An integrated analysis of the TARGET and RECORD phase III trials data.

Charles Ferte, Laurence Albiges, Jean-Charles Soria, Yohann Loriot, Karim Fizazi, Bernard J. Escudier; Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; Institut Gustave Roussy, Villejuif, France

Background: RECIST criteria may not be sufficient to evaluate targeted therapies in mRCC. TGR includes the time between each evaluation and is expected to overcome some of the RECIST pitfalls. How TGR is modified under targeted therapies and how it correlates with outcome in mRCC remains unknown. **Methods:** Medical records from all patients (pts) prospectively treated at Institut Gustave Roussy (IGR) in the TARGET (n=84) and in the RECORD (n= 52) phase III trials were extracted. Results were subsequently validated in the entire TARGET cohort (TARGET) (n=902). TGR was computed by dividing tumor shrinkage by the time between the two related evaluations (% RECIST x 100 / days). Typical treatment periods were assessed: BEFORE treatment (wash-out), UNDER treatment (first cycle), at PROGRESSION (pts still receiving the drug) and AFTER treatment interruption (wash-out). **Results:** As compared to placebo, TGR UNDER was significantly decreased following sorafenib (-23.6 vs. 20 (IGR) and -19 vs. 22 (TARGET)) and everolimus (-5.2 vs. 30 (IGR)). The great majority of pts (IGR) had a decrease in the TGR UNDER vs. BEFORE, regardless of the RECIST evaluation, both with sorafenib (28/29) or everolimus (36/37). TGR AFTER sorafenib or everolimus interruption was significantly higher than TGR at PROGRESSION in both settings (IGR) (14.6 vs. 31 and 17.9 vs. 32.1 respectively). No significant difference was observed between TGR AFTER vs. BEFORE either in sorafenib or in everolimus pts (IGR). High TGR UNDER is associated with poor progression free survival (HR= 2.6) and overall survival (HR= 2.3) in sorafenib-treated pts (multivariate analysis, trained in IGR and validated in TARGET cohorts) and with poor overall survival in everolimus-treated pts (IGR)(HR= 1.2). **Conclusions:** Adding TGR assessment in mRCC unravels interesting traits that make it potentially adaptable for clinical practice: (i) better evaluation of the tumor response, regardless of RECIST criteria, (ii) independent prognosis value, (iii) it suggests that maintaining sorafenib or everolimus after disease progression might benefit to patients and should be prospectively evaluated.

4541 Poster Discussion Session (Board #20), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

PFS to predict long-term OS after first-line treatment for advanced renal cell carcinoma (aRCC): Correlation and power analysis of randomized trials (RCT).

Michele Milella, Francesco Massari, Francesca La Russa, Francesca Maines, Alessandra Felici, Vanja Vaccaro, Camillo Porta, Sergio Bracarda, Francesco Cognetti, Diana Giannarelli, Giampaolo Tortora, Emilio Bria; Regina Elena National Cancer Institute, Rome, Italy; Medical Oncology, University of Verona, Verona, Italy; Medical Oncology, Regina Elena National Cancer Institute, Rome, Italy; Oncologia Medica, Fondazione IRCCS Policlinico Universitario San Matteo, Pavia, Italy; Department of Oncology, USL-8, Ospedale San Donato, Arezzo, Italy

Background: Targeted agents (TA) have become standard 1st line aRCC treatment based on evidence of PFS advantage. Retrospective series indicatePFS as a reliable intermediate end-point in this setting; however, correlation, surrogacy testing, and validation are required. **Methods:** RCT evaluating the efficacy of TA as 1st line treatment for aRCC were eligible. PFS/OS Response/Disease Control rates (ORR, DCR) and HR were extracted from papers/updated presentations. Correlations between 6-, 9-, and 12-mo PFS and OS rates according to parametric (Pearson's r) and non-parametric (Spearman's Rho and Kendall's Tau) coefficients (with 95% CI) were analyzed to avoid lead-time biases. Regression analysis (parametric R2) and a power-analysis-model to determine patients' sample necessary to detect 3%, 5% and 10% OS gain were developed. **Results:** Six RCT (4096 pts) were gathered. The best overall correlation between PFS and OS at concurrent timepoints was found at 9 mos. With regard to overall rates, 3- and 6-mo PFS significantly correlated with 9-mo OS, as shown in the table below. Pearson's coefficients for the correlation between 3-mo PFS and 6- and 12-mo OS were 0.70 ($p=0.01$) and 0.67 ($p=0.01$); the correlation between 6-mo PFS and 12-mo OS was also significant (Pearson 0.74, $p=0.005$; Spearman 0.83, $p=0.005$; Tau 0.71, $p=0.001$). The regression equation was: $Y=0.391861 + 0.4914X$ [R2 0.44, p(slope)$=0.01$]; based on this model, the demonstration of a 3-mo PFS absolute difference of 6%, 10% and 21% (corresponding to a 9-mo OS benefit of 3%, 5% and 10%) would require 2043, 696 and 155 patients, respectively. A significant correlation was also found between DCR and OS. **Conclusions:** Early PFS is an acceptable intermediate end-point for OS in the context of 1st line TA for aRCC. Individual patient data analysis to verify Prentice criteria would be required for definitive confirmation.

	Correlation coefficient (p value)		
Sample	**Pearson**	**Rho**	**Tau**
Overall	0.66 (0.01) 0.75 (0.004)	0.78 (<0.01) 0.91 (0.002)	0.67 (0.03) 0.79 (0.004)
TA arm	0.69 (n.s.) 0.90 (0.01)	0.94 (0.03) 0.90 (0.04)	0.85 (0.02) 0.82 (0.03)
Control arm	0.76 (n.s.) 0.68 (n.s.)	0.84 (n.s.) 0.89 (0.04)	0.69 (n.s.) 0.82 (0.03)

4542 Poster Discussion Session (Board #21), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Sunitinib objective response (OR) in metastatic renal cell carcinoma (mRCC): Analysis of 1,059 patients treated on clinical trials.

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Background: Sunitinib achieves robust OR and improved progression-free survival (PFS) in mRCC patients (N Engl J Med 2007;356:115). A retrospective analysis was performed to characterize the OR rate with sunitinib treatment (Tx) and OR-associated patient features and survival. **Methods:** Data from six phase II and III trials were pooled from 1,059 patients who received sunitinib on the approved 50 mg/d 4-week-on/2-week-off schedule (n=689; 65%) or at 37.5 mg continuous once-daily dosing (n=370; 35%), in both the 1st- (n=783; 74%) and 2nd-line (n=276; 26%) Tx settings. Median PFS and overall survival (OS) were estimated by the Brookmeyer and Crowley method, and compared between responders and nonresponders, and early and late responders (response $\leq$ and $>$12 weeks, respectively), by a log-rank test. Baseline characteristics were compared by Fisher-exact Test, T-Test, or Wilcoxon Rank-sum Test. **Results:** Of 1,059 patients, 398 (38%) had a confirmed investigator-assessed OR by RECIST (including 12 with a complete response), of whom 105 (26%), 243 (61%), 314 (79%), and 342 (86%) had a response by 6, 12, 18, and 24 weeks, respectively. Median (range) time to tumor response (TTR) in all patients was 10.6 (2.7–94.4) weeks, which was similar in the 1st- and 2nd-line Tx settings. Responders had better baseline ECOG scores, more favorable risk factor classification based on published MSKCC data, a longer interval since initial diagnosis, more prior nephrectomy, and less presence of baseline bone metastases (all $p<0.05$). Early responders had more lung metastases ($p<0.01$). Median PFS (16.3 vs. 5.3 months) and OS (40.1 vs. 14.5 months) were significantly longer in responders vs. nonresponders (both $p<0.001$), with similar results regardless of 1st- or 2nd-line Tx setting. Median OS did not differ between early and late responders ($p=0.1438$). **Conclusions:** OR was achieved in 38% of 1,059 mRCC patients treated with sunitinib and was predicted by favorable pretreatment prognostic factors. Patients with OR had longer PFS and OS. Median TTR was 10.6 weeks, and characteristics and outcome of early and late responders were similar, except for higher frequency of lung metastases among early responders.

4543 Poster Discussion Session (Board #22), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Association of inherited genetic variation with clinical outcome in patients with advanced renal cell carcinoma treated with mTOR inhibition.

Mark M Pomerantz, Kathryn P. Gray, Fabio Augusto Barros Schutz, Andrew Percy, Megan Lampron, Sabina Signoretti, Michelle S. Hirsch, Jonathan E. Rosenberg, Gwo-Shu Mary Lee, David F. McDermott, Michael B. Atkins, Philip W. Kantoff, Matthew L Freedman, Toni K. Choueiri; Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Department of Biostatistics and Computational Biology, Harvard School of Public Health, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Harvard Medical School/Brigham and Women's Hospital, Boston, MA; Brigham and Women's Hospital, Boston, MA; Dana-Farber Cancer Institute, Broad Institute, Harvard Medical School, Boston, MA

Background: Mammalian target of rapamycin (mTOR)-targeted therapy is standard in patients with metastatic renal cell carcinoma (mRCC). Predictive biomarkers for response are lacking. We sought to characterize outcome after mTOR inhibition based on germline variation in 2 critical genes in the mTOR pathway: phosphoinositide-3-kinase catalytic alpha (PIK3CA) and mTOR. **Methods:** 76 Americans of European ancestry treated with temsirolimus or everolimus for mRCC were included. Germline DNA was genotyped for all common genetic variation (minor allele frequency [MAF] >0.05) across PIK3CA and mTOR, tagging with single nucleotide polymorphisms (SNPs) at $r^2>0.8$. Associations between genotype and progression-free survival (PFS) and overall survival (OS) from the start of mTOR-targeted therapy were measured using univariate Cox model. **Results:** Among 76 patients, 66% were poor or intermediate risk and 89% received prior systemic therapies. Median follow up was 23.7 months. Median PFS and OS were 4.3 and 12.7 months, respectively. Two intronic PI3KCA SNPs were significantly associated with PFS and OS, and a SNP in the 5' UTR of mTOR was associated with OS. Associations were maintained when adjusted for age, gender and MSKCC RCC risk categories using Cox PH model (Table). The PI3KCA SNPs are in modest linkage disequilibrium (r^2 ~0.36). **Conclusions:** We suggest that inherited variation at PIK3CA is associated with PFS and OS after mTOR inhibition. If results are validated, prospective studies could explore the role of genotyping in treatment selection for mRCC. Further work will be needed to identify causal alleles and define the mechanism underlying the associations.

PFS and OS after mTOR-targeted therapy by genotype.

Gene	SNP	MAF	Genotype	Median PFS (months)	HR (95% CI)	P value*	Median OS (months)	HR (95% CI)	P value*
PIK3CA	rs2699905	0.25	TC, TT	6	1		13.1	1	
			CC	4.4	2.1 (1.23,3.57)	0.006	12.2	1.86 (1.05,3.3)	0.03
PIK3CA	rs13082485	0.08	AA, AG	10.6	1		33.9	1	
			GG	4.2	3.1 (1.37,7)	0.007	12.2	4.11 (1.46,11.61)	0.008
mTOR	rs12732063	0.07	AA, AG	3.5	1		7.7	1	
			GG	4.8	0.58 (0.28,1.2)	0.14	12.9	0.36 (0.16,0.8)	0.01

Abbreviations: HR, hazard ratio; CI, confidence interval. * Adjusted for age, gender, MSKCC risk groups.

4544^ Poster Discussion Session (Board #23), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Phase II trial of RAD001 in renal cell carcinoma patients with non-clear cell histology.

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Background: In non-clear cell renal cell carcinoma (ncRCC), the efficacy of VEGF tyrosine kinase inhibitor (TKI) is controversial. In the while, a mTOR inhibitor, temsirolimus showed a promising efficacy in ncRCC patients in ARCC trial. Hence, we investigated the role of everolimus in ncRCC with this phase II trial. **Methods:** ncRCC patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. We included patients who had received VEGF TKI previously, while excluded patients who received previous mTOR inhibitor. The primary end point was progression free survival (PFS). **Results:** A total of 49 patients were enrolled from 5 centers. Their median age was 57 years (range 24-75 years) and male to female ratio was 37:12. Histology of the patients included papillary (n=29), chromophobe (n=8), collecting duct (n=2), sarcomatoid (n=4), and unclassifiable (n=6) RCC. Twenty-three patients had been treated with VEGF-TKI prior to the study enrollment. Among 49 patients, 46 patients underwent radiologic response assessment after everolimus treatment. Partial response was observed in 5 patients (10.2%) and stable disease in 25 patients (51.0%). Diseases of 16 patients (32.7%) progressed despite of everolimus administration. Histology of 5 patients who showed objective response to everolimus included chromophobe carcinoma (n=2), papillary carcinoma (n=2) and unclassifiable carcinoma (n=1). During the study period, 34 patients experienced PFS events and median PFS was 5.2 months. Patients with chromophobe histology showed longer PFS than patients with the other histologies (median PFS 18.8 months vs. 3.5 months, p=0.027). Estimated median PFS were not significantly different between patients VEGF-TKI treatment and patients without previous VEGF-TKI treatment (median PFS 7.1 vs. 3.7 months, p=0.110). Toxicity profiles were commensurable with previous reports. **Conclusions:** Everolimus shows considerable efficacy in ncRCC. Patients with chromophobe histology might earn benefit from everolimus treatment especially. Previous treatment with VEGF-TKI seems not to significantly influence outcome of everolimus therapy in these patients. (ClinicalTrials.gov number, NCT00830895)

4545 Poster Discussion Session (Board #24), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Safety and efficacy of MET inhibitor tivantinib (ARQ 197) combined with sorafenib in patients (pts) with renal cell carcinoma (RCC) from a phase I study.

Igor Puzanov, Jeffrey Alan Sosman, Armando Santoro, Robert E. Martell, Grace K. Dy, Laura Williams Goff, Wen Wee Ma, Gerald J. Fetterly, Shaunita A. Michael, Julie Ann Means-Powell, Feng Chai, Maria Lamar, Gary M. Strauss, Paolo A. Zucali, Wendy M. Chiang, Jamie Jarboe, Brian E. Schwartz, Alex A. Adjei; Vanderbilt University Medical Center, Nashville, TN; Istituto Clinico Humanitas, Milan, Italy; Tufts Medical Center Cancer Center, Boston, MA; Roswell Park Cancer Institute, Buffalo, NY; ArQule, Inc., Woburn, MA

Background: Inhibitors of vascular endothelial growth factor (VEGF) and VEGF receptor are standard therapy for RCC, and the MET signaling pathway is implicated in tumor angiogenesis. Tivantinib is an oral, selective MET inhibitor. In several tumor models, tivantinib plus sorafenib exhibited synergistic antitumor activity vs single-agent activity. This phase I dose-escalation study assessed the safety of tivantinib plus sorafenib in pts with advanced solid tumors. **Methods:** Endpoints were safety, the recommended phase II dose (RP2D) of tivantinib plus sorafenib, and antitumor activity. Previously, dose escalation established the RP2D as tivantinib 360 mg twice daily (BID) plus sorafenib 400 mg BID. Extension cohorts enrolled $\leq$ 20 pts each with RCC or other tumors. Patients were treated until disease progression or unacceptable toxicity. **Results:** 20 pts (mean age, 60 yr) including 16 clear cell, 3 papillary, and 1 clear cell/chromophobe RCC pts received treatment at the RP2D (n = 19) or tivantinib 360 mg BID plus sorafenib 200 mg BID (n = 1). 4 pts are still on study. 16 pts (13 with clear cell RCC) received $\geq$ 1 previous systemic therapy (median, 2; range, 0-4) including VEGF (14 pts) and/or mTOR (5 pts) inhibitors. The most common ($\geq$ 25%) adverse events were rash (65%), diarrhea (45%), alopecia (40%), hypophosphatemia (35%), and fatigue, stomatitis, palmar-plantar erythrodysesthesia syndrome, and pruritus (25% each). Best response was partial response (PR) in 3 pts (all clear cell RCC pts) and stable disease (SD) in 15 pts (11 clear cell, 3 papillary, and 1 clear cell/chromophobe RCC pts). 7 pts with SD had $\geq$ 10% tumor size reduction. The overall response rate (ORR) and disease control rate (DCR; PR + SD) were 15% and 90%, respectively. Median progression-free survival (mPFS) was 12.7 mo (95% CI, 7.1-14.5 mo). In 14 pts previously treated with a VEGF inhibitor, best response was 2 PR and 10 SD, the ORR and DCR were 14% and 86%, respectively, and mPFS was 12.7 mo (95% CI, 5.3-NR mo). **Conclusions:** Oral combination therapy with tivantinib plus sorafenib was well tolerated and exhibited preliminary anticancer activity in pts with RCC, including pts pretreated with VEGF inhibitors.

4546 Poster Discussion Session (Board #25), Sat, 8:00 AM-12:00 PM and 12:00 PM-1:00 PM

Phase III AXIS trial of axitinib versus sorafenib in metastatic renal cell carcinoma: Updated results among cytokine-treated patients.

M. Dror Michaelson, Brian I. Rini, Bernard J. Escudier, Joseph Clark, Bruce Redman, Jamal Christo Tarazi, Brad Rosbrook, Sinil Kim, Robert John Motzer; Massachusetts General Hospital Cancer Center, Boston, MA; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Institut Gustave Roussy, Villejuif, France; Loyola University Chicago Cardinal Bernardin Cancer Center, Maywood, IL; University of Michigan, Comprehensive Cancer Center, Ann Arbor, MI; Pfizer Oncology, San Diego, CA; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Axitinib, a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors, improved progression-free survival (PFS) compared to sorafenib in patients with metastatic renal cell carcinoma (mRCC) in the phase III AXIS trial. In patients previously treated with cytokines, median PFS (mPFS) was 12.1 mo. In a prior phase II study of axitinib for cytokine-refractory mRCC, mPFS was 13.7 mo and the 5-yr overall survival (OS) rate was 20.6%. We report updated PFS and OS for cytokine-treated patients from the AXIS trial. **Methods:** 723 patients with clear-cell mRCC and progressive disease after 1 systemic therapy were enrolled, of whom 251 received prior interleukin-2 (IL-2) or interferon-α (IFN-α). Patients were randomized 1:1 to axitinib (5 mg twice daily [BID] starting dose) or sorafenib (400 mg BID). **Results:** As of Jun 3, 2011, mPFS (95% confidence interval [CI]) for cytokine-treated patients was 12.0 mo (10.1, 13.9) with axitinib (n=126) vs 6.6 mo (6.4, 8.3) with sorafenib (n=125): hazard ratio [HR] (95% CI) 0.519 (0.375, 0.720); $p<0.0001$. For those treated with an IL-2-containing regimen, mPFS (95% CI) was 15.7 mo (8.3, 19.4) with axitinib (n=37) vs 8.3 mo (4.7, 15.7) with sorafenib (n=38). For those treated with IFN-α alone, mPFS (95% CI) was 12.0 mo (10.0, 13.8) with axitinib (n=89) vs 6.5 mo (6.4, 8.2) with sorafenib (n=87). As of Nov 1, 2011, median OS (95% CI) in the cytokine-treated subgroup was 29.4 mo (24.5, not estimable) with axitinib vs 27.8 mo (23.1, 34.5) with sorafenib: HR (95% CI) 0.813 (0.555, 1.191); p=0.144. Adverse event (AE) profiles were similar in both arms. Few cytokine-treated patients (5.6%) discontinued axitinib due to toxicity. AEs reported in >25% of cytokine-treated patients receiving axitinib were diarrhea (49.2%), hypertension (47.6%), fatigue (35.7%), dysphonia (29.4%), and hand–foot syndrome (28.6%). **Conclusions:** Axitinib showed median PFS and OS of 1 and 2.5 yr, respectively, in cytokine-treated patients, confirming prior phase II study results, and was well tolerated. PFS was superior to that of sorafenib in second-line mRCC and compares favorably with historical results of other agents in second-line mRCC.

4551 Poster Discussion Session (Board #5), Mon, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Radium-223 chloride (Ra-223) impact on skeletal-related events (SREs) and ECOG performance status (PS) in patients with castration-resistant prostate cancer (CRPC) with bone metastases: Interim results of a phase III trial (ALSYMPCA).

A. Oliver Sartor, Daniel Heinrich, Joe M. O'Sullivan, Sophie D. Fossa, Ales Chodacki, Pawel J. Wiechno, John P. Logue, Mihalj Seke, Anders Widmark, Dag Clement Johannessen, Sten Nilsson, Peter Hoskin, David Bottomley, Robert Edward Coleman, Nicholas J. Vogelzang, C. Gillies O'Bryan-Tear, Jose E. Garcia-Vargas, Minghua Shan, Chris Parker; Tulane Cancer Center, New Orleans, LA; Akershus University Hospital, Lørenskog, Norway; Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Ireland; Radiumhospitalet, Oslo, Norway; Hospital Kochova, Chomutov, Czech Republic; Centrum Onkologii – Instytut im Sklodowskiej-Curie, Warsaw, Poland; Christie Hospital, Manchester, United Kingdom; Centrallasarettet Växjö, Växjö, Sweden; Norrlands University Hospital, Umeå, Sweden; Ullevål University Hospital, Oslo, Norway; Karolinska Universitettsjukhuset, Stockholm, Sweden; Mount Vernon Hospital Cancer Centre, Middlesex, United Kingdom; St. James's Hospital, Leeds, United Kingdom; Weston Park Hospital, Sheffield, United Kingdom; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Algeta ASA, Oslo, Norway; Bayer HealthCare Pharmaceuticals, Montville, NJ; The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: Ra-223, a 1st-in-class alpha-pharmaceutical, targets bone metastases (mets) with high-energy alpha-particles of short range (<100 μm). ALSYMPCA, a phase III, double-blind, randomized, multinational study, compared Ra-223 plus best standard of care (BSC) v placebo (pbo) plus BSC in patients (pts) with bone mets in CRPC. The primary endpoint was OS; secondary endpoints included SREs and ECOG PS. **Methods:** Eligible pts had progressive, symptomatic CRPC with ≥ 2 bone mets on scintigraphy and no known visceral mets; were receiving BSC; and either previously received docetaxel, were docetaxel ineligible, or refused docetaxel. Pts were randomized 2:1 to 6 injections of Ra-223 (50 kBq/kg IV) q4 wks or matching pbo and stratified by prior docetaxel use, baseline ALP level, and current bisphosphonate use. **Results:** 921 pts were randomized from 6/2008-2/2011. In a planned interim analysis (n = 809), Ra-223 significantly improved OS v pbo (median OS 14.0 v 11.2 mo, respectively; two-sided P = .00185; HR = .695; 95% CI, .552-.875).SREs were lower in the Ra-223 v pbo group, and time to 1st SRE was significantly delayed (median time to SRE 13.6 mo v 8.4 mo, respectively; P = .00046; HR = .610; 95% CI, .461-.807). The proportion of pts with ECOG PS deterioration (≥ 2 points) was less in Ra-223 v pbo group at Wk 12 and Wk 24 (4%, 15/389 v 9%, 16/180 and 7%, 16/236 v 12%, 10/83, respectively). Time to ECOG PS deterioration (≥ 2 points) was significantly delayed by Ra-223 v pbo (*P* = .003; HR = .62; 95% CI, .46-.85). **Conclusions:** Ra-233 significantly delayed time to 1st SRE and SRE components, notably SCC. Fewer pts in the Ra-223 group had ECOG PS deterioration. Ra-223 improves OS with excellent safety and may provide a new standard of care for CRPC pts with bone mets.

	No. (%) of patients		Time to 1st event (Ra-223 vs Pbo)	
SRE component	Ra-223 n = 541	Pbo n = 268	p value*	HR (95%CI)
External beam radiotherapy	122 (23)	72 (27)	.0038	.65 (.48-.87)
Spinal cord compression	17 (3)	16 (6)	.016	.44 (.22-.88)
Pathologic bone fracture	20 (4)	18 (7)	.013	.45 (.24-.86)
Surgical intervention	9 (2)	5 (2)	.69	.80 (.27-2.4)

*Not adjusted for multiplicity.

4603 General Poster Session (Board #5B), Sun, 8:00 AM-12:00 PM

Phase I results of a phase I/II trial of BNC105P with everolimus in metastatic renal cell carcinoma (mRCC) patients previously treated with VEGFR tyrosine kinase inhibitors.

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Background: BNC105P is an investigational agent that destabilizes tubulin polymers leading to selective damage of tumor vasculature, causing disruption of blood flow to tumors, hypoxia and associated tumor necrosis. BNC105P also has a direct anti-proliferative action on cancer cells. Preclinical investigations have demonstrated that BNC105P is effective at selectively damaging the vasculature in both primary and metastatic lesions. Up regulation of the mTOR pathway has been identified as a survival response by the tumor to hypoxic insult. It follows that the combined use of BNC105P with an agent active against mTOR may improve clinical outcome in patients with progressive mRCC who are refractory to VEGFR-directed tyrosine kinase inhibitors (TKI). **Methods:** A phase I/II study in mRCC patients who have received 1-2 prior TKIs was undertaken. Using a classic 3+3 design, the phase I component of this study enrolled 12 subjects at 4 dose levels of BNC105P (4.2, 8.4, 12.6, 16 mg/m^2; IV infusion Days 1 and 8, 21-day repeating cycle). Everolimus was administered concurrently (10 mg p.o.). PK analysis was performed during Cycle 1. **Results:** The phase I component has been completed. The BNC105P / everolimus combination was well tolerated. No DLTs (drug-related, during cycle 1) were observed in any of the phase I subjects. Toxicities on study deemed to be drug-related (either single agent or combination) included single grade 3 events of anemia and pericardial effusion. Grade 2 events (more than 1 occurrence) of fatigue, anemia and oral mucositis were also observed. Seven phase I subjects achieved at least disease stabilization with a minimum time on therapy of 18 weeks (6 cycles). Across all subjects a median of 6 cycles (range: 1-15) was administered. PK analysis confirmed no drug-drug interaction. The randomized phase II component of the study continues and will compare everolimus given in combination with BNC105P to a sequential approach (everolimus followed by BNC105P). **Conclusions:** The MTD of BNC105P (16 mg/m^2) can be combined with full dose everolimus and is being evaluated in the randomized phase II study.

4604 General Poster Session (Board #5C), Sun, 8:00 AM-12:00 PM

Genetic determinants of long-term response to rapalog therapy in advanced renal cell carcinoma (RCC).

Martin Henner Voss, Abraham A. Hakimi, Sasinya N. Scott, Shugaku Takeda, Han Liu, Yingbei Chen, Robert John Motzer, Michael F. Berger, James Hsieh; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Temsirolimus (T) and everolimus (E) are rapalog inhibitors of the mammalian target of rapamycin (mTOR) with efficacy in advanced RCC [NEJM;356(22):227-81; Lancet;372(9637):449-56]. With reported median progression-free survival (PFS) of 5.5 and 4.9 months (mo), respectively, benefit is typically modest, yet a subset of patients (pts) achieves long-term disease control evident by extended PFS. The oncogenomic background for this is unclear. **Methods:** We analyzed frozen specimens of tumor and adjacent normal kidney from pts with advanced RCC and documented long-term response to T or E, defined as PFS of $\geq$ 20mo. Samples from pts with PFS $\leq$ 2mo served as comparators. Specimens were subjected to whole exome sequencing; a targeted next-generation sequencing platform was used for deep sequencing and investigation of copy number variations (CNV) in 230 genes of interest. **Results:** In 5 pts with long-term response to T [n=3] or E [n=2], histologic subtypes were clear cell [n=3] and unclassified [n=2] RCC. Median number of prior treatments was 2 (1-3). Two pts remain on therapy, 3 have stopped drug for disease progression; treatment duration was 20, 25+, 27, 28, and 28+ mo. Three control pts progressed after 1, 2, and 2 mo on therapy. Mean target coverage was 86x for whole exome and 443x for targeted sequencing. Three of 5 long-term responders harbored acquired somatic mutations and/or CNV in genes encoding for members of the Phosphoinositide 3-Kinase (PI3K) / mTOR pathway. Effects on amino acid sequence and gene function suggest a hyperactive pathway in all 3. For the other 2 long-term responders genomic changes with possible indirect link to the pathway, but no apparent determinants of treatment response were seen. In 3 control patients with rapid disease progression no genomic alterations suggesting hyperactivation of the pathway were seen. **Conclusions:** In this retrospective discovery set of RCC pts with unusually long response to rapalog therapy, next generation sequencing using pre-treatment tissue specimens revealed plausible oncogenomic determinants of treatment benefit in 3 of 5 cases. These findings provide basis for further biomarker development and studies in a larger sample set are ongoing.

4605 General Poster Session (Board #5D), Sun, 8:00 AM-12:00 PM

Correlation of chromosome (Chr) 14 loss and 5q gain with outcomes of pazopanib treatment in patients (pts) with metastatic clear cell renal cell carcinoma (mRCC).

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Background: The identification of molecular prognostic and/or predictive determinants of outcome in pts with mRCC is an important challenge. We hypothesized that specific tumor DNA copy number alterations (CNAs) - loss of chr 14 or 14q (14/14q-), and gain of chr 5q (5q+) may predict likelihood of pazopanib treatment benefit in pts with mRCC. **Methods:** Pts DNA samples from the Phase II (VEG102616) pazopanib trial were analyzed by using Affymetrix OncoScan. Copy no. data were moving smoothed and normalized. The copy no. and allele difference were profiled according to their chromosome locations to interrogate CNA and LOH. Objective response (OR, RECIST) and progression free survival (PFS) were determined by investigators (IN) and an independent review (IR) committee. OR and PFS data were analyzed using exact and Kaplan-Meier tests. **Results:** Tumor DNA samples from 75 pts were adequate for CNA analysis. 14/14q- was found in 35/75 pts (46.7%), and 5q+ was found in 37/75 (49.3%). 14/14q- was present in the tumors of 12/31 pts (39%) with OR by IR compared with 23/44 (52%) nonresponding pts (p=0.347). 14/14q- did not affect PFS. 5q+ was present in tumors of 17/31 pts (55%) with OR and 20/44 (45%) nonresponding pts (p=0.486). PFS was longer in pts with 5q+ tumors compared with those without 5q+ (log rank p=0.026), with median PFS of 66 vs 35 wks, respectively. The odds of achieving OR decreased as the total number of chromosomal gains/losses increased (p=0.032, odds ratio 0.49), but this had no effect on PFS. In exploratory analysis, we examined the combined effect of both 14/14q- and 5q+ on PFS (Table). **Conclusions:** Pts with 5q+ tumors have significantly longer PFS, with no effect on OR rate. While 14/14q- alone had no effect on outcomes, the combination of 5q+ and no 14/14q- was associated with significantly greater PFS. Pts with more genetically complex tumors were less likely to obtain OR with pazopanib.

		Median PFS wks (95% confidence limits)	
Copy no. change	**No. pts**	**By IN**	**By IR**
14/14q- , no 5q+	14	18 (8, 52)	28 (18, -)
No 14/14q-, no 5q+	24	36 (20, 60)	44 (20, 84)
14/14q-, 5q+	21	36 (24, -)	60 (28, -)
No 14/14q-, 5q+	16	83 (36, 100)	84 (43, -)
Total	75	p=0.005	p=0.071

4606 General Poster Session (Board #5E), Sun, 8:00 AM-12:00 PM

Safety and efficacy of AMG 386 in combination with sunitinib in patients with metastatic renal cell carcinoma (mRCC) in an open-label multicenter phase II study.

Michael B. Atkins, Alain Ravaud, Gwenaelle Gravis, Kazimierz Drosik, Tomasz Demkow, Piotr Tomczak, Karolyn Kracht, Markus Puhlmann, David Michael Weinreich; Beth Israel Deaconess Medical Center, Boston, MA; Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint André, Bordeaux, France; Department of Medical Oncology, Institut Paoli Calmettes, Marseille, France; Regional Cancer Center, Opole, Poland; Maria Skodowska-Curie Memorial Cancer Center, Warszawa, Poland; University of Medical Sciences, Clinic of Oncology, Poznan, Poland; Amgen Inc., Thousand Oaks, CA; Amgen, Thousand Oaks, CA

Background: AMG 386, an investigational peptide-Fc fusion protein, inhibits angiogenesis by disrupting the angiopoietin/Tie2 axis. We evaluated the safety and efficacy of AMG 386 plus sunitinib in patients (pts) with mRCC. **Methods:** Adults with mRCC who were naïve to angiogenesis inhibitors were sequentially enrolled to 2 cohorts: sunitinib 50 mg PO QD (4 wks on, 2 wks off) plus AMG 386 at 10 mg/kg (A) or 15 mg/kg (B) IV QW. Primary endpoints: adverse events (AEs), dose interruptions/reductions due to AEs in the first 12 wks of treatment; secondary endpoints included: progression-free survival (PFS) and response rate (ORR). **Results:** 85 pts received ≥1 dose of study medication (A/B, n=43/42). In A/B, 88%/76% were male and 30%/36% were age ≥65; MSKCC risk scores were low (40%/36%) or intermediate (60%/62%). For A/B: median follow-up time was 19.6/12.0 mos; AMG 386 discontinuations due to AEs were 16%/29%; and grade ≥3 treatment-related AEs occurred in 72%/74% with virtually all attributed to sunitinib. Grade 3 AEs occurring with >5% frequency were hypertension, hand foot syndrome, asthenia, fatigue, elevated lipase, diarrhea, mucositis, vomiting, thrombocytopenia, and neutropenia, with no distinction between dose levels. The percentage of pts with sunitinib dose interruptions within the first 12 wks (A/B, 58%/57%) met the prespecified criteria. One pt in B had fatal acute pulmonary edema. No pt developed anti-AMG 386 antibodies. The Kaplan-Meier estimate (95% CI) of PFS was 13.9 (10.4, 19.2) mos in A; PFS in B is not yet mature with only 21% of pts having disease progression. ORR (95% CI) was 58% (42, 73) in A including 1 CR, and 59% (42, 74) in B. **Conclusions:** In pts with mRCC, AMG 386 at 10 and 15 mg/kg combined with sunitinib appeared to be tolerable. Reported sunitinib dose modifications for the observation period were within the prespecified range. Efficacy results suggest potential benefit for the addition of AMG 386 to sunitinib.

4607 General Poster Session (Board #5F), Sun, 8:00 AM-12:00 PM

Evolving trends in non-clear cell renal cell cancer (RCC) epidemiology: A large registry analysis of 4,483 patients.

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Background: Non-clear cell (ncc) RCC is uncommon but includes a heterogeneous group of histologic subtypes such as papillary, chromophobe (Chr), medullary (Med), and collecting duct (CD) cancers. We used a large cancer registry to define nccRCC clinical features and outcomes, identify prognostic variables, and to generate hypotheses for further study. **Methods:** Invasive RCC tumors in the California Cancer Registry from 1998-2009 among adults > 18 years of age (n=38,251) were analyzed. Baseline clinical and tumor variables were collected. Primary outcome measures were 3-year cause-specific (CSS) and overall survival (OS). Uni- and multivariate survival analysis were used to identify predictors of CSS and OS. **Results:** Of 38,251 RCC cases, 19,149 (50%) were of clear cell type; 14,619 (38.2%) were "unclassified." Thus, 4,483 (11.7%) nccRCC cases were identified and included in this analysis. Of these, 3,304 (73.7%) were diagnosed in 2004-09, suggesting a shift to more precise coding of histologic subtypes starting in the early 2000s. Histology distribution (n, %): papillary - 2,863 (63.9%); Chr - 1,507 (33.6%); and other including Med and CD - 113 (2.5%). Variables associated with significantly better OS and CSS (univariate analysis) were Chr histology, female sex, and higher socioeconomic status (SES). Significantly worse OS and CSS were seen in Med+CD, age > 65 yrs, no nephrectomy (Nx), and higher stage. Non-hispanic blacks had significantly worse OS and CSS, while the "targeted therapy era" (2004-2009) was associated with better OS. Multivariate analysis showed the following to be independently associated with outcomes (all p <0.001; Hazard Ratios [HR] shown for CSS and OS): Chr histology (0.48, 0.56), Med+CD histology (2.99, 2.42), no Nx (2.84, 3.18), regional stage (5.84, 1.98), distant stage (25.7, 7.67); and non-hispanic blacks (1.5,2 p=0.006; 1.25, p=0.03). Age > 65 yrs (HR 1.78, p<0.001) and high SES (HR 0.88, p=0.001) were associated with OS but not CSS. **Conclusions:** This is among the largest registry analyses of nccRCC ever performed, showing emerging trends in this uncommon RCC subset. Clinical variables associated with CSS and OS were identified that can inform the design of future clinical trials in nccRCC.

4608 General Poster Session (Board #5G), Sun, 8:00 AM-12:00 PM

Selecting renal cell carcinoma therapy: Ranking of patient perspective on toxicities.

Michael K.K. Wong, Ateesha F Mohamed, A. Brett Hauber, Jui-Chen Yang, Zhimei Liu, Jaqueline Willemann Rogerio, Carlos A. Garay; Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; RTI Health Solutions, Research Triangle Park, NC; Novartis Pharmaceuticals, East Hanover, NJ

Background: Oral therapies (angiogenesis inhibitors and mammalian target of rapamycin (mTOR) inhibitors) for renal cell carcinoma (RCC) have demonstrated significant improvements in progression-free survival but also possess toxicities. The objective of this study was to evaluate whether different toxicities of oral RCC therapies had equal importance to patients. **Methods:** US adults from the Kidney Cancer Association with a self-reported diagnosis of RCC completed a web-enabled survey. Respondents were asked to select the 3 most and 3 least troublesome toxicities from a list of 20 common RCC therapy toxicities. For each respondent, a value of 1 was assigned to each of the 3 most troublesome toxicities, a value of -1 was assigned to each of the 3 least troublesome toxicities, and a value of 0 was assigned to the remaining toxicities. A straight count method was applied to estimate the mean relative importance of each toxicity. Respondents also answered 10 treatment-choice questions, each of which included a pair of hypothetical RCC medication profiles described by survival, toxicities, and serious adverse events. Four toxicities including fatigue, mouth sores, hand-foot syndrome, and stomach problems were included in both exercises. **Results:** 264 of the 272 respondents completed the entire ranking exercise. Among the 20 toxicities, stomach problems was the most troublesome and was assigned an importance of 10. Changes in hair color was the least troublesome and was assigned an importance of 0. Patients ranked fatigue (8.2), mouth sores (7.7), hand-foot syndrome (6.6) by order of importance. When given choices among eliminating severe toxicities, fatigue was as important as stomach problems, both fatigue and stomach problems were more import than mouth sores, and mouth sores was more important than hand-foot syndrome; although not statistically significant. **Conclusions:** This statistical approach offers insight into those toxicities important to patients on chronic RCC therapies.

4609 General Poster Session (Board #5H), Sun, 8:00 AM-12:00 PM

Post-axitinib systemic therapy in metastatic renal cell carcinoma (mRCC).

Housam Haddad, Brian I. Rini, Eric Jonasch, Nizar M. Tannir, Robert Dreicer, Jorge A. Garcia, Laura S. Wood, Paul Elson; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; University of Texas M. D. Anderson Cancer Center, Houston, TX; Cleveland Clinic, Cleveland, OH; Cleveland Clinic Taussig Cancer Center, Cleveland, OH

Background: Axitinib is a potent and selective inhibitor of the VEGF receptor family with efficacy as a second-line therapy in mRCC. Evaluation of further systemic therapy following axitinib has not been previously reported. **Methods:** The medical records ofmRCCpatients (pts) treated at The Cleveland Clinic or MD Anderson Cancer Center who received axitinib were retrospectively reviewed. Patient characteristics including best response and duration of treatment on axitinib and each subsequent line of therapy were recorded. **Results:** Eighty-one patients were initially identified; 29 patients received at least one approved targeted agent following axitinib and are included in this analysis. The remainder of pts were excluded due to ongoing axitinib (n=16), lack of subsequent therapy (n=13), lost to follow up (n=11), received experimental agents post-axitinib (n=7) or were inevaluable (n=2). Three pts were excluded due to ≤ 21 days on axitinib. Pt characteristics at start of axitinib included 76% male, median age 59 (range, 44-78); 97% clear cell; 93% prior nephrectomy; 64% previously-treated. Pts were favorable (39%) or intermediate (60%) risk based on Heng criteria. Overall response rate to axitinib was 52% and median duration of treatment of 11.2 months (range, 1.1-90). Thirty eight percent of patients had new brain, bone, and/or liver metastases at disease progression on axitinib. For the first subsequent therapy post axitinib (n=25), pts were treated with tyrosine kinase inhibitors (72%) or mTOR inhibitors (28%). Overall 8% of pts achieved partial responses (one pt each to sunitinib and pazopanib) and 52% had a best response of stable disease. Estimated median duration of therapy was 4.4 months (range, 0.2-27.5+). Fifteen pts received a second post-axitinib targeted therapy with mTOR inhibitors (60%) or TKIs (40%). One patient (7%) achieved a partial response to pazopanib and 8 patients (53%) had a best response of SD. Estimated median treatment duration was 4.8 months (range, 0.7-19.1+). **Conclusions:** There are objective responses and stable disease to post-axitinib targeted therapies, consistent with previous series and trials in refractory RCC patients.

4610 General Poster Session (Board #6A), Sun, 8:00 AM-12:00 PM

Incidence and severity of cardiotoxicity in metastatic renal cell carcinoma (RCC) patients treated with targeted therapies.

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Background: Almost all patients with advanced RCC are treated with therapies targeting the hypoxia inducible factor axis. The potential for these agents to cause cardiovascular (CV) toxicity has been increasingly recognized but the overall incidence and extent have not been well described. We sought to identify and characterize the incidence and severity of CV toxicity among RCC patients treated with targeted therapies. **Methods:** Between 2004 and 2011, all RCC patients treated with targeted therapies directed against the VEGF or mTOR axes were identified at our institution. The incidence of hypertension, left ventricular (LV) dysfunction, changes in serum markers of CV toxicity (e.g., troponin I, NT-proBNP) and heart failure were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE v.4.0). **Results:** Cardiovascular toxicity developed in 116 of 159 patients (73%). Excluding hypertension, 52 of 159 (33%) developed cardiovascular toxicity. Cardiac toxicity ranged from asymptomatic drops in LV ejection fraction (LVEF) to rises in NT-proBNP to severe heart failure. Asymptomatic cardiotoxicity as defined by decrease in LVEF or increase in NT-proBNP occurred in 43 patients (27%). Symptomatic heart failure (grade 2-3) and grade 3-4 decrease in LVEF each occurred in 4%. Sunitinib was the most frequently used and most common offending agent, with 66 of 101 sunitinib-treated patients (65%) developing a form of CV toxicity, or 32 of 101 (32%) excluding hypertension. However, it was notable that CV toxicity was observed in 68%, 66%, and 51% of patients treated with bevacizumab, sorafenib, and pazopanib as well. The mTOR inhibitors elicited significantly less CV toxicity, but sample sizes were small. **Conclusions:** Cardiovascular toxicity is an important adverse event related to targeted therapy administration. Close monitoring for the development of CV toxicity with the use of these agents should become standard of care as early detection of asymptomatic patients could preempt symptomatic toxicity and reduce treatment-related morbidity and mortality.

4611 General Poster Session (Board #6B), Sun, 8:00 AM-12:00 PM

Outcome of rapid disease progression in the treatment break following cytoreductive nephrectomy (CN) after presurgical sunitinib in patients with primary metastatic renal cell carcinoma (RCC).

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Background: There is concern that interruption of tyrosine kinase inhibitors (TKI) triggers disease progression (PD) and metastasis. This is based on preclinical models and observation of rapid PD in the postsurgical treatment break in patients pretreated with TKI. Little is known about the frequency of PD during postsurgical TKI interruption and its outcome. These data may have implications for neoadjuvant or presurgical treatment concepts. **Methods:** Of 66 patients from two closed phase II trials investigating 2-3 months presurgical sunitinib for primary metastatic clear-cell RCC, 45 were evaluated in this retrospective analysis because they had absence of PD prior to planned surgery and underwent CN (35 [78%] MSKCC intermediate and 10 [22%] poor risk). Patients had CT scans at the end of pretreatment and at 4 weeks post-nephrectomy before restarting sunitinib. In patients with postsurgical RECIST PD at 4 weeks when compared to the preoperative CT scan overall survival (OS) was measured from the time of nephrectomy and compared to patients without treatment break PD. **Results:** Median OS of 45 patients from the time of surgery was 22 months (13.0-31.5 months). Overall 14 patients progressed during treatment break (31%), with new sites of disease in 5/14 (35%). Reintroduction of sunitinib resulted in disease stabilisation or better in 13. Patients with poor risk were represented in the progressors (n=4[28%]) and non-progressors (n=6 [19%]) (p=0.7 fishers exact test). The hazard ratio (HR) for death associated with PD during treatment break was 1.90 (95% CI 0.89-4.08). OS for non-progressors was 25 months (15-NA) and 13 months (6-27) for progressors. **Conclusions:** A significant proportion of patients develop PD upon sunitinib withdrawal in a 4 week recovery period following CN. In view of the small sample size these data suggest a strong trend toward treatment break PD being associated with a poor outcome. It is not clear whether this PD is related to interruption of TKI, surgery or a combination of factors. The EORTC SURTIME trial investigates treatment break PD after immediate CN and CN after sunitinib and may answer this question.

4612 General Poster Session (Board #6C), Sun, 8:00 AM-12:00 PM

Overall and progression-free survival with everolimus, temsirolimus, or sorafenib as second targeted therapies for metastatic renal cell carcinoma: A retrospective U.S. chart review.

Hongbo Yang, Michael K.K. Wong, James E. Signorovitch, Xufang Wang, Zhimei Liu, Nathan S. Liu, Zhengyun Qi, Daniel J. George; Analysis Group, Inc., Boston, MA; Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA; Novartis Pharmaceuticals, Florham Park, NJ; Novartis Pharmaceuticals, East Hanover, NJ; Duke University Medical Center, Durham, NC

Background: Tyrosine kinase inhibitors (TKIs) (sorafenib, sunitinib, pazopanib) and inhibitors of the mammalian target of rapamycin (mTORs) (everolimus, temsirolimus) are used for treating metastatic renal cell carcinoma (mRCC) following initial treatment with a TKI. This study's objective was to establish the effectiveness of the most commonly used 2nd line treatments based on real-use data. **Methods:** mRCC patients who received a TKI as their 1st targeted therapy and everolimus, temsirolimus or sorafenib as their 2nd therapy were identified by oncologists (85% in community practice) throughout the US as part of an online chart review study. Baseline characteristics were assessed prior to 2nd targeted therapy, including type and duration of initial TKI, response, histological subtype, performance status, and sites of metastasis. Overall survival (OS) and progression free-survival (PFS) were assessed after initiating 2nd targeted therapy. OS and PFS were compared between treatment groups using Cox proportional hazards models adjusted for baseline characteristics. **Results:** Charts were reviewed for 233, 178, and 123 mRCC patients receiving everolimus, temsirolimus, and sorafenib after an initial TKI, respectively. Median age was 64 years and 70.4% were male. Prior to initiating a 2nd targeted therapy, 86.0% used sunitinib and 85.9% had disease progression. After adjusting for baseline characteristics, everolimus was associated with significantly prolonged OS compared to temsirolimus (hazard ratio [HR] 0.56; CI 0.40-0.78; $p<0.001$) and sorafenib (HR 0.65; CI 0.42-0.99; $p=0.047$). Everolimus was associated with significantly longer PFS compared to temsirolimus (HR 0.73; CI 0.55-0.96; $p=0.025$), and non-statistically significant longer PFS compared to sorafenib (HR 0.75; CI 0.53-1.07; $p=0.110$). Results were similar in the subgroup with sunitinib as 1st targeted therapy and the subgroup with progression on 1st TKI. **Conclusions:** Among mRCC patients with prior TKI treatment, everolimus was associated with significantly prolonged OS and PFS compared to temsirolimus and significantly prolonged OS compared to sorafenib.

4613 General Poster Session (Board #6D), Sun, 8:00 AM-12:00 PM

Xp11.2 translocations in adult renal cell carcinomas with clear cell and papillary features.

Susanne M. Chan, Christopher G. Sherman, Manal Y. Gabril, Ingrid J. Zbieranowski, Linda M. Sugar, George M. Yousef, Georg A. Bjarnason; Department of Anatomical Pathology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada; Department of Pathology, London Health Sciences Centre, University of Western Ontario, London, ON, Canada; Department of Laboratory Medicine and Keenan Research Centre, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada; Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Xp11.2 translocation renal cell carcinoma (RCC) is a rare tumor with unpredictable clinical course and prognosis in adults. Recognition of these tumors depends on the identification of a RCC with unique histology, particularly clear cell and papillary (CCP) features. Our objectives were to determine the incidence of Xp11.2 translocations in adult RCCs with clear cell and papillary features, and to characterize the clinicopathological features and prognosis of adult Xp11.2 RCCs. **Methods:** Slides for 1047 RCCs in adults (1999-2009) were retrieved from multiple institutions. Cases were reviewed histologically in order to detect any degree of clear cell and papillary change. Tissue microarrays were constructed from the clear cell and papillary RCCs as well as 40 non-papillary clear cell, 5 papillary, 3 chromophobe and 2 unclassified RCCs. Immunohistochemistry using TFE3, a marker highly sensitive (97.5%) and specific (99.6%) for Xp11.2 translocations was performed. Four pathologists independently reviewed the TFE3 results. Clinical and pathologic data were also retrieved. **Results:** Out of 1047 RCCs, 140 (13%) exhibited clear cell and papillary features. Four out of these 140 (3%) were positive for TFE3. All of the non-papillary clear cell, papillary, chromophobe and unclassified RCCs were negative for TFE3. Mean follow up for TFE3+ RCCs was 55 months. **Conclusions:** Xp11.2 translocation RCCs diagnosed by TFE3 immunohistochemistry were identified in 3% of adult RCCs that had clear cell and papillary changes. These tumors appear to present with smaller tumour size, lower stage and better prognosis in comparison to non-Xp11.2 CCPRCC and clear cell RCCs. In addition to Xp11.2 translocation carcinoma, coexistence of clear cell and papillary features may be present in other subsets of tumors that have yet to be characterized.

Comparison of clinicopathological features and prognosis.

	TFE3+ CCPRCC (n=4)	TFE3- CCPRCC (n=136)	Non-papillary clear cell RCC (n=40)
Average age	54	62	60
Average tumor size	4.1	6.0	5.2
pT1	4 (100%)	80 (60%)	28 (70%)
pT2	0 (0%)	17 (13%)	2 (5%)
pT3	0 (0%)	35 (26%)	10 (25%)
pT4	0 (0%)	1 (1%)	0 (0%)
Local recurrence	0 (0%)	13 (10%)	9 (23%)
Distant metastasis	0 (0%)	31 (23%)	5 (13%)
Death due to RCC	0 (0%)	11 (8%)	4 (10%)

4614 General Poster Session (Board #6E), Sun, 8:00 AM-12:00 PM

A phase I study of pazopanib (P) combined with bevacizumab (B) in patients with metastatic renal cell carcinoma (mRCC) or other advanced refractory tumors.

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Background: Since previous experiments of B with VEGFR tyrosine kinase inhibitors showed overlapping and limiting toxicities, a dose-finding study was designed to explore the safety and feasibility of the combination of a new VEGFR inhibitor P with B, in mRCC treatment-naive patients (pts) or in pts with other advanced refractory solid tumors. **Methods:** This bicentric trial is conducted with 3+3+3 escalation doses of P + B. The MTD is the highest dosage not expected to cause a dose limiting toxicity (DLT) in more than 2/3, 3/6 or finally 3/9 pts, during the first 8 weeks of treatment. The effect of B on steady-state pharmacokinetic (PK) of P is also investigated. Major inclusion criteria are: ECOG PS ≤1, ALT and AST <=2.5 x ULN, serum creatinine <=1.5 mg/dL or creatinine clearance <=50 mL/mn and absence of uncontrolled hypertension. **Results:** 15 pts were enrolled with mRCC (n=7), melanoma (n=2), adrenocortical carcinoma (n=1), mesothelioma (n=1), pancreatic cancer (n=1), oesophageal cancer (n=1), bladder cancer (n=1) and seminoma (n=1). Median age is 61 (43-78), 12 pts are male. No DLT were reported at DL1 (P 400 mg/d + B 7.5 mg/kg q2w) (n = 9), or at the first step of DL2 (P 600 mg/d + B 7.5 mg/kg q2) (n=3), but the 3 following nephrectomized pts experienced DLT: a grade 3 transaminitis, a grade 3 pulmonary embolism and a reversible microangiopathic hemolytic anemia. Inclusion of nephrectomized pts was completed, but enrolment of 3 additional non-nephrectomized pts at DL2 was approved by IDSMB in November 2011 and these treatments are ongoing. Preliminary results of PK analysis showed a significantly higher P AUC at steady-state in pts with DLT. Moreover, lower P apparent clearance was observed in nephrectomized pts. **Conclusions:** The MTD of the combination of P and B is 400 mg/d and 7.5mg/kg respectively, in nephrectomized patients, but is not yet reached in other patients. Unexpected effect of nephrectomy status was observed on P pharmacokinetics.

4615 General Poster Session (Board #6F), Sun, 8:00 AM-12:00 PM

Outcomes of patients (pts) with metastatic renal cell carcinoma (mRCC) treated with pazopanib after progression on other targeted therapies (TT): A single-institution experience.

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Background: Pazopanib is an approved multi-tyrosine kinase inhibitor that prolongs progression-free survival (PFS) compared to placebo in treatment-naive and cytokine-refractory mRCC. Outcomes and safety data on its use after TT are limited. **Methods:** We retrospectively reviewed pts with mRCC who received salvage pazopanib between 11/09-11/11. Kaplan-Meier method was used to estimate survival outcomes. PFS was calculated from start of pazopanib until progressive disease (PD) or death. Univariable and multivariable Cox proportional hazards models were fitted to evaluate associations of PFS with covariables. **Results:** 114 consecutive pts met inclusion criteria (median age 62.6 years, 66% males, 83% clear cell). All pts had PD after other TT (median # of prior TT 2, range 1-5; median time on prior TT 23.3 mos). 79% of pts had PD on sunitinib, 39% on sorafenib, 19% on temsirolimus, 59% on everolimus, and 23% on bevacizumab. 25% received prior chemotherapy and 16% received prior cytokines in addition to TT. 87% had prior nephrectomy. 11% had favorable-risk, 68% intermediate-risk, and 21% poor-risk per MSKCC criteria. 85 events (PD or death) occurred. Median OS was 17 mos (95% CI: 10.3-NA). Median PFS was 6.4 mos (95% CI: 4.5-9.5). By multivariable analysis, PFS was associated with male gender (HR=0.433, 95%CI: 0.269-0.696; p=0.0006), # of metastatic sites (HR=1.252; 95%CI: 1.04-1.503; p=0.016), hypertension exacerbation (HR=0.378; CI: 0.175-0.813; p=0.0128) and PS 2+ vs.0-1 (HR=2.067; CI: 1.243-3.437; p=0.0052). 58% discontinued pazopanib due to PD, 12% died of PD on treatment, and 11% discontinued pazopanib due to adverse events (AEs), mostly GI complaints or fatigue. There were no treatment related deaths. Common AEs included: fatigue (44%), diarrhea (29%), nausea/vomiting (15%), anorexia (14%), hypertension exacerbation (11%), hypothyroidism (11%), hand-foot skin reaction (9%), and increase LFTs (4%). 86% of AEs were grade 1/2. **Conclusions:** In this retrospective study, pazopanib demonstrated efficacy in mRCC following PD with other TT. AEs were mild/moderate and manageable.

4617 General Poster Session (Board #6H), Sun, 8:00 AM-12:00 PM

Circulating mir-21 and mir-378 are predictive of progression-free survival (PFS) in patients treated with everolimus in metastatic renal cell cancer (mRCC).

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Background: The oral mTOR inhibitor, everolimus, affects tumor growth by targeting cellular metabolic proliferation pathways and modestly delays RCC progression. We hypothesized that circulating microRNAs, which have been associated with renal cancer and inflammation, may serve as predictive biomarkers to help better define a population more sensitive to treatment. **Methods:** Plasma from mRCC pts refractory to VEGF inhibition were obtained prior to treatment with standard dose everolimus as part of a clinical trial examining FDG-PET as a potential predictive biomarker. As we were specifically interested in tumor response to drug, only pts who died, remained on trial, or had radiographic progression by RECIST criteria were profiled. Pts who were unable to tolerate drug were excluded. MicroRNAs were extracted and profiled without pre-amplification using Exiqon LNA PCR panels. Crossing point (Cp) values within 5 of the negative control were removed. MicroRNAs must have been present in >90% of samples and varied at least $p > 0.10$ from mean to be further analyzed. Cox-proportional hazards model and Kaplan-Meier analyses were performed. **Results:** 28 patients had available plasma and met criteria for profiling. Pt characteristics included: 20 (71%) clear cell histology, median age 57.7 (43 – 76), median number of prior systemic therapies 2 (1 – 3). 103 microRNAs were expressed in at least 90% of all samples. Mir-21 and mir-378 were independently correlated with PFS (FDR: 0.02 and 0.06, respectively). Low circulating plasma mir-21 and mir-378 levels resulted in a median PFS prolongation of 370d vs. 101d ($p=0.027$) and 368d vs. 106d ($p=0.001$). Analysis of the clear cell cohort for mir-21 and mir-378 also demonstrated a significant median PFS difference of 350d vs. 173d ($p=0.045$) and 345d vs. 147d ($p=0.004$). **Conclusions:** Elevated levels of circulating mir-21 and mir-378 have been associated with systemic inflammatory states, and in our study are correlated with decreased PFS in mRCC pts undergoing everolimus therapy. Further prospective studies will be required to validate these exploratory results for their potential role as prognostic or predictive biomarkers.

4618 General Poster Session (Board #7A), Sun, 8:00 AM-12:00 PM

Evaluation with DCE-US of antiangiogenic treatments in 539 patients allowing the selection of one surrogate marker correlated to overall survival.

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Background: A prospective study of dynamic contrast-enhanced ultrasound (DCE-US) with quantification for the evaluation of antiangiogenic treatments was launched (19 centers), supported by the French National Cancer Institute. The objectives were the diffusion of the standardized method, a cost evaluation and the identification of perfusion parameters predicting tumor response. **Methods:** All patients had DCE-US at baseline, D7, D14, D30, D60 and every two months. Each examination included a bolus injection of sonovue (Bracco) and 3 minutes of raw linear data with an Aplio (Toshiba). Raw data were analyzed with a mathematical model (patent PCT/IB2006/003742) to evaluate 7 parameters characterizing the tumor perfusion curve. Response to treatment was evaluated every 2 months with RECIST criteria. In order to have sufficient follow-up data, the statistical analysis has to be performed more than 6 months after the inclusion of the last analyzed patient. Inclusions were closed in March 2010. **Results:** A total of 539 patients have been included (mainly RCC (157) and HCC (107)); more than 2 000 DCE-US and 1700 CT-scan were performed. A follow-up more than 12 months showed that 3 parameters have a strong significant difference ($p<0.0003$) according to the response at 6 months. The decrease of more than 40% of AUC at one month is correlated to the TTP ($p< 001$) and OS ($p< 0.04$). **Conclusions:** Final results confirm the usefulness of this tool to monitor anti-angiogenic treatments. The criteria: the decrease of more than 40% of AUC at one month is predictive of response.

4619 General Poster Session (Board #7B), Sun, 8:00 AM-12:00 PM

Use of bisphosphonates (Bis) combined with sunitinib (Su) to improve the response rate (RR), progression-free survival (PFS), and overall survival (OS) of patients (pts) with bone metastases (mets) from renal cell carcinoma (RCC).

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Background: Bis are used to prevent skeletal events of bone mets, and may exhibit anti tumor effects. We aimed to evaluate whether Bis can bring a RR, PFS, and OS benefit to pts with bone mets from RCC that are treated with Su. **Methods:** We performed an international multicenter retrospective study of pts with bone mets from RCC who were treated with Su. Pts were divided into Bis users (group 1) and nonusers (group 2). The effect of Bis on RR, PFS and OS, was tested with adjustment for known prognostic factors using a chisquare test from contingency table and partial likelihood test from Cox regression model. **Results:** Between 2004-2011, 244 pts with metastatic RCC were treated with Su. 92 pts had bone mets, 41 group 1 and 51 group 2. The groups were balanced regarding the following known prognostic factors: past nephrectomy, clear cell vs non clear cell histology, initial diagnosis to sunitinib treatment (tx) time, presence of $\geq$ 2 mets sites, presence of lung/liver mets, ECOG performance status, anemia, calcium level $>$ 10 mg/dL, elevated alkaline phosphatase (AP), pre-tx neutrophil to lymphocyte ratio (NLR) $>$3, sunitinib induced HTN, and the use of angiotensin system inhibitors. They were also balanced with regard to past cytokines/targeted tx, and mean sunitinib dose/cycle. Objective response was partial response/stable disease 85% (n=35) vs 71% (n=36), and progressive disease 15% (n=6) vs 29% (n=15) (OR 3.287, p=0.07) in group 1 vs 2 respectively. Median PFS was 15 vs 5 months (HR 0.433, p=0.035), and median OS not reached with a median folloup time of 43 mos vs 12 months (HR 0.398, p=0.003), in favor of group 1. In multivariate analysis of the entire pt cohort (n=92), factors associated with PFS were Bis use (HR 0.433, p=0.035), pre-tx NLR $\leq$3 (HR 0.405, p=0.016), and elevated AP (HR=3.63, p=0.012). Factors associated with OS were Bis use (HR 0.32, p=0.003), elevated AP (HR 3.18, p=0.002), and Su induced HTN (HR 0.193, p$<$ 0.001). **Conclusions:** Bis may improve the outcome of Su tx in RCC with bone mets. This should be investigated prospectively, and if validated applied in clinical practice and clinical trials.

4620 General Poster Session (Board #7C), Sun, 8:00 AM-12:00 PM

Prospective exploratory analysis of the association between genetic polymorphisms and sunitinib toxicity and efficacy in metastatic renal-cell carcinoma.

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Background: Sunitinib (SU) is a multi-targeted receptor tyrosine kinase inhibitor treatment that is approved for metastatic renal cell carcinoma (mRCC). However, several patients either do not respond to treatment or they experience significant toxicity.Our study aims to find genetic markers of toxicity and efficacy using a commercially available DNA microarray genotyping system. **Methods:** 30 patients with newly diagnosed mRCC, from January 2010 to May 2011, were evaluated prospectively at Hospital 12 de Octubre (Madrid, Spain). Pts received SU 50 mg/day, 4 wks on / 2 wks off treatment schedule. A total of 92 of single nucleotide polymorphisms (SNPs) in 34 genes in the pharmacokinetic and pharmacodynamic pathways of drugs were analyzed using Drug inCode pharmacogenetic service. SNPs in candidate genes, together with clinical characteristics were tested univariately for association with the number of days of SU treatment until the first reduction of dose, PFS and OS. **Results:** Complete analysis was possible in 25 pts. Pts with *CYP1A2*1/*1*.a low metabolizing genotype, had an increased risk of dose reductions due to toxicity compare to allele *1F (Median time to dose reduction : 2.33 months vs NR; $p<0.006$). Pts with *CYP2C19*1/*1* , wild type genotype, had an increased risk of dose reductions due to toxicity vs. other genotypes (Median time to dose reduction: 2.8 vs 9.73 months; $p<0.021$). Catechol-O-methyltransferase (*COMT*) V158M polymorphisms, was associated with PFS and OS (Met/Met carriers median PFS and OS NR; Met/Val pts PFS= 15 months; OS=17.2 months and Val/Val pts PFS=3.3 months; OS= 4.4 months ; $p=0.005$ for PFS and $p=0.003$ for OS). **Conclusions:** This preliminary analysis suggests that *CYP1A2* and *CYP2C19* SNPs may be associated with toxicity in patients with RCC treated with SU. As CYP1A2 and CYP2C19 activity could be affected by a variety of non-genetic factors, if these is confirmed, it could lead to the necessity of controlling toxic and dietary habits of pts treated with SU. SNPs associated with toxicity and survival in this preliminary analysis are being validated in an independent cohort of RCC treated with SU (García-Donas J, et al. Lancet Oncol 2011).

4621 General Poster Session (Board #7D), Sun, 8:00 AM-12:00 PM

Prognostic role of body composition parameters in renal cell carcinoma (RCC).

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Background: Previous studies have shown that body component i.e. muscle tissue (MT) and adipose tissue (AT) are linked to overall survival (OS) and progression free survival (PFS). The aim of our study is to analyze whether MT and AT have a prognostic role in metastatic RCC treated with targeted therapy. **Methods:** We investigated body mass index (BMI), MT and AT in RCC pts. Analysis of CT image was used to evaluate cross-sectional areas (cm^2) of total AT (TAT), MT, and the grey level image (GLI) of MT, reflecting physical properties of the scanned tissue and used as a proxy to describe the quality of muscle. The 3rd lumbar vertebra (L3) was chosen as a landmark since L3 and whole-body measurements are linearly related. Images were analyzed using Slice-O-Matic software V4.3 (Tomovision). Indexed on height MT (cm^2/m^2), indexed on height TAT (cm^2/m^2) and mean GLI of MT were computed and described stratified on sex. For each measurement, population was divided in two groups: patients with values < or >= median observed in patient of the same gender and OS and PFS were estimated using Kaplan-Meier method and compared with the log-rank test. Multivariable Cox proportional hazards model were adjusted for modified MSKCC risk group and treatment (active versus placebo). **Results:** There were 113 men aged of 60 (interquartile range=52-56) years with BMI of 26 (24-29) kg^2/m^2 and 36 women aged of 58 (54-65) years with BMI of 23 (20-26) kg^2/m^2. After adjustment for MSKCC (OS and PFS) and active treatment (PFS), GLI of MT over the median was associated with longer OS (HR=1.85, 95%CI=[1.22;2.82], p=.004) and PFS (HR=1.81, 95%CI=[1.22;2.65], p=.002) **Conclusions:** Quality of muscular tissue is independently associated with better outcome in RCC. Surprisingly, adipose tissue as well as BMI is not associated with survival in this study.

	OS in months				PFS in months			
Label	Median	P25	P75	p	Median	P25	P75	p
Indexed MT>= 14 cm^2/m^2 (men) or 13 cm^2/m^2 (women)	24	14	49	.1213	6	4	13	.3128
Indexed MT< 14 cm^2/m^2 (men) or 13 cm^2/m^2 (women)	19	10	39		5	3	9	
Mean GLI >= 38 (men) or 36 (women)	29	18	62	.0011	8	4	15	.0007
Mean GLI < 38 (men) or 36 (women)	14	7	30		4	3	8	
Indexed TAT >=326 cm^2/m^2 (men) or 231 cm^2/m^2 (women)	24	14	45	.1725	6	4	11	.6124
Indexed TAT<326 cm^2/m^2 (men) or 231 cm^2/m^2 (women)	20	8	42		5	3	10	

4622 General Poster Session (Board #7E), Sun, 8:00 AM-12:00 PM

Adherence to oral anticancer drugs (OAD) in patients (pts) with metastatic renal cancer (mRCC): First results of the prospective observational multicenter IPSOC study (Investigating Patient Satisfaction with Oral Anti-cancer Treatment).

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Background: Patient adherence to oral therapy is a critical issue in cancer treatment. The aim of this study is to investigate the prevalence and severity of non-adherence to OAD in mRCC and to identify factors predictive of non-adherence. **Methods:** Prospective observational multicenter trial performed at 11 Belgian academic and non-academic centers. All pts with mRCC starting OADs (sunitinib, pazopanib, everolimus or sorafenib) are eligible for the study. Pts are contacted by phone at baseline and at 1, 3, 6 and 12 months. At each contact, pts are asked to complete questionnaires investigating 1) medication adherence (MMAS), 2) patient satisfaction with treatment (CTSQ) and with treatment education (PS-CaTE), 3) the extent of information desire (EID), 4) quality of life (FACT-G and FKSI) and 5) the role of the pharmacist (SWiP). Adherence is measured using an electronic medication event monitoring system (MEMS, Aardex). **Results:** Between 02/2011 and 11/2011, 49 pts (m: 33, f: 16) with a median age of 63 years (range 25 - 87) have participated in the IPSOC study. Twenty-nine pts (64%) were treated with an OAD in first-line, 15 pts (33%) in second-line. With a median follow-up of 131 days (range 2 - 313) 45 pts (92%) claimed to be fully adherent to their treatment (based on MMAS and CTSQ data). Four patients indicated to have missed at least one dose, of whom two indicated they occasionally forgot their medication and two others interrupted treatment because of side effects. Based on MEMS data, mean adherence, defined as the percentage of days with at least the prescribed number of dosage taken, was 98.91%. **Conclusions:** The IPSOC study, the first to examine adherence to OAD among mRCC pts, shows that mRCC pts are almost fully adherent to treatment recommendations. This seems to be in contrast to adherence data for other, long-lasting, anti-cancer treatments. Further investigations will focus on the question whether extensive counseling and participation in side-effect programs contribute to the high percentage of adherence in this study.

4623 General Poster Session (Board #7F), Sun, 8:00 AM-12:00 PM

Trends in the use of cytoreductive nephrectomy for metastatic renal cell carcinoma in the VEGFR tyrosine kinase inhibitor era.

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Background: Two large randomized trials (SWOG, EORTC) published in 2001 established the role of cytoreductive nephrectomy (CyNx) for the treatment of metastatic renal cell carcinoma (mRCC) in the cytokine era. A paradigm shift occurred in 2005 with the approval of VEGFR tyrosine kinase inhibitors (TKIs). We hypothesized that uncertainty regarding the role of CyNx in the VEGFR TKI era has resulted in a change in practice patterns. **Methods:** Using the Surveillance, Epidemiology and End Results (SEER) registry, we identified 2780 patients with histologically-confirmed mRCC between 2000 and 2008 who underwent CyNx or no surgery. Patients were separated into pre- or VEGFR TKI-eras (2000-2005 vs. 2006-2008). Differences in baseline characteristics between these patient groups were assessed and controlled for in a logistic regression analysis to determine the likelihood of undergoing CyNx. **Results:** Overall, 1202 of 2780 patients (43%) underwent CyNx. CyNx increased from 41% in 2000 to 49% in 2005, and decreased to 35% in 2008, with a 20% decreased likelihood of undergoing CyNx in the VEGFR TKI era compared to the pre-VEGFR TKI era. Logistic regression analysis showed that tumor size, age, race, marital status and pre- versus post-2005 periods were independent predictors of CyNx (Table). Patients who were non-Caucasian, single, with primary tumor <3cm, or older were less likely to undergo CyNx. **Conclusions:** Use of CyNx increased after supporting level I evidence was published in 2001, and decreased after regulatory approval of VEGFR TKIs in 2005. Racial and demographic differences exist in the utilization of CyNx. The results of pending randomized trials evaluating the role of CyNx in the TKI-era are awaited to optimize use of this modality and address potential disparities.

Logistic regression model for use of CyNx in 2000-2008.

Variable (reference)	Odds ratio	Std error	p value
Post-2005 (Pre-2005)	0.802	0.092	0.0161
Primary tumor size >3cm (<3cm)	1.005	0.001	<0.0001
Age (+1 year)	0.961	0.004	<0.0001
Female (male)	1.016	0.095	0.8686
Black (white)	0.609	0.167	0.0030
Hispanic (white)	0.736	0.138	0.0211
Other race (white)	0.676	0.173	0.0234
Married (not married)	1.587	0.092	<0.0001

4624 General Poster Session (Board #7G), Sun, 8:00 AM-12:00 PM

Molecular characterization of SETD2, a histone methyltransferase, in clear cell renal cell carcinoma (ccRCC).

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Background: Although the von Hippel-Lindau (VHL) tumor suppressor is mutated in 60% of ccRCC, deletion of VHL in mice is insufficient for tumorigenesis. Sequencing of ccRCC tumors identified mutations in SETD2, a histone H3 lysine 36 (H3K36) trimethyltransferase. We hypothesize that loss of SETD2 methyltransferase activity decreases H3K36 trimethylation (H3K36Me3) in ccRCC, and contributes to the cancer phenotype. **Methods:** H3K36Me3 immunohistochemical (IHC) staining was quantitated in wild-type and mutant SETD2 nephrectomy tissue. To establish frequency of SETD2 loss of heterozygosity (LOH), genomic DNA was isolated from 51 VHL deficient ccRCC specimens and analyzed with Affymetrix single-nucleotide polymorphism (SNP) arrays. To evaluate alterations of histone modifications in advanced ccRCC, H3K36Me3 IHC was quantitated on tissue microarrays (TMAs) representing 28 paired ccRCC specimens with unaffected kidney parenchyma and 40 metastases. To identify kidney-specific H3K36Me3 binding sites, chromatin immunoprecipitation (ChIP) sequencing was performed on nephrectomy specimens. **Results:** Nephrectomy specimens with SETD2 truncating mutations have decreased H3K36Me3 ($>$50%) compared to uninvolved kidney tissue. Using SNP arrays, LOH at chromosome 3p (location of VHL and SETD2 genes) was detected in $>$90% of the tested tumors. IHC reveals a 27.4% and 52.0% decrease in H3K36Me3 positive nuclei in primary ccRCC and metastases, respectively, when compared to matched adjacent unaffected kidney tissue ($p < 0.0001$). Using ChIP sequencing, 421 and 1,718 genomic regions were upregulated in the tumor and unaffected kidney tissue. **Conclusions:** SETD2 truncating mutations in patient-derived tissue have decreased H3K36Me3 indicating that SETD2 is a non-redundant H3K36 methyltransferase. LOH of VHL and SETD2 occurs in $>$90% of tested ccRCC tumors. Genomic regions enriched for H3K36Me3 binding are being validated in additional patient-derived tissues. H3K36Me3 is decreased in primary ccRCC and even more in metastases, suggesting that SETD2 methyltransferase activity is progressively misregulated in RCC. Loss of SETD2 activity may cooperate with VHL silencing to promote tumorigenesis.

4625 General Poster Session (Board #7H), Sun, 8:00 AM-12:00 PM

Updated results on long-term overall survival (OS) of the French randomized phase II trial TORAVA in metastatic renal cell carcinoma (mRCC) patients.

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Background: Temsirolimus combined with bevacizumab (T+B) failed to improve the progression rate in treatment naive mRCC pts when treated in parallel to sunitinib (S) or B + Interferon (B+I) combination (Lancet Oncol 2011; 12:673-80). Long term updated survival and data on 2d line treatments were analyzed. **Methods:** 171 pts were treated with T+B (n=88), S (n=42) and B+I (41) respectively. Updated survival data (December 2011) and 2d line therapy after failure of the randomly assigned treatment were updated. OS was defined from the date of randomization until the date of death due to any cause, or the date of last contact. A two-tailed log-rank test was used to compare the OS distribution between the 3 arms with a 5% alpha level. **Results:** The median follow-up is 35.1 months (range 24.2 to 44.7). In an intent-to-treat analysis, 35-month OS rates were 37% (95% CI 27 to 48), 55% (95% CI 40 to 69) and 62% (95% CI 47 to 76) in arms T+B, S and B+I respectively (3-arm global comparison: p-value=0.0279). OS was not significantly lower in T+B arm than S arm (HR = 0.67, 95% CI 0.40 to 1.12), but significantly lower in T+B arm than B+I arm (HR = 0.48, 95% CI 0.27 to 0.86). Tyrosine kinase inhibitors were administered in 55 (79.7%), 19 (79.2%) and 23 (63.9%) pts in arms T+B, S and B+I respectively, without significant difference between arms (Fisher's exact test: p=0.20). To note, 21% pts in S arm and 15% pts in B+I arm received an mTOR inhibitor in 2d line therapy. **Conclusions:** A large majority of pts in all treatment groups received a 2d line therapy after initial treatment failure. The OS rates confirm the absence of synergy or addictive effect of the B+T combination as well as the prolonged survival of pts treated with B+I.

4626 General Poster Session (Board #8A), Sun, 8:00 AM-12:00 PM

Impact of maximum standardized uptake value (SUVmax) evaluated by 18-fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography (FDG PET/CT) on survival for patients with advanced renal cell carcinoma.

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Background: In this era of molecular targeting therapy when various systematic treatments can be selected, prognostic biomarkers are required for the purpose of risk-directed therapy selection. Numerous reports of various malignancies have revealed that 18-Fluoro-2-deoxy-D-glucose (^{18}F-FDG) accumulation, as evaluated by positron emission tomography, can be used to predict the prognosis of patients. The purpose of this study was to evaluate the impact of the maximum standardized uptake value (SUVmax) from 18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG PET/CT) on survival for patients with advanced renal cell carcinoma (RCC). **Methods:** A total of 67 patients with advanced or metastatic RCC were enrolled in this study. The FDG uptake of all RCC lesions diagnosed by conventional CT was evaluated by FDG PET/CT. The impact of SUVmax on patient survival was analyzed prospectively. **Results:** The mean duration of observation was 461 days (range, 7-1229 days). The SUVmax before treatment of 67 patients ranged between undetectable level and 16.6 (mean 7.6±3.6). The patients with RCC tumors showing high SUVmax before treatment demonstrated poor prognosis ($p<0.001$ hazard ratio 1.289, 95% CI 1.161-1.430). The median survival time of 36 patients with RCC showing SUVmax less or 7.0 was 1229±991 days, that of 21 patients with RCC showing SUVmax between 7.0 and 12.0 was 446±202 days, and that of 10 patients RCC showing SUVmax higher than 12.0 was 95±43 days (≤7.0 vs. 7.0< ≤12.0 $p=0.0052$, 7.0< ≤12.0 vs. 12.0<:$p=0.0169$, log-rank test). SUVmax demonstrated a tendency to predict the survival compared with the Memorial Sloan-Kettering Cancer Center classification ($p=0.015$ vs 0.315, multivariate Cox analyses). **Conclusions:** The survival of patients with advanced RCC can be predicted by evaluating their SUVmax using FDG PET/CT. FDG PET/CT has potency as an "imaging biomarker" to provide helpful information for the clinical decision-making.

4627 General Poster Session (Board #8B), Sun, 8:00 AM-12:00 PM

Natural history of malignant bone disease in renal cancer: Final results of an Italian bone metastases survey.

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Background: bone metastases (mts) are an emerging clinical problem in renal cancer patients related to survival increase. We report the final data of largest survey never published in literature. **Methods:** 398 renal cancer patients (pts) with evidence of bone mts, all died at the moment of study inclusion, have been included. Clinico-pathological data, data on survival and Skeletal Related Events (SRE) data and skeletal related therapies have been collected and statistically analyzed. **Results:** 286 males/112 females; median age: 63 (16-87); pts with bone mts at the moment of renal cancer diagnosis: 31.4%; pts with single bone mts: 31.1%. Type: lytic 77%, mixed: 14.6%, blastic: 7.6 %. Sites: spine (65.8%), pelvis (38.4%), long bones (31.6%), other (18.8%). Median time to bone mts: 8 months (0-288) (all patients); 24 months (1-288) (pts without bone mts at diagnosis). Pts with at least 1 SRE: 71.1%. Types of SREs: pathologic fracture (12.6%), radiotherapy (61.8%), spinal compression (7.6%), bone surgery (14.8%), hypercalcaemia (3.2%). Median number of SRE for patient: 1 (0-4). Median time to first SRE: 2 (0-72), to second SRE: 4 (0-113), to third SRE: 11 (1-108). Median survival after bone mts diagnosis: 12 (1-178). Median survival after first SRE: 10 (0-144). Median survival in pts with at least one SRE: 14 (1-178); median survival in pts without SREs: 9 (0-62). In according with MKSCC criteria median time to skeletal disease was in patients with good prognosis was 24 (0-288), intermediate was 5 (0-180) and poor prognosis was 0 (0-77). A total of 168 pts received zoledronic acid until performance status worsening or death. 162 pts have been analysed as control group. The median time to first SRE in the zoledronic treated pts was 3 mths (0-101) compared with 1 mth (0 - 25) in the control group ($p < 0.05$). 5 cases of ONJ have been diagnosed. **Conclusions:** The present survey is the largest descriptive study concerning the natural history of bone disease in renal cancer patients. The effects of biological therpies on bone met will be presented during the meeting.

4628 General Poster Session (Board #8C), Sun, 8:00 AM-12:00 PM

Sorafenib treatment of Asian patients with advanced renal cell carcinoma (RCC) in daily practice: Subset analysis of the large non-interventional PREDICT study.

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Background: Previous studies with sorafenib in Asian patients with advanced RCC were relatively small and used strict entry criteria. Here we investigated safety and efficacy in a large subset of Asian patients in the prospective, non-interventional PREDICT study of sorafenib in routine practice (NCT 00895674). **Methods:** Patients were eligible based on a diagnosis of advanced RCC and the decision by the investigator to prescribe sorafenib under compliance of the local product label. Tumor status, patients' performance and physician assessment of efficacy and tolerability were collected up to 12 months. **Results:** Between Jan 2007 and June 2010, 1092 patients were enrolled in China (n=1033), South Korea (n=55), the Philippines (n=3) and Indonesia (n=1). In the efficacy population (n=909), baseline characteristics were: 71% male; 89% <70 years old; 89% clear cell histology; 78% prior nephrectomy; 56% prior systemic therapy; 16% high MSKCC risk; 35% ECOG PS ≥2; 5% brain metastases. Overall, 19% of patients had ≥1 concomitant disease at baseline; the most frequent concomitant diseases were hypertension (14%) and diabetes (6%). Initial sorafenib dose was 800 mg daily in 97% of patients, of whom 91% were also receiving 800 mg daily as last dose. Median duration of sorafenib treatment was 9.7 months (range 0.2–24.1), and in clinically relevant subgroups was as follows: treatment-naïve, 9.7 months; high MSKCC risk, 9.3 months; brain metastases, 8.4 months; age ≥70 years, 7.6 months; ECOG PS 2, 9.7 months; ECOG PS 3, 6.1 months. At last follow up, 63% of physicians reported good/very good efficacy and 59% good/very good tolerability. Sorafenib was well tolerated; <2% of the safety population (n=1022) reported serious drug-related adverse events (SDRAEs) and only 3% discontinued due to DRAEs. In all, 35% of patients reported a DRAE, with the most frequent being hand-foot skin reaction (21%), diarrhea (7%), rash (7%), alopecia (5%), hypertension (3%). **Conclusions:** In this large subset of Asian patients with advanced RCC treated in daily practice settings, sorafenib was well tolerated and provided benefit, including in clinically relevant patient subgroups.

4629 General Poster Session (Board #8D), Sun, 8:00 AM-12:00 PM

Overall survival (OS) in metastatic renal cell carcinoma (mRCC) sequentially treated with different targeted therapies (TTs): Results from a large cohort of patients.

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Background: Targeted Therapies (TTs) have definitely improved survival in patients with mRCC. However the optimal therapeutic strategy is not shared. This study was performed to assess the overall survival (OS) in a consecutive series of mRCC patients receiving TTs. **Methods:** Characteristics and outcomes of 336 patients affected by mRCC receiving TTs were collected from the database of Istituto Nazionale Tumori of Milan. The main characteristics of patients were: ECOG PS 0/1/2 186 (55%)/131 (39%)/19 (6 %); clear-cell histology 291 (87%); previous nephrectomy 293 (87%). According to Motzer criteria 32% of patients showed low risk, 48% intermediate risk and 20% poor. Overall, 167 (50%) patients received one TTs, while 116 (34%), 42 (13%) and 11 (3.3%) received 2, 3 and 4 TTs, respectively. 245 (73%) patients received sorafenib (So), 212 (63%) sunitinib (Su), 33 (10%) a bevacizumab regimen and 73 (22%) other TTs, including everolimus, temsirolimus and axitinib. The Kaplan Meier curves were used to describe the survival.The uni- and multi-variate analyses for OS were carried out by means of Cox proportional hazard regression analysis. **Results:** Ata median follow-up of 43 months, 199 patients (57 %) had died. The median OS was 24 months (95%CI: 20.0-27.0) and the 5-year OS was 24.6 % (95 %CI: 18.7-30.8). In univariate analyses, there were no significant differences in the hazard ratios (HR) for So followed by Su compared to Su followed by So ($HR_{SU\text{-}SO\ /\ SO\text{-}SU} = 1.16$; 95%CI: 0.57-2.33) or compared with other therapies ($HR_{Other\ sequential\ th.\ /\ SO\text{-}SU} = 1.21$; 95%CI: 0.78-1.88; $p=0.674$).In the multivariate analysis, in terms of OS any statistical difference was reported as regards the sequence used (Su/So *vs* So/Su; $p>0.05$) or bevacizumab regimen as compared to Su and/or So used sequentially ($p>0.05$). In the uni and multivariate analysis ECOG PS, nephrectomy, Fuhrman grade and number of sites of disease are independent predictive factors of outcome ($p< 0.01$). **Conclusions:** These data suggest that TTs improve OS in mRCC without any statistical difference when using different sequences of TTs. No cross-resistance between several sequences of TTs was documented.

4630 General Poster Session (Board #8E), Sun, 8:00 AM-12:00 PM

Hypoxia-inducible factor (HIF) 1α and 2α as predictive markers of outcome to VEGFR tyrosine kinase inhibitors (TKI) in renal cell carcinoma (RCC).

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Background: Relevant biomarkers in RCC are needed to identify appropriate candidates for selected targeted therapies. Mutations in the von Hippel-Lindau (*VHL*) gene result in the accumulation of HIF and increased expression of proangiogenic factors, including VEGF. **Methods:** Metastatic clear RCC patients with available baseline tumor samples who received first-line oral VEGFR-TKI were included in this analysis. *VHL* mutation/hypermethylation status and HIF1α and HIF2α immunohistochemical staining were analyzed from paraffin-embedded tumors. Additionally, a panel of candidate VEGF and VEGFR2 genetic SNPs was determined from peripheral blood samples. HIF was scored as negative or positive based on staining intensity (0-10% and $>$ 10%, respectively). Results were evaluated for associations with clinical outcome. **Results:** 80 patients were included: 71 evaluable for HIF expression, 63 for VHL status and 52 for SNPs. 73% received treatment with sunitinib and median follow-up was 21.5 months. Unlike *VHL* status, HIF1 and HIF2 positive expression showed a significant correlation with PFS and OS. HIF1α was also predictive for response rate (RR). On multivariate analysis adjusting for other prognostic factors, HIF1α and HIF2α remained the most significant independent predictive factors for survival (adjusted HR 0.09, 95% CI 0.03-0.28, $p < 0.0001$ and HR 0.13, 95% CI 0.04-0.37, $p < 0.0001$; respectively). We did not find any statistically significant differences based on the VEGF and VEGFR2 SNPs analyzed. **Conclusions:** HIF1α and HIF2α levels represent the most important independent predictive factors of outcome for VEGFR-TKI therapy in metastatic RCC. These findings may contribute to optimize treatment with targeted agents.

	HIF1α		HIF2α	
	HIF1α +	HIF1α -	HIF2α +	HIF2α -
N (%)	38 (53.5)	33 (46.5)	46 (64.8)	25 (35.2)
RR (%)	67	27	55	37
OR (p value)	0.18 (p=0.001)		0.50 (p=0.20)	
Median PFS (months)	22.8	13.6	21.4	9.6
HR (p value)	0.36 (p<0.0001)		0.61 (p=0.04)	
Median survival (months)	43.7	16.6	42.5	20.3
HR (p value)	0.31 (p<0.0001)		0.52 (p=0.04)	

4631 General Poster Session (Board #8F), Sun, 8:00 AM-12:00 PM

Use of early tumor shrinkage as a response to VEGF inhibitors as a predictor of progression-free survival (PFS) and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC).

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Background: Several novel targeted agents significantly prolong overall survival (OS) in metastatic renal cell cancer (mRCC) patients (pts.). Translational research, however, has not identified any prospectively validated prognostic or predictive biomarkers. Recently, progression free survival (PFS), overall response rate (ORR) and early tumor shrinkage were proposed as putative predictors for clinical outcome. In this study we aim to explore the potential role of treatment induced tumor remission as a prognostic or predictive parameter in mRCC. **Methods:** In our analyses we investigated the putative prognostic role of best response according to RECIST 1.1 criteria (complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD)) in first line Tyrosine-kinase inhibitor (TKI) treatment in n=83 pts. Responders were defined by achieving CR, PR or SD at any time during the course of treatment. Furthermore, we tested whether tumor shrinkage of 10% or more within 12 weeks of treatment qualifies as a potential cut-off-parameter to predict PFS or OS. Uni- and multivariate analyses were performed using Log-rang test, Kaplan-Meier-, and Cox-regression analysis. **Results:** Univariate analyses revealed that first-line treatment non-responders had a significantly shorter OS than responders ($p < 0.0001$). Tumor shrinkage of $<10\%$ or $\geq 10\%$ also correlated with an OS of 14.5 vs. 29.1 mo. ($p = 0.001$) and a PFS of 3.0 vs. 11.5 mo. ($p < 0.001$). In multivariate analyses tumor shrinkage of $\geq 10\%$ was tested with other common variables such as ECOG, MSKCC-score, histology, and metastatic sites and proved to be a significant independent prognostic (HR 0.361; 95% CI 0.156-0.833) and predictive (HR 0.306; 95% CI 0.152-0.612) parameter. **Conclusions:** Our results outline that sensitivity to first line treatment of mRCC is an important prognostic factor in mRCC. Hereby tumor shrinkage of $\geq 10\%$ within 12 weeks of treatment reveals a novel cut-off-parameter, which showed to be a promising prognostic and predictive marker in mRCC. Further investigations are needed to validate this parameter.

4632 General Poster Session (Board #8G), Sun, 8:00 AM-12:00 PM

Updated safety results from EXIST-2: Everolimus therapy for angiomyolipoma (AML) associated with tuberous sclerosis complex (TSC) or sporadic lymphangioleiomyomatosis (sLAM).

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Background: EXIST-2 (NCT00790400) is a randomized, double-blind, placebo-controlled, phase 3 trial assessing the efficacy and safety of everolimus, an oral mTOR inhibitor, for treating AML in patients with TSC or sLAM. We have previously reported that everolimus resulted in a significantly higher AML response rate vs placebo (41.8% vs 0%; 95% CI: 23.5–58.4; $p<0.0001$) with a consistent safety profile (Bissler et al. *J Am Soc Nephrol*. 22, 2011, Abstract LB-PO3159). Here we present a 90-day safety update. **Methods:** 118 eligible patients were randomized 2:1 to receive everolimus 10 mg daily (n=79) or placebo (n=39). The primary efficacy endpoint was AML response rate (proportion of patients with best overall AML response status of "response"). Original cut-off date for data analysis was 30 Jun 2011. An updated analysis of the safety data for the safety set (all patients receiving ≥1 dose of double-blind study drug with a valid post-baseline assessment) to 14 Oct 2011 are presented here. **Results:** As of 14 Oct 2011, median treatment duration was 48.1 and 45.0 weeks for everolimus and placebo arms, respectively. Discontinuations in the double-blind period were the same in the everolimus arm as the initial analysis, but had increased by 4 patients in the placebo arm since initial analysis (3 due to disease progression, 1 withdrew consent). The majority of adverse events (AEs) continued to be grade 1 or 2; the incidence of serious AEs was slightly higher than initially reported, particularly in the placebo arm (everolimus 20.3%, placebo 23.1%). AE incidence leading to discontinuation was the same as initially reported (everolimus 3.8%, placebo 10.3%). In the updated data, 3 additional everolimus patients required dose interruption or reduction due to AEs; dose reduction/interruption remained more common in the everolimus arm (51.9% vs. 20.5%). **Conclusions:** Overall, the 90-day updated safety data analysis from the EXIST-2 trial has not revealed any additional safety concerns. No other patients receiving everolimus withdrew for any reason, whereas 3 more patients receiving placebo withdrew due to disease progression.

4633 General Poster Session (Board #8H), Sun, 8:00 AM-12:00 PM

Use of miRNA profiling in metastatic renal cell carcinoma to reveal a tumor suppressor effect for mir-215.

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Background: Renal cell carcinoma (RCC) is the most common neoplasm of the adult kidney. Metastatic RCC is difficult to treat. The five-year survival rate for metastatic RCC is <10%. Recently, microRNAs (miRNAs) have been shown to have a role in cancer metastasis and potential as prognostic biomarkers in cancer. **Methods:** We performed a miRNA microarray to identify a miRNA signature characteristic of metastatic compared to primary RCC. Results were validated by quantitative real time PCR. Target prediction analysis and gene expression profiling identified many of the dysregulated miRNAs could target genes involved in tumor metastasis. The effect of miR-215 on cellular migration and invasion was shown in a RCC cell line model. **Results:** We identified 65 miRNAs that were significantly altered in metastatic when compared to primary RCC. Nine (14%) miRNAs had increased expression while 56 (86%) miRNAs showed decreased expression. miR-10b, miR-196a, and miR-27b were the most downregulated while miR-638, miR-1915, and miR-149* were the most upregulated. A non-supervised 2D-cluster analysis showed that a sub-group of the primary tumors clustered under the metastatic arm with a group of miRNAs that follow the same pattern of expression suggesting they have an inherited aggressive signature. We validated our results by examining the expressions of miR-10b, miR-126, miR-196a, miR-204, and miR-215, in two independent cohorts of patients. We also showed that overexpression of miR-215 decreased cellular migration and invasion in a RCC cell line model. In addition, through gene expression profiling, we identified direct and indirect targets of miR-215 that can contribute to tumor metastasis. **Conclusions:** Our analysis showed that miRNAs are altered in metastatic RCC and can contribute to kidney cancer metastasis through different biological processes. Dysregulated miRNAs represent potential prognostic biomarkers and may have therapeutic applications in kidney cancer.

4634 General Poster Session (Board #9A), Sun, 8:00 AM-12:00 PM

Evaluation of selective inhibitors of nuclear export (SINE) CRM1 inhibitors for the treatment of renal cell carcinoma (RCC).

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Background: For the ~30% of patients who present with RCC at the metastatic stage, multi-kinase inhibitors have been used with moderate success: progression-free survival remains at only one to two years, and thus it is imperative to discover novel therapeutic approaches for metastatic disease. We asked whether (1) SINE inhibitors of chromosome region maintenance protein 1 (CRM1) attenuate key cell cycle regulatory and apoptotic molecules and whether these compounds exert salutary effects in a human RCC xenograft mouse model. **Methods:** Four RCC cell lines (ACHN, Caki-1, 786-O, and A498) with distinct genotypes, and primary normal human kidney (NHK) cell lines, were used in this study. The cells were treated with the chemically related SINE CRM1 inhibitors KPT-185 or 251 and MTT assays were performed. In addition, cell cycle analyses, immunofluorescence for p53 and p21, and immunoblotting for CRM1, p53, p21, p27, and p-MDM2 were performed for all cell lines. RCC mice with Caki-1 xenografts were treated with vehicle, the orally-available CRM1 inhibitor KPT-251, or sorafenib for 26 days. Tumor volume was measured over several days. **Results:** Both KPT185 and 251 specifically reduced CRM1 protein levels in RCC cells. KPT-185 caused dose-dependent cytotoxicity in RCC cells, which was greater than sorafenib in RCC cell lines but less in NHK cells, suggesting a possible clinical advantage of KPT-185 over sorafenib. By FACS analysis, we showed that KPT-185 arrests the cell cycle in both G2/M and G1, and increased the sub-G0 cell population. KPT-185 and 251 both increased p53 and p21 in RCC cells, and KPT-185 confined these proteins to the nucleus. In vivo, KPT-251 inhibited Caki-1 xenografts in mice compared to both vehicle and sorafenib without obvious systemic adverse effects. **Conclusions:** We introduce a completely novel therapeutic approach to the treatment of RCC based on inhibition of the nuclear export of key cell cycle regulatory proteins. Inhibition of CRM1 leads to forced nuclear retention, and thereby activation, of several key p53-pathway proteins, leading to cell cycle arrest and apoptosis in RCC cell lines in vitro and tumor growth inhibition in vivo.

4635 General Poster Session (Board #9B), Sun, 8:00 AM-12:00 PM

Genetic polymorphisms' influence in outcome of metastatic renal cell cancer patients treated with VEGF-targeted agents.

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Background: Single nucleotide polymorphisms (SNP) in critical signaling pathways may impact the outcome of metastatic renal cell cancer (mRCC) patients (pts) treated with VEGF targeted agents. **Methods:** Germline DNA was extracted from 263 pts of European-American ancestry enrolled in a prospective protocol with full baseline and follow up clinical data. A total of 113 common SNPs within select genes involved in RCC pathogenesis, angiogenesis and drugs metabolism were genotyped and associations sought with clinical outcome. The primary endpoint was progression free survival (PFS), defined as time from VEGF targeted therapy to progression or death. Cox model tested for the association between SNPs with PFS in univariate and multivariate model that adjusted for age, gender, type of VEGF inhibitor and MSKCC risk score. The false discovery rate (pFDR) was used to control for the number of tests performed. **Results:** The median follow-up time was 51.6 months (mo), 81% of pts had progression or death events. All patients were treated with an approved VEGF targeted agent (bevacizumab, sunitinib, sorafenib or pazopanib). Fifty three percent (140/263) of pts were treated with sunitinib. Two SNPs, one in HIF2α and one in VEGFR2, showed a significant association with the risk of progression. Compared to the dominant genotype (frequency 83%, median PFS 10.1mo), the VEGFR2 rs2305948 variant genotype (frequency 17%) showed a superior PFS (median 19.2mo) corresponded to an adjusted hazard ratio (HR) of 0.56 (95%CI: 0.37-0.84; p=0.005). Similarly and compared to the dominant genotype (frequency 94%, median PFS 10.6mo), the HIF2a rs11687512 variant genotype (frequency 6%) had a superior PFS (median 26.5mo) with an adjusted HR of 0.33 (95%CI 0.16-0.68; p=0.002). The analysis adjusted for age, gender, type of VEGF targeted therapy (Sunitinib vs. others) and MSKCC risk score. False discovery rate was $<$20% with both SNPs. **Conclusions:** Inherited variants may influence the PFS of pts with mRCC treated with VEGF targeted agents. Validation of these findings in an independent cohort is required. If validated, these results could help identifying subset of pts that are more likely to remain progression free on treatment.

4636 General Poster Session (Board #9C), Sun, 8:00 AM-12:00 PM

Efficacy and safety of cancer vaccine with 4-fold gene-modified allogeneic tumor cells: Results of the phase I/II ASET study in patients with advanced renal cell carcinoma.

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Background: MGN1601 was tested in the first-in-man phase I-II clinical study in patients with advanced renal cell carcinoma (RCC) who failed several previous therapy lines and had no further standard therapy available. MGN1601 consists of two active pharmaceutical ingredients in fixed combination: fourfold gene-modified allogeneic tumor cells expressing IL-7, GM-CSF, CD80 and CD154 through MIDGE vectors and a TLR-9 agonist, the immunomodulator dSLIM. **Methods:** The ASET study is a multicentric, single-arm phase I-II clinical trial. Clinical response was evaluated using CT scans (RECIST 1.1 or immune related Response Criteria, irRC). Efficacy data were evaluated in terms of PFS and OS for the intended to treat and the treated per protocol (TPP) populations, clinical parameters and quality of life. Immune response was determined using DTH to MGN1601, LTT assay, frequency and activation of blood cells, and mRNA, chemokine and cytotoxic T cells analysis as well as tumor tissue evaluation. **Results:** Nine of 19 included patients completed the TPP, the others discontinued the study earlier due to PD. Median PFS in the TPP group was 12 wks (3 months) and OS (not reached yet) 46 wks (11 months). Three patients achieved disease control (1 PR, 2 SD) after 12 wks. Two patients are continuing treatment in the extension phase and are progression free since 37 and 46 wks, respectively. Re-evaluation of tumor response data using irRC revealed 1 additional patient with a delayed tumor response 4 wks after treatment stop. Herewith, 4 out of 9 TPP patients (45%) achieved disease control. Of 7 patients receiving targeted therapy upon stop of study treatment, 4 had substantial objective responses, providing evidence that the study drug is able to render their tumors more vulnerable to subsequent therapies. Immune analysis showed trends towards increases of T-, NKT-cell and pDC frequencies and other immune parameters in those patients with clinical responses, indicating anti-tumor immunity of study treatment. **Conclusions:** The therapeutic cancer vaccine MGN1601 shows promising efficacy in late stage mRCC patients. Results warrant further clinical studies with MGN1601.

TPS4678 General Poster Session (Board #14E), Sun, 8:00 AM-12:00 PM

Neoadjuvant therapy preceding cytoreductive nephrectomy to develop individualized first-line therapy with everolimus for advanced renal cell carcinoma (RCC).

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Background: Everolimus (E), an orally administered mTOR inhibitor, is the conventional agent for progressive disease following vascular endothelial growth factor (VEGF) inhibitors for advanced RCC. Given the excellent tolerability and convenient oral administration, a rationale may be made to develop E as first-line therapy for selected patients. The period between diagnosis and cytoreductive nephrectomy (CN) may be utilized for brief therapy to capture biologic activity in tumor tissue and facilitate individualized systemic therapy. The agent may be resumed following CN and continued until progression. Pharmacodynamic (PD) alterations from baseline to CN tumor tissue may predict progression-free survival (PFS). We hypothesized that the application of this paradigm to E may enable the employment of first-line E in patients predicted to optimally benefit. **Methods:** This is a 27-patient phase II trial being conducted at the Baylor College of Medicine and University of Texas Southwestern, and 5 patients have been enrolled currently. Patients with $\geq$3 poor risk factors or those who refuse or are ineligible for VEGF inhibitors and have untreated metastatic RCC are eligible. Adequate hematologic, renal and hepatic function is required. The primary endpoint is PFS and secondary endpoints are response, survival and toxicities. Exploratory endpoints are tumor tissue, peripheral blood mononuclear cell (PBMC) and plasma PD studies and pharmacokinetic (PK) studies, and their association with PFS. PD studies include DNA, mRNA, protein and miRNA studies to evaluate the mTORC1 among other pathways. Patients initially undergo 4 core biopsies of the primary renal mass for fresh frozen tumor. Patients then receive E 10 mg orally once daily for 3-5 weeks. CN is performed within 24-48 hours after the last dose of E. At the time of CN and before separation from the vascular supply, 3 core biopsies are performed. E is resumed 2-4 weeks after CN and continued until progression or intolerable toxicities. Clinical and laboratory assessments are performed every 4-5 weeks, and imaging is performed every 8 weeks. A progressing metastatic site will be biopsied (4 core biopsies).

TPS4679 General Poster Session (Board #14F), Sun, 8:00 AM-12:00 PM

An observational study of metastatic renal cell carcinoma patients prior to initiation of initial systemic therapy.

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Background: The biology of metastatic RCC is extremely diverse, including a subpopulation of patients with indolent growth of metastases. Because of the acute and chronic toxicity and assumed non-curative nature of current systemic targeted therapy, a select subset of patients may be better served with initial surveillance. Such an approach may allow for deferral of systemic therapy to minimize overall treatment-related toxicity burden while maintaining treatment benefit. **Methods:** A prospective phase II trial is being conducted to characterize the clinical course of patients with mRCC who defer initial systemic treatment. Appropriate patients are selected by the treating physician based on an observed indolent growth pattern. As such, there is a 12 month window allowed between the first diagnosis of metastatic disease and study entry. Patients must be treatment-naïve, asymptomatic, with histologically confirmed mRCC and clinically-evident, measurable disease to be eligible. Radiographic assessment is performed at baseline, every 3 months for year 1, every 4 months for year 2, then every 6 months. The primary objective is to characterize the clinical outcome of patients on observation in terms of time to RECIST defined disease progression and time to initiation of systemic treatment. Secondary endpoints include measurement of disease-related symptoms and depression/anxiety using standardized questionnaires (FKSI-DRS and HADS), as well as correlative endpoints analyzing the immune response over time for which blood is being collected for immune assays (TH1/TH2 phenotype, Tregs). Pts remain on study until initiation of systemic therapy due to radiographic disease progression, development of disease-related symptoms, withdraw of consent or clinical change that renders the patient unacceptable for further observation. Local therapy (e.g. surgery, radiation) during the observation period is permitted. Currently, 29 patients have been accrued at 5 collaborating sites. The target accrual of 50 pts provides adequate power for the primary descriptive endpoint as well as 80% power to detect changes from baseline for the correlate endpoints based on a two-sided Wilcoxon signed rank test.

TPS4680 General Poster Session (Board #14G), Sun, 8:00 AM-12:00 PM

A phase II study of bevacizumab and erlotinib in subjects with advanced hereditary leiomyomatosis and renal cell cancer (HLRCC) or sporadic papillary renal cell cancer (RCC).

Eric A. Singer, Julia C. Friend, Geri Hawks, Cathy Vocke, Adam R. Metwalli, Peter A. Pinto, Gennady Bratslavsky, W. Marston Linehan, Ramaprasad Srinivasan; Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Chevy Chase, MD

Background: There are currently no treatment options of proven efficacy for patients with advanced papillary RCC. The evaluation of families with inherited forms of RCC has allowed for the identification of genetic alterations associated with papillary RCC. HLRCC is one such familial condition with a propensity for the development of a clinically aggressive variant of papillary RCC characterized by unique histopathologic features. Germline mutations in the gene for the Krebs cycle enzyme fumarate hydratase (*FH*) are the genetic hallmark of HLRCC. Mutational inactivation of *FH* leads to von Hippel-Lindau-independent upregulation of hypoxia inducible factors (HIF) and their downstream transcriptional targets such as vascular endothelial growth factor (VEGF) and transforming growth factor-alpha (TGF-α) / epidermal growth factor receptor (EGFR). Upregulation of the HIF pathway may also be important in sporadic papillary RCC, although the prevalence of *FH* inactivation in these patients is unknown. We propose to evaluate the activity of dual VEGF/EGFR blockade with bevacizumab/erlotinib in patients with HLRCC-associated RCC and sporadic papillary RCC. **Methods:** This is a single arm phase II study based on an open label Simon two-stage minmax design with a maximum accrual of 20 patients in each of two cohorts: Cohort 1- patients with HLRCC; Cohort 2- patients with sporadic papillary RCC. The primary endpoint is RECIST overall response rate, assessed independently in each cohort. Patients will receive bevacizumab (10mg/Kg IV every 2 weeks) and erlotinib (150mg PO daily). Dose reductions and drug interruptions for toxicity are allowed. Patients will be evaluated for response every 8 weeks. Major eligibility criteria include: advanced RCC associated with HLRCC or sporadic papillary RCC; age $>$18 years; ECOG 0-2; measurable disease by RECIST; no brain metastases; no more than 2 prior regimens containing a VEGF inhibitor; and no prior therapy with bevacizumab. The prespecified activity goal for the first stage of accrual has been met for both cohorts. NCT01130519.

TPS4681 General Poster Session (Board #14H), Sun, 8:00 AM-12:00 PM

EVERSUN: A phase II trial of everolimus alternating with sunitinib as first-line therapy for advanced renal cell carcinoma (RCC) (ANZUP trial 0901).

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Background: Treatment of RCC has improved due to better understanding of its biology. New targeted therapies have improved time to progression and overall survival but the optimal sequencing of agents is unknown. Currently drugs are given sequentially, usually starting with sunitinib and often followed by an mTOR inhibitor or another VEGFR-targeted therapy, but resistance to both drugs eventually occurs probably due to host adaptive responses. We hypothesize that resistance might be delayed by planned alternation of treatments. **Methods:** EVERSUN is a single-arm, two-stage, multicenter, phase II clinical trial aiming to determine the activity and safety of an alternating regimen of two therapies with different targets (sunitinib and everolimus) in patients with advanced RCC. Key eligibility criteria: RCC with a clear cell component; metastatic or locally advanced disease not suitable for resection; ECOG performance status 0-1; low or intermediate MSKCC prognostic score. The primary endpoint is the status of being alive and progression-free (RECIST 1.1) 6 months after registration. Target accrual of 55 subjects gives 95% power and 95% confidence to distinguish between 6-month progression free survival rates of 64% or lower vs 84% or higher using a Simon 2-stage minimax design. The criteria for further evaluation come from the pivotal trial of single agent sunitinib as first line therapy for RCC, in which the 6-month progression free survival rate was 74%. Trial treatment is administered in 12-week (wk) cycles consisting of 4 wks of sunitinib (50 mg daily) followed by 2 wks rest, followed by 5 wks of everolimus (10 mg daily) followed by 1 wk rest. Disease progression is interpreted as failure of the most recent drug taken. Participants who stop one drug because of toxicity or disease progression, on or before the 6 month assessment, will continue the other drug until subsequent progression or prohibitive toxicity on the second drug. EVERSUN is an ANZUP Cancer Trials Group Ltd. trial coordinated by the NHMRC Clinical Trials Centre. Accrual commenced in September 2010 with 38/55 participants recruited as of the 31-Jan-12 from 17 Australian sites (ACTRN12609000643279).

TPS4682 General Poster Session (Board #15A), Sun, 8:00 AM-12:00 PM

Treatment of refractory metastatic renal cell carcinoma (RCC) with lenvatinib (E7080) and everolimus.

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Background: Lenvatinib (E7080) is an oral tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR) 1-3, fibroblast growth factor receptor 1-4, RET, KIT and platelet-derived growth factor receptor beta. Lenvatinib has demonstrated acceptable toxicity and antitumor activity in Phase I and II studies (Glen H et al. JCO 2008, 26;15S: 3526;Yamada K et. al. Clin Cancer Res 2011, 17:2528-2537; Sherman S I et al. JCO 2011, 29; 15S: 5503). Improved understanding of the molecular basis of renal cell carcinoma (RCC) has led to the development of targeted therapies (inhibitors of mTOR and of the VEGF pathway) that have shown clinical benefit in patients with metastatic RCC. However patients develop resistance and ultimately progress during treatment with available single agents. Combination therapy targeting different pathways have the potential to improve efficacy. **Methods:** This multicenter, randomized, open-label, phase Ib/II study is investigating everolimus (an oral mTOR inhibitor) in combination with lenvatinib in RCC patients with unresectable or metastatic disease (NCT01136733). The study is being conducted in two phases. The phase Ib dose-escalation component will determine the maximum tolerated dose (MTD) of the combination; starting doses are 12 mg/day lenvatinib and 5 mg/day everolimus. A cohort expansion will follow to confirm the MTD and establish a recommended phase II dose (RP2 dose). Approximately 150 patients will be enrolled in phase II and randomized 1:1:1 to receive: lenvatinib and everolimus at the RP2 dose (Arm A); lenvatinib 24 mg/day (Arm B); or everolimus 10 mg/day (Arm C). Patients with clear cell RCC, ECOG performance score <2 and progression during or after one prior VEGF-targeted treatment are eligible for phase II. The primary endpoint for Phase II is to compare progression-free survival of the investigational arms (A and B) with single agent everolimus (Arm C). Three phase Ib dose escalation cohorts have completed enrollment, and enrollment of the expansion cohort commenced in November 2011. Participating phase II centers will be located in the US, UK, Spain, Poland and Czech Republic and are expected to enroll patients throughout 2012.

TPS4683 **General Poster Session (Board #15B), Sun, 8:00 AM-12:00 PM**

Phase III trial of dovitinib (TKI258) versus sorafenib in patients with metastatic renal cell carcinoma after failure of anti-angiogenic (VEGF-targeted and mTOR inhibitor) therapies.

Robert John Motzer, Camillo Porta, Georg A. Bjarnason, Cezary Szcylik, Sun Young Rha, Emilio Esteban, Ugo De Giorgi, Mary J. MacKenzie, Paul N. Mainwaring, Scott North, Roberto Sabbatini, Istvan Bodrogi, Fairooz Kabbinavar, Giacomo Carteni, Cora N. Sternberg, Nicholas J. Vogelzang, Michael Shi, Gladys Urbanowitz, Bernard J. Escudier; Memorial Sloan-Kettering Cancer Center, New York, NY; Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; Wojskowy Instytut Medyczny, Warszawa, Poland; Yonsei Cancer Center, Seoul, South Korea; Hospital general de Asturias, Oviedo, Spain; Istituto Tumori Romagna, Meldola, Italy; London Regional Cancer Program, London, ON, Canada; Haematology and Oncology Clinics of Australasia, Mater Medical Centre, South Brisbane, Australia; Cross Cancer Institute, Edmonton, AB, Canada; Azienda Ospedaliero Universitaria, Policlinico di Modena, Modena, Italy; Országos Onkológiai Intézet, Budapest, Hungary; University of California Los Angeles, Los Angeles, CA; Azienda Ospedaliero di Rilievo Nazionale A. Cardarelli, Naples, Italy; San Camillo Forlanini Hospital, Department of Medical Oncology, Rome, Italy; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Novartis Pharmaceuticals, East Hanover, NJ; Institut Gustave Roussy, Villejuif, France

Background: Standard first- and second-line treatments in metastatic renal cell carcinoma (mRCC) target the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) signaling pathways. However, signaling through other pathways, including the fibroblast growth factor receptor (FGFR) pathway, may account for tumor resistance to these standard therapies. Dovitinib (TKI258) is an oral FGF, VEGF, and platelet-derived growth factor (PDGF) receptor tyrosine kinase inhibitor, with IC_{50} values of $\approx$ 10 nM. In a phase II study of 59 RCC patients, many of whom had failed prior VEGF-targeted and mTOR inhibitor therapies, dovitinib (500 mg/day on a 5-days-on/2-days-off schedule) was well tolerated and demonstrated promising anti-tumor effects, with progression-free survival (PFS) of 5.5 months (Angevin et al, ASCO 2011). **Methods:** Approximately 550 patients from over 26 countries will be randomized 1:1 in this multicenter, open-label, randomized phase III trial (NCT01223027) to receive dovitinib (500 mg/day on a 5-days-on/2-days-off schedule) or sorafenib (400 mg twice daily). Eligible mRCC patients must have failed 1 VEGF-targeted therapy and 1 mTOR inhibitor (disease progression on or within 6 months of stopping the prior treatment). Patients will remain on study until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. No treatment crossover is planned. The primary endpoint is PFS as determined by central radiology assessment according to RECIST v1.1, with evaluations performed every 8 weeks. Secondary endpoints include overall survival, overall response rate, safety, patient-reported outcomes, and pharmacokinetics. The pharmacodynamic effects of dovitinib on plasma/serum biomarkers will also be explored. The data monitoring committee last reviewed the trial on 20 December 2011 and recommended that the trial continue as planned. This is the first third-line randomized clinical trial in mRCC to evaluate a multitargeted inhibitor of FGFR.

TPS4684 General Poster Session (Board #15C), Sun, 8:00 AM-12:00 PM

A phase II study of intermittent sunitinib in previously untreated patients (pts) with metastatic renal cell carcinoma (mRCC).

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Background: Sunitinib is a standard of care initial treatment in mRCC. One challenge is balancing the acute and chronic toxicity of therapy with clinical benefit. Pre-clinical and retrospective clinical data support the concept that treatment breaks are feasible and not associated with a reduction in efficacy of sunitinib. It is hypothesized that an intermittent dosing regimen of sunitinib in mRCC pts is feasible, and may lead to prolonged duration of disease control with improved tolerance. **Methods:** Eligibility criteria include treatment-naïve clear cell mRCC, measurable disease, and adequate organ function. Pts will be treated for 4 cycles of sunitinib (50 mg 4/2) in the absence of unacceptable toxicity or RECIST-defined progression. Pts with $\geq$ 10% reduction in tumor burden per RECIST following 4 cycles will have sunitinib held, with re-staging CT scans approximately every 10 weeks thereafter to assess tumor burden. Sunitinib will be re-initiated in those patients with an increase in tumor burden of 10% or greater (per RECIST) compared to the scan obtained just prior to holding sunitinib. Pts who have RECIST tumor burden reduction of 10% or more compared to scans at the start of the most recent treatment period will again have sunitinib held. This intermittent sunitinib dosing will continue until RECIST-defined disease progression while on sunitinib. Patients not initially achieving at least a 10% reduction in tumor burden will continue sunitinib. The primary objective is the feasibility of intermittent sunitinib, defined as the proportion of patients eligible for and who undergo intermittent therapy. The alternative hypothesis is a feasibility rate of $>$ 80% vs. the null hypothesis of $<$ 50%. Thirty pts provides 80% power based on a two-sided exact test with a .05 type I error. Secondary endpoints include PFS and toxicity. Twenty five of planned 30 patients have been enrolled.

TPS4685 **General Poster Session (Board #15D), Sun, 8:00 AM-12:00 PM**

Prospective assessment of circulating endothelial cells (CECs) as early markers of clear cell renal cell carcinoma (CCRCC) progression in first line setting: The Circles study (SOGUG 2011-01).

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Background: Since the identification of Von Hippel Lindau (VHL) gene mutations as a critical step in the development of most Clear Cell Renal Cell Carcinomas (CCRCC), neoangionesis inhibition has become a cornerstone in their treatment. Despite the proven efficacy of antiangiogenic drugs, most patients will not achieve partial response by RECIST criteria. Thus, to accurately determine tumor progression is a challenging question incompletely answered by traditional radiological assessment. In recent years CECs counts have been proposed as surrogate biomarkers of angiogenesis that could be used for monitoring tumor evolution while on targeted therapies. We aim to figure out if CECs elevations could anticipate radiological progression in CCRCC. **Methods:** An observational prospective study is being performed in 10 institutions members of the Spanish Oncology Genitourinary group (SOGUG). Patients older than 18 years with histologically proven CCRCC on first line treatment with any targeted drug who have not progressed after 3 months of therapy are considered elegible. Recruitment begun on August the 1st 2011 and 15 of the 75 scheduled patients have been included so far. CECs are periodically collected in peripheral blood every 6 weeks for 15 months or radiological tumor progression, whatever occurs first. Median CEC values will be calculated and stated by descriptive statistics (Cellsearch, VERIDEX). To explore the evolution of CECs counts along treatment a linear model will be constructed. An association among CECs counts changes and time to progression will be analyzed with Cox model.

TPS4686 General Poster Session (Board #15E), Sun, 8:00 AM-12:00 PM

A phase II biomarker assessment of tivozanib in oncology (BATON) trial in patients (pts) with advanced renal cell carcinoma (RCC).

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Background: Tivozanib is an oral, potent, and selective tyrosine kinase inhibitor targeting all three vascular endothelial growth factor (VEGF) receptors; it showed efficacy and tolerability in a Phase II trial in pts with advanced RCC (Nosov *et al*. *JCO* 2011;29[18S]:4550). Preclinical studies have identified a 42-gene tivozanib resistance signature (Jie *et al.* EORTC-NCI-AACR 2010; abstract 608) that may be predictive of tivozanib sensitivity. This study (NCT01297244) is designed to evaluate these potential biomarkers for tivozanib activity in pts with advanced RCC. **Methods:** Pts with advanced RCC (stratified as clear cell or non-clear cell) who underwent nephrectomy and received ≤1 prior systemic treatment (no prior VEGF- or mammalian target of rapamycin–targeted therapy) entered this open-label, single-arm study conducted in the United States and Canada beginning January 2011. Pts receive tivozanib 1.5 mg/d orally (3 weeks on, 1 week off schedule). Primary objectives include correlation of biomarkers in blood (e.g. VEGF, hepatocyte growth factor [HGF]) and tumor tissue (e.g. CD68, hypoxia-induced factor, VEGF, HGF, and gene expression profiles) with clinical activity and/or treatment-related toxicity, and 6-month progression-free survival (PFS) rate. Secondary objectives include overall response rate (ORR), PFS, safety and tolerability, and pharmacokinetics. Contingency table methods will be used for biomarker correlation with ORR, and Cox proportional-hazards regression for correlation with PFS. Sample size (100 pts) is estimated based on clinical considerations and the precision with which 6-month PFS can be estimated. Biomarkers were defined at study outset; the requirement of prior nephrectomy ensured availability of primary tumors as controls for correlative analysis. As of January 2012, the study completed enrollment of 100 pts, demonstrating a large number of pts can be enrolled to a biomarker study with well-defined candidate genes and critical inclusion criteria to facilitate compliance. Tivozanib biomarkers evaluated in this study, along with those evaluated in other solid tumors, may play an important role in optimizing patient selection.

TPS4687 General Poster Session (Board #15F), Sun, 8:00 AM-12:00 PM

Phase I/II study of high-dose interleukin 2, aldesleukin, in combination with the histone deacetylase inhibitor entinostat in patients with metastatic renal cell carcinoma.

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Background: Immunosuppressive factors such as regulatory T cells (Tregs) limit the efficacy of immunotherapies. Histone deacetylase (HDAC) inhibitors have been shown to have anti-tumor activity in different malignancies and to induce immuno-modulatory effects. We have previously reported that a class I specific HDAC inhibitor, entinostat, has synergistic anti-tumor effect in combination with high dose interleukin-2 (IL-2) in a renal cell carcinoma model (Kato Y *et al Clinical Cancer Res* 2007). Our group has also recently showed that low dose entinostat induces STAT3 acetylation, down-regulates Foxp3 expression in Tregs, and blocks Tregs suppressive function without affecting T effector cells (Shen Li *et al PLoSONE* 2012). **Methods:** Based on these preclinical evidences we have initiated a Phase I/II clinical study with entinostat and high dose IL-2 in patients with metastatic renal cell carcinoma. The primary objective of the study is to evaluate the safety, tolerability and efficacy of this combination strategy. The main eligibility criteria are clear cell histology, no prior treatments and being fit to receive high dose IL-2. The Phase I portion consists of two dose levels of entinostat (3 and 5 mg) and a fixed standard dose of IL-2 (600,000 units/Kg every 8 hrs.) according to a 3+3 design. The sample size of 36 patients in the Phase II portion is powered to detect an increase in objective response rate from 20% to 40% as compared to historical data with high dose IL-2 alone. Correlative studies include assessment of CD4+, CD8+, CD4+/Foxp3, NK cells in tumor and blood samples by immunohistochemistry and FACS analysis, and tumor metabolism by FDG PET. We are also exploring the relationship between entinostat exposure with pharmacodynamic endpoints. To date dose level one has been completed without DLT. Enrollment to dose level two has begun in the Fall 2011. The results from this study may confirm the role of entinostat in enhancing the effect of IL-2 and may be translated into other combination strategies involving immunotherapies. The clinical trial and correlative studies are supported by the National Cancer Institute- R21CA137649.