

LBA4500

Oral Abstract Session, Sat, 1:15 PM-4:15 PM

A phase III trial of personalized chemotherapy based on serum tumor marker decline in poor-prognosis germ-cell tumors: Results of GETUG 13.

Karim Fizazi, Lance C. Pagliaro, Aude Flechon, Jozef Mardiak, Lionnel Geoffrois, Pierre Kerbrat, Christine Chevreau, Remy Delva, Frederic Rolland, Christine Theodore, Guilhem Roubaud, Gwenaëlle Gravis, Jean-Christophe Eymard, Jean-pierre Malhaire, Claude Linassier, Muriel Habibian, Florence Journeau, Christopher Logothetis, Stephane Culine, Agnes Laplanche; Institut Gustave Roussy, Villejuif, France; The University of Texas MD Anderson Cancer Center, Houston, TX; Centre Léon Bérard, Lyon, France; 2nd Oncology Department, Comenius University, Medical School and National Cancer Institute, Bratislava, Slovakia; Centre Alexis VAUTRIN, Vandoeuvre-lès-Nancy, France; Centre Eugène Marquis, Rennes, France; Institut Claudius Regaud, Toulouse, France; Institut de Cancérologie de l'Ouest Paul Papin, Angers, France; Centre René Gauducheau, Saint-Herblain, France; Hospital Foch, Suresnes, France; Institut Bergonie, Bordeaux, France; Department of Medical Oncology, Institut Paoli Calmettes, INSERM UMR 891, Marseille, France; Institut Jean Godinot; University Reims Champagne Ardenne, UFR Médecine, Reims, France; Centre Hospitalo-Universitaire, Brest, France; Department of Medical Oncology, Centre Hospitalier Universitaire Tours, Tours, France; UNICANCER, Paris, France; Institut Gustave Roussy, Villejuif, France; Hopital Saint-Louis, Paris, France

The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Saturday, June 1, 2013, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2013, issue of *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

Paclitaxel, ifosfamide, and cisplatin (TIP) efficacy for first-line treatment of patients (pts) with intermediate- or poor-risk germ cell tumors (GCT).

Darren Richard Feldman, James Hu, Tanya B. Dorff, Sujata Patil, Lindsay Joy Van Alstine, Lamia Momen, Maryann Carousso, Amanda Hughes, Jolie Snively-Solomon, Charlean Ketchens, Joel Sheinfeld, Manjit S. Bains, Dean F. Bajorin, George J. Bosl, Robert John Motzer, David I. Quinn; Memorial Sloan-Kettering Cancer Center, New York, NY; USC Norris Comprehensive Cancer Center, Los Angeles, CA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: Durable progression-free survival (PFS) rates for pts with intermediate- and poor-risk GCT approximate only 75% and 50%, respectively with standard BEP. This multicenter phase II study investigated first-line TIP in this population. **Methods:** Pts age ≥ 18 with untreated, IGCCCG intermediate- (LDH modified to ≥ 3 x upper limit of normal) or poor-risk GCT were eligible. Pts received 4 cycles of TIP every 21 days, consisting of paclitaxel 120mg/m² days 1-2; ifosfamide 1200mg/m² days 1-5; and cisplatin 20mg/m² days 1-5, followed by G-CSF and levofloxacin for neutropenic fever prophylaxis. The primary endpoint was the complete response (CR) rate; secondary endpoints included PFS and toxicity. A Simon's 2-stage design required a CR in $\geq 11/18$ pts to proceed to stage 2, where with $\geq 27/41$ CRs overall, the regimen would be considered active and worthy of further study. **Results:** Of 44 men (median age 27) enrolled; 38 had nonseminoma and 6 seminoma; 29 were poor-risk and 15 intermediate-risk. Primary site was testis in 30, mediastinum in 11, and retroperitoneum in 3. 42 pts had elevated markers and 14, 6, and 1 had liver, bone, and brain metastasis, respectively. The trial met its primary endpoint; of 41 evaluable pts, 28 achieved a CR (see Table) and 6 pts (5 with seminoma) achieved a partial response with negative markers (PR-). Two pts relapsed. With a median follow-up of 2.2 years, estimated 3-year PFS was 79% and 3-year overall survival (OS) 98% (see Table). There were no treatment-related deaths. Grade 3/4 toxicities were primarily hematologic and 6 (14%) pts developed neutropenic fever. **Conclusions:** TIP demonstrates promising efficacy and is well-tolerated in intermediate- and poor-risk GCT pts. A randomized trial of TIP vs. BEP has been initiated to compare efficacy. Clinical trial information: NCT00470366.

Outcome	Intermediate-risk N=15 (14 evaluable for response)	Poor-risk N=29 (27 evaluable for response)	Total N=44 (41 evaluable for response)
Response			
CR %	57	74	68*
PR- %	36	4	15
Favorable response (CR + PR-) %	93	78	83
Incomplete response %	7	22	17
Survival			
3-year PFS % (95% CI)	87 (56-96)	76 (55-88)	79 (64-89)
3-year OS % (95% CI)	100	97 (76-99)	98 (84-100)

*Crude CR rate 68%; estimated CR rate 70% (90% CI: 58% – 76%).

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Oral Abstract Session, Sat, 1:15 PM-4:15 PM

A nationwide cohort study of surveillance for stage I seminoma.

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Background: The standard treatment for stage I seminoma remains a topic for discussion. Survival rates are excellent irrespective of treatment modality (radiotherapy, carboplatin or surveillance). However, late effects might differ between treatment options. Only smaller surveillance studies with limited follow-up have previously been published. We present data from a large nationwide cohort study on surveillance in stage I seminoma patients. **Methods:** A nationwide and population based clinical database covering germ cell cancer patients diagnosed 1984-2007 was constructed. The database included 4,683 cases. All stage I seminoma patients followed by surveillance were identified. Possible prognostic factors for relapse were collected from patient files and pathology reports. By merging our data with the national patient registry we were able to collect data on late relapses, vital status and cause of death on all patients up to December 2012. **Results:** 1,822 patients with stage I seminoma were followed on a surveillance program. The median follow-up time was 15.4 years. Ten year cancer specific survival (CSS) was 99.6%. A total of 355 (19.5%) patients had a relapse after a median time of 13.7 months (range 1.2-173.7 months). Within 2-5 years after orchiectomy, 72 patients (4.0 %) had a relapse and 26 patients (1.4 %) had a relapse more than 5 years after orchiectomy. Invasion of blood or lymphatic vessels, tumor size > 4 cm and serum human chorionic gonadotropin > 200 IU/L were all predictive factors for relapse in both univariate and multivariate analyses ($p < 0.01$). Invasion of rete testis was significant in the univariate analysis but not in the multivariate analyses ($p = 0.53$). **Conclusions:** We present the largest cohort ever published of stage I seminoma patients followed on a surveillance program. The prognosis was excellent with a 10 year CSS of 99.6%. Prognostic factors for relapse were identified. The relapse rate after 5-years of follow-up was 1.4%. Surveillance should be the preferred option of management in stage I seminoma patients. Several international guidelines are now in agreement with this statement.

Characterization of relapse in patients with clinical stage I (CSI) nonseminoma (NS-TC) managed with active surveillance (AS): A large multicenter study.

Christian K. Kollmannsberger, Torgrim Tandstad, Philippe L. Bedard, Michael A. S. Jewett, Gabriella Cohn-Cedermark, Peter W. M. Chung, Gedske Daugaard, Pdraig Richard Warde, Malcolm J. Moore, Craig R. Nichols; BC Cancer Agency, Vancouver, BC, Canada; Department of Oncology, St. Olavs University Hospital, Trondheim, Norway; Princess Margaret Cancer Center, University Health Network, Division of Medical Oncology & Hematology, Department of Medicine, University of Toronto, Toronto, ON, Canada; Department of Urology, Princess Margaret Hospital and University of Toronto, Toronto, ON, Canada; Department of Oncology-Pathology, Karolinska Institute and University Hospital, Stockholm, Sweden; Department of Radiation Oncology, Princess Margaret Hospital and University of Toronto, Toronto, ON, Canada; Department of Oncology, Rigshospitalet, Copenhagen, Denmark; Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; Virginia Mason Medical Center, Seattle, WA

Background: Large single institution trials have demonstrated that AS for patients with CSI NS-TC is safe and effective. Information on timing and extent of relapse following AS has the potential to guide intensity and duration of imaging on AS. **Methods:** Retrospective clinical data on CSI patients were obtained from existing large databases, including institutions/regions which have a standardized policy of centralized management of testicular cancer including AS for patients with CSI NS-TC. In all, 1,034 patients with CSI NS-TC managed with AS were reviewed of whom 886 had no lymphovascular invasion (LVI-), 220 had lymphovascular invasion (LVI+) and 28 had unknown lymphovascular status (LVI unknown). **Results:** A total of 221 relapses occurred with 150/886 (17%) of LVI- pts, 60/120 (50%) LVI+ pts and 11/28 (39%) of LVI unknown pts (Table). Median follow-up was 63 months (1-163 months). At last follow up 1,013/1,034 (98%) were alive without disease, 16/1,034 (1.5%) were dead of other causes and 7/1,035 (0.05%) were alive with disease or dead of disease. Relapse was identified by marker elevation and/or abdominal imaging in almost all patients. Few patients relapsed with IGCCCC intermediate (18/221, 8%) or poor risk disease (3/221, 1.4%). **Conclusions:** AS for CSI NS-TC is safe and effective, using a policy of centralized management with loco-regional delivery of care. Our multinational outcomes compare well to single institutional reports. Relapse other than with IGCCC good risk disease was uncommon and death from disease was rare. Compared to patients with LVI-, relapses in LVI + CSI patients occur earlier and few relapses are detected past the first year of follow-up. This data may help in the design of follow up schedules tailored towards the relapse risk in CSI NS-TC AS.

Characteristics of relapsing LVI- and LVI+ CSI NS-TC.

	Stage at relapse				Timing of relapse			
	Good risk	Intermediate risk	Poor risk	Stage not available	1-12 mo.	1-24 mo	1-36 mo	> 36 mo
LVI- n= 150	117/150 78%	15/150 10%	3/150 2%	15/150 10%	112/150 75%	135/150 90%	140/150 93%	10/150 7%
LVI + n=60	57/60 95%	1/60 2%	0	2/60 3%	56/60 93%	58/60 97%	59/60 98%	1/60 2%
LVI unknown N=11	10/11 91%	1/11 9%	0	0	6/11 55%	10/11 91%	0	1/11 9%

Record-3: Phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC).

Robert John Motzer, Carlos H. Barrios, Tae Min Kim, Silvia Falcon, Thomas Cosgriff, W. Graydon Harker, Kenneth B. Pittman, Gabriele Luppi, Sun Young Rha, Thomas W. Flaig, Ray D. Page, Sevil E. Bavbek, J. Thaddeus Beck, Poulam M Patel, Edward Schiff, Alexandra Vaury, Julie Niolat, Sven Gogov, Ozlem Anak, Jennifer Knox; Memorial Sloan-Kettering Cancer Center, New York, NY; PUCRS School of Medicine, Porto Alegre, Brazil; Seoul National University Hospital, Seoul, South Korea; Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru; Hematology and Oncology Specialists, Metairie, LA; Utah Cancer Specialists, Salt Lake City, UT; The Queen Elizabeth Hospital, Adelaide, Australia; Azienda Ospedaliero-Universitaria, Modena, Italy; Yonsei Cancer Center, Seoul, South Korea; University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO; The Center for Cancer and Blood Disorders, Fort Worth, TX; American Hospital, Istanbul, Turkey; Highlands Oncology Group, Fayetteville, AR; University of Nottingham, Nottingham, United Kingdom; Novartis Oncology, Novartis Pharmaceuticals, Florham Park, NJ; Novartis Oncology, Novartis Pharma SAS, Rueil-Malmaison, France; Novartis Pharma AG, Basel, Switzerland; University of Toronto, Princess Margaret Hospital, Toronto, ON, Canada

Background: Sequential SUN (tyrosine kinase inhibitor, TKI) until progression of disease (PD) followed by EVE (mTOR inhibitor) is standard therapy for patients with mRCC. This open-label, multicenter, phase II trial compared 1st-line EVE to 1st-line SUN (NCT00903175). Sequential EVE→SUN was also compared with standard SUN→EVE. **Methods:** Patients with mRCC (clear or non-clear cell) naive to prior systemic therapy were randomized 1:1 to either 1st-line EVE 10 mg/day or SUN 50 mg/day (4 weeks on, 2 weeks off) until PD. Patients then crossed over and continued on the alternate drug until PD. Primary objective was to assess PFS noninferiority of 1st-line EVE to 1st-line SUN; defined as an observed hazard ratio (HR)_{1st EVE/SUN} ≤ 1.1. Overall survival (OS), combined 1st-line and 2nd-line PFS, and safety were secondary end points. **Results:** From 10/09 to 6/11, 471 patients enrolled (EVE→SUN, n = 238; SUN→EVE, n = 233). Median age was 62 years, 85.4% had clear-cell RCC, and MSKCC favorable/intermediate/poor risk was 30/56/14%. Median follow-up was 22.7 months. A total of 53.7% of patients who discontinued 1st-line EVE entered into 2nd-line SUN and 51.6% of patients who discontinued 1st-line SUN entered into 2nd-line EVE. Median PFS (95% CI) was 7.9 (5.6-8.2) months for 1st-line EVE and 10.7 (8.2-11.5) months for 1st-line SUN. HR_{1st EVE/1st SUN} (95% CI) was 1.43 (1.15-1.77). Median OS (95% CI) was 22.4 (19.7-NA) months for EVE→SUN and 32.0 (20.5-NA) months for SUN→EVE; HR_{EVE-SUN/SUN-EVE} (95% CI) was 1.24 (0.94-1.64). A trend in favor of SUN→EVE for OS was observed, but will need to be confirmed with final OS analysis. Additional efficacy results for secondary end points are forthcoming. Common treatment-emergent adverse events for 1st-line EVE vs SUN, respectively, were stomatitis (53% vs 57%), fatigue (45% vs 51%), and diarrhea (38% vs 57%). **Conclusions:** Noninferiority of PFS for 1st-line EVE compared with SUN was not achieved in this randomized phase II trial of mRCC patients. The treatment paradigm remains SUN→EVE since the sequence achieved optimal clinical benefit. Clinical trial information: NCT00903175.

Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with metastatic renal cell carcinoma (mRCC).

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Background: Human RCC expresses PD-L1 and has been shown to respond to immune-based therapy. MPDL3280A, a human monoclonal antibody containing an engineered Fc-domain designed to optimize efficacy and safety, targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1. **Methods:** Pts with mRCC received MPDL3280A administered IV q3w at doses between 3-20 mg/kg in a Phase I expansion study. Pts were treated for up to 1 y. Response was assessed by RECIST v1.1. **Results:** As of Jan 10, 2013, 53 RCC pts were evaluable for safety and treated at doses of 3 (n=2), 10 (n=12), 15 (n=18) and 20 mg/kg (n=21). These pts had a median age of 62 y (range 33-79 y), 100% were PS 0-1 and all had had prior surgery. 83% of pts had received prior systemic therapy; 38% received immunotherapy, 57% received TKIs and 36% received anti-angiogenic therapy. Pts received treatment with MPDL3280A for a median duration of 190 days (range 21-317). The incidence of G3/4 AEs in RCC pts was 43%, regardless of attribution, with hypophosphatemia, fatigue, dyspnea and hyperglycemia (all 4%) being the most common. 13% of G3/4 AEs were attributable to study drug. 1 case of myasthenia gravis was observed in a pt who was retrospectively found to have anti-acetylcholine receptor antibodies prior to starting therapy. No G3-5 pneumonitis or diarrhea was reported. No treatment-related deaths occurred. 39 RCC pts enrolled prior to Jul 1, 2012, were evaluable for efficacy. RECIST responses, including CR, were observed across dose levels, with all responses ongoing at the time of data cutoff. Some RCC pts experienced prolonged SD prior to experiencing RECIST response. The 24-week PFS was 50%. Analysis of biomarker data from mandatory archival tumors demonstrated a correlation between PD-L1 status and efficacy. In addition, response correlated with low IL-17 expression in tumor tissue. Updated data will be presented. **Conclusions:** MPDL3280A was well tolerated, with no pneumonitis-related deaths. PD-L1-positive status correlates with response to MPDL3280A. Durable responses have been observed in RCC pts treated with MPDL3280A and further study is warranted. Clinical trial information: NCT01375842.

Phase II efficacy and safety study of nintedanib versus sunitinib in previously untreated renal cell carcinoma (RCC) patients.

Tim Eisen, Yaroslav Shparyk, Robert Jones, Nicholas James MacLeod, Graham Temple, Helen Finnigan, Rolf Kaiser, Matus Studeny, Arsene Bienvenu Loembe, Igor Bondarenko; Cambridge University Health Partners, Addenbrooke's Hospital, Cambridge, United Kingdom; Lviv State Oncology Regional Treatment and Diagnostic Centre, Lviv, Ukraine; Cancer Research UK Clinical Research Unit (CRU), Glasgow, United Kingdom; Boehringer Ingelheim GmbH, Bracknell, United Kingdom; Boehringer Ingelheim GmbH, Biberach, Germany; Boehringer Ingelheim GmbH, Vienna, Austria; Municipal Institution Dnipropetrovsk, Ukraine

Background: Sunitinib (S) is established as a standard first-line therapy for patients (pts) with advanced RCC. However, treatment can be limited by the occurrence of drug-related adverse events (AEs). This Phase II study assessed the efficacy and safety of nintedanib (N) – a potent, triple angiokinase inhibitor of VEGFR-1–3, PDGFR- α/β , and FGFR-1–3, as well as RET and Flt3 – vs S in previously untreated pts with RCC. **Methods:** Ninety-nine eligible pts (96 of whom were treated) with advanced, unresectable/recurrent clear cell RCC, an ECOG performance status of 0–1, and no prior systemic therapy were randomized 2:1 to receive N 200 mg twice daily (n=64; given in 4-week cycles) or S 50 mg once daily (n=32; 4 weeks on, 2 weeks off schedule). Treatment continued until disease progression or unacceptable drug-related AEs. Primary endpoints were progression-free survival at 9 months (PFS-9) and, in N-treated pts only, QTc interval change (baseline to day 15). Secondary endpoints included PFS, objective response rate (ORR; RECIST 1.1), overall survival (OS), time to progression (TTP), time to treatment failure (TTF), and AEs. **Results:** Baseline characteristics were balanced between the arms. PFS-9 was not statistically significantly different between N- and S-treated pts (43 vs 45%; p=0.85). There were also no statistically significant differences between N and S with regard to PFS (median: 8.44 vs 8.38 mo; hazard ratio: 1.16; 95% CI: 0.71–1.89; p=0.56), confirmed ORR (18.8 vs 31.3%; p=0.19), OS (median: 20.37 vs 21.22 mo; p=0.63), TTP (median: 8.48 vs 8.54 mo; p=0.52), and TTF (median: 8.41 vs 8.36 mo; p=0.46). Grade ≥ 3 AEs occurred in 47% of N-treated pts and 56% of S-treated pts. Common AEs (all grades; N vs S) included diarrhea (61 vs 50%), nausea (38 vs 34%), fatigue (both 25%), and vomiting (16 vs 22%). Dermatologic AEs (8 vs 47%) were less frequent with N than S. There was no increase from baseline in QTc >60 ms on days 1 or 15 in N-treated pts, and there was no relationship between N exposure and QT interval change. **Conclusions:** N demonstrated similar efficacy to S and had a manageable safety profile, including a lower incidence of dermatologic AEs vs S. In addition, N was not associated with QT prolongation. Clinical trial information: NCT01024920.

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Oral Abstract Session, Sat, 1:15 PM-4:15 PM

ARISER: A randomized double blind phase III study to evaluate adjuvant cG250 treatment versus placebo in patients with high-risk ccRCC—Results and implications for adjuvant clinical trials.

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Background: cG250 (Rencarex) is a chimeric monoclonal antibody that binds to the CAIX cell-surface antigen present on 95% of ccRCC. Its safety and activity in phase II studies provided the rationale to investigate its use as an adjuvant monotherapy in subjects with clinically localized high-risk ccRCC—50% of whom progress to metastatic disease. **Methods:** We performed an international, prospective, multicenter, phase III trial of the efficacy and safety of adjuvant cG250 vs placebo (randomized 1:1) by assessing disease-free (DFS) and overall survival (OS) in 864 RCC patients after nephrectomy. Inclusion criteria were: 1) T3/T4 N0/M0; 2) any T stage and N+/M0; or 3) T1b/T2 N0/M0 high-grade ccRCC. Treatment consisted of a 50 mg loading dose followed by 23-weekly infusions of 20 mg. DFS and CAIX antigen expression were quantified by an independent radiological review and a central pathologist. CAIX score was derived by multiplying the intensity of staining (1–3) by the fraction of positive cells (0–1), yielding a range of 0.0–3.0. **Results:** Baseline demographics were well balanced across groups. Treatment demonstrated an excellent safety profile. There were 360 confirmed recurrences and 181 deaths during follow up. When compared with the placebo group, cG250-treated subjects did not enjoy a statistically significant DFS (HR=0.99, p=0.74) or OS advantage (HR=1.01, p=0.94). Median DFS and OS were over 6 years and never reached irrespective of treatment, respectively. However, on subset analysis, subjects with high CAIX expression (>2.0) who received cG250 experienced a statistically significant treatment effect with improved DFS (HR=0.55; p=0.01). **Conclusions:** While cG250 appears not to have clinical benefit in the adjuvant treatment for all high-risk patients, cG250-treated patients with a high CAIX score appeared to have a significantly improved DFS. The CAIX score may help in stratifying patients who may benefit from cG250 adjuvant therapy. Notwithstanding this benefit, the surprising median DFS of over 6 years and outstanding OS in high-risk patients represent a significant challenge to adjuvant ccRCC drug development. Clinical trial information: NCT00087022.

Pazopanib prior to planned nephrectomy in metastatic clear cell renal cancer: A clinical and biomarker study.

Thomas Powles, Naveed Sarwar, Andrew Stockdale, Ekaterini Boleti, Robert J. Jones, Andrew Protheroe, Simon Chowdhury, John Peters, Grenville Oades, Tim S. O'Brien, Mark Sullivan, Grant Stewart, Michael Aitchison, Shah-Jalal Sarker, Dan Berney, Charlotte Rofe, Kevin Sharpe, Simon J. Crabb; St. Bartholomew's Hospital, London, United Kingdom; University Hospital, Coventry, United Kingdom; Royal Free Hospital, London, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Medical Oncology Department, University of Oxford, Oxford, United Kingdom; Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; Whipps Cross Hospital, London, United Kingdom; The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Oxford University Hospitals NHS Trust, Oxford, United Kingdom; University of Edinburgh, Edinburgh, United Kingdom; Barts Cancer Institute, London, United Kingdom; University of Southampton, Faculty of Medicine, Southampton, United Kingdom

Background: The safety and efficacy of upfront pazopanib, prior to nephrectomy in metastatic clear cell renal cancer (mRCC), has not been prospectively evaluated. The toxicity profile of pazopanib potentially makes it an attractive agent in this setting. **Methods:** A single arm phase II study (2009-016675-29) evaluated 12-14 weeks of pazopanib prior to planned nephrectomy in 102 untreated patients with mRCC. Patients had MSKCC intermediate (n=80) and poor risk disease (n=22). The Primary endpoint of the trial was to achieve at least a 75% clinical benefit rate (absence of disease progression) with pazopanib at the time of surgery. Sequential tissue was used for biomarker analysis (exploratory endpoint). Tissue from a previous sunitinib trials with a similar design was included for comparative purposes. **Results:** Overall 81% of patients obtained clinical benefit prior to surgery. The partial response rate of the primary tumor was 14% by RECIST v1.1. The median reduction in the size of the primary tumor was 14% (range 33% to -41%). No patients became inoperable due to local progression of disease. A nephrectomy was performed in 66% of patients. The two commonest reasons for not having surgery were patient choice (9%) and progression of disease (16%). There were 2 (3%) post operative surgical death. Delayed wound healing occurred in 5%. Progression during the treatment free interval for surgery was 26%. Median PFS has not been reached. Results from biomarker analysis of sequential tissue revealed therapy resulted in a significant decrease in CD31 (-49%), PDL-1 (-31%) and pS6K (-26%), while FGF-2 (+147%), MET (+34%) and Ki-67 expression increased with therapy. Increased ki-67 and CD31 correlated with a poor outcome. **Conclusions:** Nephrectomy after upfront pazopanib can be performed safely in mRCC and obtains control of disease in the majority of patients. Biomarker analysis shows dynamic changes some of which are prognostically significant. Clinical trial information: NCT01512186.

LBA4510

Clinical Science Symposium, Mon, 11:30 AM-1:00 PM

Duration of androgen deprivation therapy in high-risk prostate cancer: A randomized trial.

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The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Monday, June 3, 2013, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2013, issue of *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

A first-in-human study of the oral selective androgen receptor down-regulating drug (SARD) AZD3514 in patients with castration-resistant prostate cancer (CRPC).

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Background: AZD3514 is a first in class, orally bio-available drug that inhibits androgen-dependent and -independent androgen receptor (AR) signaling through two distinct mechanisms; inhibition of ligand-driven nuclear AR translocation and down-regulation of AR levels. **Methods:** A rolling six design was employed initially using a once a day (QD) schedule (A). PK assessments led to a change to twice daily (BD) dosing (B) to increase exposure. PK profiles were studied over 96 hours after a single dose and over 24 hours at start of/following 21 days continuous dosing. PD analyses included PSA and CTC quantification. **Results:** 49 CRPC patients (pts) have been treated with escalating doses of AZD3514 (A 35 pts, B 14 pts). Starting doses were 100 mg (A) and 1000 mg (B). The AZD3514 formulation was switched from capsules to tablets at 1000mg (QD). 2000mg BD was considered non-tolerable due to multiple grade 2 toxicities (nausea [N], vomiting [V], fatigue). No adverse events (AEs) met the DLT definition. The most frequent drug-related AE's were N; G1/2 36/49 (73%), G3 2/49 (4%) and V; G1/2 24/49 (49%) & G3 3/49 (6%). N/V were managed with oral anti-emetics. Dose proportional increases in plasma concentrations were observed following a single dose. Geometric mean (%CV) C_{max} and AUC at MTD were 9,608 (38.5) ng/mL and 61,734 (40.6) ng.hr/mL, respectively. Compared with single dose continuous dosing led to a mean decrease of 26% in exposure. Maximum PSA and CTC declines are summarized below. Objective soft tissue responses per RECIST1.1 were observed in 2/26 (8%) pts. One pt with abiraterone resistant disease remained on study for 19 months. At 6 and 12 months 21 (43%) and 8 (16%) pts remained on study without evidence of bone or soft tissue progression, respectively. **Conclusions:** AZD3514 has antitumor activity in patients with advanced CRPC. Clinical trial information: NCT01162395.

AZD3514 Dose (mg)	N	PSA decline ≥50%	PSA decline ≥30%	CTC conversion (N/Eval. pts; %)	CTC decline ≥30% (N/Eval. pts; %)
100 QD	5	0%	0%	0/1 (0%)	0/1 (0%)
250 QD	6 ^a	0%	0%	1/5 (20%)	2/5 (40%)
500 QD	12	17% (2)	25% (3)	1/5 (20%)	3/5 (60%)
1000 QD	12	25% (3)	42% (5)	2/6 (33%)	5/6 (83%)
1000 BD	9 ^a	25% (2)	38% (3)	1/3 (33%)	3/3 (100%)
2000 BD	5 ^b	NA	NA	1/2 (50%)	2/2 (100%)

^a1 pt. ^b All pts non evaluable.

4512

Poster Discussion Session (Board #1), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Combination of antiangiogenic therapy and cytotoxic chemotherapy for sarcomatoid renal cell carcinoma.**

M Dror Michaelson, David F. McDermott, Michael B. Atkins, Daniel C. Cho, Kara M. Olivier, Abraham B. Schwarzbarg, Toni K. Choueiri; Massachusetts General Hospital Cancer Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; Beth Israel Deaconess Medical Center, Boston, MA; Massachusetts General Hospital, Boston, MA; Cancer Center of South Florida, Lake Worth, FL

Background: Numerous treatment options exist for metastatic renal cell carcinoma (mRCC), but optimal treatment for patients (pts) with sarcomatoid features remains undefined. Sarcomatoid differentiation is a particularly unfavorable prognostic feature in mRCC. Cytotoxic chemotherapy has modest activity, with a response rate of 16% for doxorubicin plus gemcitabine (Gem). Retrospective data has suggested a response rate of 10% for antiangiogenic therapy. We prospectively studied the combination of antiangiogenic therapy, sunitinib (Su), with Gem chemotherapy in this mRCC subpopulation. **Methods:** Pts with mRCC and sarcomatoid differentiation were enrolled in a phase 2 clinical trial at 3 institutions. Treatment consisted of 21-day cycles of Su, 37.5 mg on a 2 weeks on/1 week off schedule, along with Gem 1000 mg/m² on days 1 and 8. The primary endpoint was radiographic response rate (RR) by RECIST. Secondary endpoints included time to disease progression (TTP), safety, and overall survival (OS). **Results:** Among 35 pts treated in total, 7 were classified as MSKCC good risk, 26 as intermediate risk, and 2 as poor risk. There were 10 partial responses and 1 complete response, for a confirmed RR of 30%. An additional 10 pts exhibited stable disease (clinical benefit rate 60%). Among the 10 pts who had progressive disease as their best response, the majority had underlying non-clear cell histology. Median TTP was 3.5 months (range 0.5-12). Eight pts discontinued due to adverse events (AEs). The most common treatment-emergent grade 3 or higher AEs were neutropenia (8 pts), fatigue (5), anemia (2), and hypertension (2). No treatment-related deaths occurred. Median OS was 11 months (range 1-38+). **Conclusions:** To our knowledge, this is the largest prospective trial combining cytotoxic chemotherapy and antiangiogenic therapy in patients with RCC and sarcomatoid features. Our results suggest that combination therapy may be more efficacious than either treatment alone in this subtype of mRCC and supports an ongoing intergroup trial (NCT01164228). Further research is necessary to define prognostic factors, including histologic and molecular biomarkers, for distinct subpopulations within this heterogeneous disease. Clinical trial information: NCT00556049.

4513

Poster Discussion Session (Board #2), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Tivozanib in patients treatment-naïve for metastatic renal cell carcinoma: A subset analysis of the phase III TIVO-1 study.**

Cora N. Sternberg, Tim Eisen, Piotr Tomczak, Andrew Louis Strahs, Brooke Esteves, Anna Berkenblit, Robert John Motzer; Department of Medical Oncology, San Camillo-Forlanini Hospital, Rome, Italy; Cambridge University Health Partners, Cambridge, England; Clinical Hospital No. 1 of the Poznan University of Medical Sciences, Poznan, Poland; AVEO Oncology, Cambridge, MA; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Tivozanib (T) is a potent, selective inhibitor of all three VEGF receptors with a long half-life of 4.5–5.1 days. Superior progression-free survival (PFS) and overall response rate (ORR) with T versus sorafenib (S) were demonstrated in a Phase III trial (TIVO-1) in patients (pts) with metastatic renal cell carcinoma (mRCC) (in ITT population, PFS: 11.9 vs 9.1 months HR=0.797, 95% CI 0.639–0.993; $P=0.042$; ORR: 33% vs 23%, $P=0.014$). Hypertension was more common with T, while lower rates of certain off-target AEs and fewer dose adjustments relative to S were reported (*J Clin Oncol* 2012;30[suppl]: Abstract 4501). Here we present efficacy and safety analyses for the pre-specified subset of pts who received no prior systemic therapy for mRCC. **Methods:** In the ITT population (N=517), pts were treatment-naïve or had received no more than 1 prior systemic therapy for metastatic disease; pts receiving prior VEGF- or mTOR-targeted therapy were excluded. Pts were randomized 1:1 to T 1.5 mg/d (once daily, 3 weeks on, 1 week off) or S 400 mg/d (twice daily, continuously). Of these, 181 pts (70%) in each treatment arm had not received prior systemic therapy for mRCC. **Results:** In pts who received no prior systemic therapy for mRCC, demographics were well balanced between the 2 arms. Median PFS was 12.7 for T vs 9.1 months for S (HR=0.756, 95% CI 0.580–0.985, $P=0.037$). ORR was 34% for T vs 24% for S ($P=0.038$). The most common adverse event (AE; All grades/Grade ≥ 3) for T was hypertension (T: 40%/25% vs S: 35%/18%), suggesting “on-target” biological activity and was manageable medically, while the most common AE for S was hand-foot syndrome (T: 11%/2% vs S: 52%/16%). Other common AEs were diarrhea (T: 22%/2% vs S: 32%/7%), fatigue (T: 19%/6% vs S: 15%/3%), and weight decrease (T: 18%/1% vs S: 17%/2%). Dose reduction (T: 12% vs S: 42%) and interruption (T: 18% vs S: 35%) rates were lower in the T arm and similar to the ITT population. **Conclusions:** T demonstrated significant improvement in PFS and ORR compared with S in pts who had received no prior systemic therapy for metastatic RCC. T was generally well tolerated, with low rates of treatment-related reduction/interruption in this pre-specified subgroup of pts. Clinical trial information: NCT01030783.

Survival, safety, and response duration results of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in a phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): Long-term patient follow-up.

Charles G. Drake, David F. McDermott, Mario Sznol, Toni K. Choueiri, Harriet M. Kluger, John D. Powderly, David C. Smith, Vindira Sankar, Andres A. Gutierrez, Jon M. Wigginton, Georgia Kollia, Ashok Kumar Gupta, Michael B. Atkins; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Dana-Farber Cancer Institute, Boston, MA; Yale Cancer Center, New Haven, CT; Yale University, New Haven, CT; Carolina BioOncology Institute, Huntersville, NC; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Bristol-Myers Squibb, Princeton, NJ; Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC

Background: Programmed death-1 (PD-1) is an immune checkpoint receptor that negatively regulates T-cell activation. PD-L1, a PD-1 ligand, has been associated with poor prognosis in mRCC pts. In a phase I study of nivolumab, a PD-1 receptor blocking antibody, in pts with previously treated mRCC and other solid tumors, an MTD was not reached at 10 mg/kg IV Q2WK. Cohorts of mRCC pts were expanded at the 1 and 10 mg/kg dose levels. **Methods:** Pts received nivolumab for ≤ 12 cycles (4 doses/cycle) until unacceptable toxicity, progression, or complete response. We report overall survival (OS), updated response data, and long-term safety for the mRCC cohorts from a data analysis in July 2012. **Results:** 34 pts with mRCC were treated at 1 mg/kg (n=18) or 10 mg/kg (n=16). 44% of pts had received ≥ 3 prior therapies (74% prior antiangiogenic therapy; 59% prior immunotherapy). Median OS across doses has not yet been reached. Median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥ 1 year. The incidence of grade 3-4 related adverse events for the RCC cohort was 21% and included hypophosphatemia (6%) and respiratory disorders (6%), with no confirmed-drug related deaths or grade 3 pneumonitis. Treatment discontinuation due to drug-related AEs occurred in 18/304 (6%) of patients in the overall treated population. **Conclusions:** Nivolumab produced durable survival and responses in a subset of heavily pretreated mRCC pts, with an acceptable safety profile, even after long term continuous dosing. Overall survival appears promising for this population of pts. These findings provide the basis for an ongoing randomized phase III trial of nivolumab in mRCC (NCT01668784). Follow-up data through a February 2013 cutoff is being collected. Clinical trial information: NCT00730639.

Dose, mg/kg	ORR, n (%)	Stable disease rate ≥ 24 weeks, n (%)	PFS rate at 24 weeks, %
1	5 (28)	4 (22)	50
10	5 (31)	5 (31)	67
1-10	10 (29)	9 (27)	58
OS rate ^a	% (95% CI)		Pts at risk, n
1 Yr	70 (55-86)		22
2 Yr	52 (32-72)		7
3 Yr	52 (32-72)		1

^a All doses. OS estimates after 1 year reflect heavy censoring and shorter follow-up for pts enrolling in the later portion of the study.

4515

Poster Discussion Session (Board #4), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**A phase II study of intermittent sunitinib (S) in previously untreated patients (pts) with metastatic renal cell carcinoma (mRCC).**

Brian I. Rini, Laura S. Wood, Paul Elson, Hui Zhu, Namita Chittoria, Kriti Mittal, Robert Dreicer, Timothy D. Gilligan, Shetal N. Shah, Jorge A. Garcia; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Cleveland Clinic, Cleveland, OH; Imaging Institute, Cleveland Clinic Foundation, Cleveland, OH

Background: S as initial treatment in mRCC is limited by balancing acute and chronic toxicity with clinical benefit. Pre-clinical and retrospective clinical data support that extended treatment breaks are feasible without a reduction in efficacy. **Methods:** Pts with treatment-naïve clear cell mRCC were enrolled on a prospective phase II trial and initially treated with 4 cycles of S (50 mg 4/2). Pts with $\geq 10\%$ reduction in tumor burden (TB) following 4 cycles had S held, with CT scans approximately every 10 weeks. S was re-initiated for 2 cycles in those pts with an increase in TB by $\geq 10\%$ and again held with $\geq 10\%$ TB reduction. This intermittent S dosing continued until RECIST-defined disease progression while on S. The primary objective was feasibility of intermittent S, defined as the proportion of eligible pts who underwent intermittent therapy. The alternative hypothesis was a feasibility of $> 80\%$ vs. a null hypothesis of $< 50\%$ ($\alpha=0.05$; power 80%). **Results:** Thirty-six pts were enrolled; 70% male, median age 60, 95% PS 0/1 and 32% favorable/65% intermediate by Heng criteria. Twenty pts were eligible for intermittent therapy and all pts (100%) entered the intermittent phase. Pts were not eligible for intermittent S due to PD ($n=13$); toxicity ($n=1$) or w/d of consent ($n=2$) prior to end of cycle #4. Sixteen pts (80%) had $\geq 10\%$ TB increase off S with a median (range) increase of 1.5 cm (1.1-2.5) compared to the TB immediately prior to stopping S, considering all off periods. Four pts did not have $\geq 10\%$ TB increase off S (3 pts after the 1st off period; off for 12, 8 and 5 months to date and 1 pt after the 2nd off period; off for 8 months prior to restarting S). Most pts exhibited a stable saw tooth pattern of TB reduction on S and TB increase off S. No pt had RECIST-defined PD while on S, but 2 pts were taken off extended breaks due to gradual TB increase over time, and 1 pt developed new CNS mets during the 2nd off period. The objective response rate was 53%. Toxicity was typical for S and completely resolved during treatment breaks. **Conclusions:** S dosing with periodic extended time off drug is feasible and associated with reduction in toxicity during the off periods. Clinical efficacy does not appear to be compromised. Clinical trial information: NCT01158222.

4516

Poster Discussion Session (Board #5), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**A phase II clinical trial examining the impact of neoadjuvant axitinib on primary tumor response in patients with locally advanced clear cell renal cell carcinoma.**

Jose A. Karam, Catherine E Devine, Marisa Lozano, Nizar M. Tannir, Kamran Ahrar, Pheroze Tamboli, Christopher G. Wood; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Previous studies have shown minimal impact of TKIs on primary renal tumor downsizing. Axitinib is a VEGFR TKI that has been recently approved for use in patients with metastatic clear cell renal cell carcinoma (RCC). In this prospective phase II trial, we sought to investigate the safety and role of axitinib in downsizing tumors in patients with non-metastatic renal cell carcinoma, prior to undergoing surgical resection. **Methods:** Patients with locally advanced (clinical stage T2-T3b N0 M0) biopsy-proven clear cell RCC were eligible for this phase II clinical trial. The primary outcome was objective response rate (using RECIST) following the administration of axitinib for 12 weeks prior to undergoing radical nephrectomy. Secondary outcomes included safety, tolerability, and feasibility of administration of axitinib in this patient population. Patients were given axitinib 5mg PO BID, and dose titration was allowed. Axitinib was continued until 36 hours prior to surgery. A dedicated radiologist independently reviewed all CT scans to evaluate for response using RECIST. **Results:** The study goal of enrolling 24 patients has been recently reached. At present, nineteen patients have completed the studies required for assessment of the primary outcome and are hereby reported. Fifteen patients were males, and four were females. Median age was 61 years (range 42-83 years). All patients had biopsy-proven clear cell RCC. All 19 patients continued axitinib for 12 weeks, and underwent surgery as planned without delay. Adverse events of any grade were: arthralgia in 6, hypothyroidism in 14, fatigue in 15, and hypertension in 16 patients. No wound complications occurred after surgery. Nine patients (47%) experienced a partial response by RECIST, and 10 patients had stable disease. There was no progression of disease while on axitinib. **Conclusions:** Axitinib is well tolerated in the neoadjuvant setting in patients with planned surgery for locally advanced non-metastatic clear cell RCC. The drug showed tumor downsizing activity when given for 12 weeks prior to surgery. Adverse events of any grade were common and easily manageable with routine care. Clinical trial information: NCT01263769.

4517

Poster Discussion Session (Board #6), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Randomized phase II CTEP study of MK2206 versus everolimus in VEGF inhibitor refractory renal cell carcinoma patients.**

Eric Jonasch, Paul Gettys Corn, Lance C. Pagliaro, Primo Lara, Xuemei Wang, Kim-Anh Do, Racheal Garza, Shelly Bird, Joseph J. Drabick, Valerie Marcott, David Quinn, Austin Doyle, Nizar M. Tannir; The University of Texas MD Anderson Cancer Center, Houston, TX; Division of Hematology and Oncology, UC Davis Comprehensive Cancer Center, Sacramento, CA; The University Of Texas MD Anderson Cancer Center, Houston, TX; Penn State Hershey Cancer Institute, Hershey, PA; University of Southern California, Los Angeles, CA; National Cancer Institute, Rockville, MD

Background: Up-regulation of the phosphoinositide-3 phosphate kinase (PI3K) pathway is associated with poorer prognosis in pts with advanced RCC. We hypothesized that optimal blockade of AKT in pts refractory to anti-VEGF therapy eliminates key drivers of tumor growth and proangiogenic signaling, and will prolong progression-free survival (PFS). We tested whether MK-2206, a selective allosteric inhibitor of AKT, will yield superior PFS to everolimus in anti-VEGF therapy refractory RCC pts. **Methods:** Eligible pts with metastatic RCC who progressed on an anti-VEGF agent were randomized (2:1 ratio) to receive MK2206 or everolimus. Up to two prior therapies allowed. Primary endpoint was PFS. The study had 80% power to detect a 67% increase in PFS with MK2206 over everolimus (8.2 vs. 4.9 mo) with a 1-sided log-rank at $\alpha = 0.10$. One interim futility analysis was planned. Secondary endpoints: safety, overall survival, & response rate. Tumor tissue was collected in correlative analyses. **Results:** A total of 43 patients were accrued; 42 were evaluable for efficacy. Demographics: Male, 77%; White, 81%; median age 62 (range 41-83). MK2206 was held in 3 pts due to grade 3 rash; 1 came off study for rash. No everolimus pt discontinued study drug due to AEs. 30 events had occurred at first futility analysis. The 1-sided log-rank p-value for rejecting null hypothesis was 0.979, exceeding p-value boundary of 0.6413 for stopping trial. Median PFS for MK2206 was 3.65 mo (95%CI 1.77-5.52) and 7.43 mo for everolimus (95%CI 1.84-13.27). Two out of 29 MK2206 pts demonstrated dramatic response with greater than 50% disease regression and PFS of 8 months and 6 months (ongoing). **Conclusions:** Monotherapy with MK2206 was not superior to everolimus in this randomized, phase II study. However, dramatic response to MK2206 was seen in a subset of patients. Planned translational studies to allow genotype-phenotype correlations may help explain this observation. Clinical trial information: NCT01239342.

4518

Poster Discussion Session (Board #7), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM

Gene expression profiling in bladder cancer to identify potential therapeutic targets.

Syed A. Hussain, Daniel H. Palmer, Wing Kin Syn, Joseph J Sacco, Bryony Lloyd, Puthen Jithesh, John R. Arrand, Darren Barton, Jawaher Ansari, David R Sibson, Nicholas David James; University of Liverpool, Liverpool, United Kingdom; The Institute of Hepatology, London, United Kingdom; Cancer Research UK Institute for Cancer Studies, Birmingham, United Kingdom; Cancer Research UK Clinical Trials Unit, School of Cancer Sciences, Birmingham, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; University of Birmingham, Birmingham, United Kingdom

Background: Characterization of gene expression patterns in bladder cancer (BC) allows the identification of pathways involved in its pathogenesis, and may stimulate the development of novel therapies targeting these pathways. **Methods:** Between 2004 and 2005, cystoscopic bladder biopsies were obtained from 19 patients and 11 controls. These were subjected to whole transcript-based microarray analysis. Unsupervised hierarchical clustering was used to identify samples with similar expression profiles. **Results:** Hierarchical clustering defined signatures, which differentiated between cancer and normal, muscle-invasive or non-muscle invasive cancer and normal, g1 and g3. Pathways associated with cell cycle and proliferations were markedly upregulated in muscle-invasive and grade 3 cancers. Genes associated with the classical complement pathway were downregulated in non-muscle invasive cancer. Osteopontin was markedly overexpressed in invasive cancer as compared to normal tissue. **Conclusions:** This study contributes to a growing body of work on gene expression signatures in BC. The data support an important role for osteopontin in BC, and identify several pathways worthy of further investigation.

Genes showing >5 fold increase in expression in MIBC versus normal tissue (FDR p < 0.05).

Gene	Gene ID	P value	Fold change (invasive vs adjacent tissue)
Secreted phosphoprotein 1/osteopontin	SPP1	0.000278942	10.9828
Anillin, actin binding protein	ANLN	0.000100265	8.49928
TPX2, microtubule-associated, homolog (Xenopus laevis)	TPX2	0.000281361	7.51978
Topoisomerase (DNA) II alpha 170kDa	TOP2A	0.000327502	7.07702
Matrix metalloproteinase 1	MMP1	4.53E-05	6.48753
Gasdermin C	GSDMC	2.47E-06	6.02525
N serpin peptidase inhibitor, clade B, member 13	SERPINB13	5.94E-06	5.98179
Chloride channel accessory 2	CLCA2	0.00335894	5.61433
Antigen identified by monoclonal antibody Ki-67	MIK167	0.000992039	5.43103
Kinesin family member 23	KIF23	0.000252044	5.32734
Serpin peptidase inhibitor, clade B (ovalbumin), member 3	SERPINB3	0.00367834	5.26492
Entomere protein F, 350/400ka (mitosin)	CENPF	0.00190184	5.1824
Family with sequence similarity 83, member A	FAM83A	3.54E-06	5.16728
Cyclin E2	CCNE2	0.000232145	5.1512

4519

Poster Discussion Session (Board #8), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Association of IL8 polymorphisms with overall survival in patients with renal cell carcinoma in COMPARZ (pazopanib versus sunitinib phase III study).**

Chun-fang Xu, Toby Johnson, Toni K. Choueiri, Keith C. Deen, Zhengyu Xue, Colin F. Spraggs, Arundathy N. Bartlett-Pandite, Christopher Carpenter, Robert John Motzer; GlaxoSmithKline, Harlow, United Kingdom; GlaxoSmithKline, Uxbridge, United Kingdom; Dana-Farber Cancer Institute, Boston, MA; GlaxoSmithKline, Collegeville, PA; GlaxoSmithKline, Research Triangle Park, NC; GlaxoSmithKline Research and Development, Collegeville, PA; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Pazopanib and sunitinib are angiogenesis inhibitors approved for treatment of advanced renal cell carcinoma (RCC). COMPARZ, a phase III randomized clinical trial comparing pazopanib vs sunitinib for RCC, demonstrated similar efficacies for the two therapies but safety profiles differed. Our genetic analyses of previous pazopanib clinical trials found that *IL8* polymorphisms may be associated with progression-free survival (PFS) and overall survival (OS). We attempted to validate these associations in the COMPARZ study. **Methods:** Of the 1110 participants in COMPARZ, 724 (65%) provided consent and DNA for pharmacogenetic analyses (pazopanib, N = 371; sunitinib, N = 353). Associations of *IL8* polymorphisms (rs1126647 and rs4073) with PFS and OS were tested using the Cox proportional hazards model with baseline factors as covariates in a combined analysis of all patients and also separately in pazopanib-treated and sunitinib-treated patients. One-tailed *P* values were calculated for effects in the same direction as previously observed. **Results:** For PFS there was no significant association in the combined analysis or in pazopanib-treated patients, but there was a significant association in sunitinib-treated patients (*P* = 0.017). For OS there were significant associations in the combined analysis (*P* = 0.010) and in sunitinib-treated patients (*P* = 0.0043) but not in pazopanib-treated patients (*P* = 0.30). Hazard ratios (HRs) for genetic effects were not significantly different between sunitinib- and pazopanib-treated patients (two-tailed *P* = 0.23 for genotype-by-treatment interaction). Kaplan-Meier plots suggested a recessive genetic model in the combined data set, with median OS (95% CI) 23.7 months (15.4–29.1) for rs1126647 TT genotype compared to 35.5 months (30.8–∞) for AA or AT genotypes (HR = 1.66, *P* = 0.0007). Similar associations were seen for rs4073. **Conclusions:** Germline variants in *IL8* are associated with survival outcome in patients with RCC who have received angiogenesis inhibitors. These findings may provide additional scientific insights in making treatment decisions and developing alternative therapies.

Identification of predictive biomarkers of overall survival (OS) in patients (pts) with advanced renal cell carcinoma (RCC) treated with interferon alpha (I) with or without bevacizumab (B): Results from CALGB 90206 (Alliance).

Andrew B. Nixon, Susan Halabi, Ivo Shterev, Mark Starr, John C Brady, Janice P. Dutcher, Judith O. Hopkins, Herbert Hurwitz, Eric Jay Small, Brian I. Rini, Phillip G. Febbo, Daniel J. George, for the Alliance for Clinical Trials in Oncology; Duke University Medical Center, Durham, NC; Department of Biostatistics and Bioinformatics, Duke University and Alliance Statistical and Data Center, Durham, NC; St Luke's-Roosevelt Hospital Center, Continuum Cancer Centers of New York, New York, NY; Forsyth Regional Cancer Center, Winston-Salem, NC; University of California, San Francisco, San Francisco, CA; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: CALGB 90206 was a phase III trial of 732 pts with RCC comparing B+I versus I alone demonstrating no difference in OS. To date, there are no validated predictive biomarkers for B in RCC. For this reason, baseline plasma samples from CALGB 90206 pts were analyzed to identify and test predictive markers for B+I in RCC pts. **Methods:** Baseline EDTA plasma samples from 424 consenting pts were analyzed using an optimized multiplex ELISA platform for 32 candidate factors related to tumor growth, angiogenesis, and inflammation. The data were randomly split into training (n=286) and validation (n=138) sets. The proportional hazards model was used to test for treatment-marker interactions of OS. The estimated coefficients from the training set were used to compute a risk score (RS) for each pt in the validation set. The RS classified pts by risk in the validation set. The model was assessed for its predictive accuracy using area under the curve (AUC). **Results:** A statistically significant 3-way interaction between interleukin-6 (IL-6), hepatocyte growth factor (HGF) and treatment was observed in the training set ($p<0.0001$). The median levels of IL-6 and HGF in the training set were 8.4 pg/ml and 89 pg/ml, respectively. In the validation set, the RS was predictive of OS ($p<0.001$) with the high and low risk groups having a median OS of 10 months and 32 months, respectively. The AUC in the validation set was 0.82 (95% CI=0.77-0.88). The median OS (in months) by median levels of IL-6 and HGF stratified by treatment arm in the validation set is presented in the table with associated 95% CI (NR=not reached). **Conclusions:** IL-6 and HGF are predictive for OS in RCC patients treated with B+I and a RS based on these factors identified patients who benefitted most from B. If independently validated, this novel RS could guide clinical decisions and pt selection in future RCC trials.

Validation set: I Arm (n=67)		
	Low HGF (n=36)	High HGF (n=31)
Low IL-6 (n=43)	27 (19-40)	18 (11-NR)
High IL-6 (n=24)	11 (6-NR)	6 (5-25)
Validation set: B+I Arm (n=71)		
	Low HGF (n=36)	High HGF (n=35)
Low IL-6 (n=34)	55 (42-NR)	16 (14-NR)
High IL-6 (n=37)	16 (12-NR)	12 (8-32)

4521

Poster Discussion Session (Board #10), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Pdl-1/pdl-3 (programmed death ligand-1/3) tissue expression and response to treatment with IL2 and antiangiogenic therapies.**

Alexandra S. Bailey, SuChun Cheng, Eugene D. Kwon, Bradley C. Leibovich, Sabina Signoretti, Janice P. Dutcher, Leonard Joseph Appleman, Jeffrey Alan Sosman, Kim Allyson Margolin, Joseph Clark, Nikhil I. Khushalani, Brendan D. Curti, Marc S. Ernstoff, Allan J. Pantuck, Ulka N. Vaishampayan, Theodore Logan, David F. McDermott, Michael B. Atkins, Cytokine Working Group; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute/Harvard Cancer Center, Boston, MA; Mayo Clinic, Rochester, MN; Brigham and Women's Hospital/Harvard Medical School, Boston, MA; St Luke's-Roosevelt Hospital Center, Continuum Cancer Centers of New York, New York, NY; University of Pittsburgh, Pittsburgh, PA; Vanderbilt University Medical Center, Nashville, TN; University of Washington, Seattle, WA; Loyola University Medical Center, Maywood, IL; Roswell Park Cancer Institute, Buffalo, NY; Earle A. Chiles Research Institute, Portland, OR; Dartmouth Hitchcock Medical Center/Norris Cotton Cancer Center, Lebanon, NH; Institute of Urologic Oncology, Department of Urology, UCLA, Los Angeles, CA; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; Dana-Farber Cancer Institute, Boston, MA; Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC

Background: Expression of PDL1 by RCC has been associated with aggressive histology and poor survival. Tissue obtained from the patients enrolled in the IL-2 Select Trial, a prospective, single arm, multicenter CWG study, was analyzed by IHC to determine if PDL1 or PDL3 expression predicted for response to initial or subsequent therapy. **Methods:** Paraffin embedded tumor tissue was stained for PDL1 and PDL3 expression, and results were correlated with RECIST defined response to IL2 treatment. Tumor tissue was considered positive for PDL1 if >5% of the tumor membranes stained for the marker. A cutoff of 10% was used for PDL3. Duration of subsequent VEGFR/mTOR inhibitor therapy was also correlated with tissue PDL1/3 expression. **Results:** 120 eligible pts were enrolled; 115 had clear cell histology. The overall response rate (ORR) to IL2 was 25% (30/120) with a median OS of 40.6 months. 113 tumors were stained. 18 (16%) were PDL1+. ORR was 19% and 50% in the patients PDL1- and PDL1+ tumors, respectively (p=0.012). 85 (75%) tumors were PDL3+. ORR was 10.7% and 29.4% in the PDL3- and PDL3+ tumors, respectively (p=0.075). In the 17 patients who were positive for both PDL1 and PDL3, ORR was 52.9%. In the 27 pts who were negative for both PDL1 and PDL3, ORR was 11.1%. 69 patients received at least 1 dose of a VEGFR TKI as next therapy following IL2 treatment. 66 tumors were stained. Pts who were PDL1+/PDL3+ had a shorter duration on VEGFR TKI therapy compared to pts who were PDL1-/PDL3- (see Table). **Conclusions:** This small, retrospective analysis suggests that PDL1 and PDL3 tissue expression may predict for better response to IL2. PDL1 expression has been suggested as a possible predictor of response to anti-PD1 therapy. The current data suggests that its expression may predict for benefit to other immune therapies. PDL3 (+/- PDL1) expression appears to correlate to less benefit from subsequent VEGFR TKI therapy. Funded by NCI SPORE Grant # 5 P50 CA101942-08.

PDL1/3 expression	Median time on VEGFR TKI Tx (mo)	Median time on 1st VEGFR TKI Tx (mo)
PDL1+/PDL3+	9.0	4.9
PDL1-/PDL3+	21.3	6.9
PDL1-/PDL3-	42.5	14.2

4522

Poster Discussion Session (Board #11), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**A validated 34-gene signature for assessing risk of recurrence in clear cell renal cell carcinoma.**

Kimryn Rathmell, Samira A Brooks, Angela Rose Brannon, Joel S Parker, Jennifer C Fisher, Oishee Sen, Matthew Edward Nielsen; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Memorial Sloan-Kettering Cancer Center, New York, NY; Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: The objective of this study is to create a molecular tool that can be applied widely to clinical specimens using existing transcript signatures for use in clinical risk prediction of clear cell Renal Cell Carcinoma (ccRCC) to improve personalized disease management. **Methods:** We developed a 34-gene subtype predictor to classify clear cell tumors according to two subtypes, clear cell A (ccA) or B (ccB). The training set consisted of 72 ccRCC microarray-analyzed tumor samples that had previously been classified by unsupervised clustering and logical analysis of data (LAD). The predictor was developed from a panel of genes significantly expressed in ccA and ccB tumors and associated with prognosis. The prognostic value of the algorithm was corroborated in RNA-sequencing data from 379 ccRCC samples from The Cancer Genome Atlas (TCGA) and further validated using the NanoString platform with a cohort of 163 archival fixed samples collected at the University of North Carolina. **Results:** Risk associated molecular subtypes, ccA and ccB, were classified in TCGA and NanoString cohorts. Subtype classification showed significant prognostic outcomes for overall survival ($p < .001$), cancer-specific survival ($p = .003$), and recurrence-free survival ($p < .05$) and remained significant in multivariate analyses that included age at diagnosis, gender, ethnicity, pathologic stage, and histologic grade. A prognostic model was built for overall and recurrence-free survival for non-metastatic ccRCC patients within the context of subtype and clinical characteristics. **Conclusions:** The ccA and ccB subtypes significantly added prognostic information to clinical parameters, particularly for non-metastatic ccRCC patients. The subtypes can be used for future analyses involving risk for developing metastatic disease and cancer-specific outcomes. This research was supported with a grant from the American Association for Cancer Research, and the UNC Lineberger Comprehensive Cancer Center Cancer Cell Biology Training Grant.

4523

Poster Discussion Session (Board #12), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Association of IGF1R overexpression (OE) with outcome in invasive urothelial carcinoma (UC) of urinary bladder.**

Nilda Gonzalez-Ribbon, Jenny J. Kim, Alcides Chaux, Enrico Munari, Shiela F. Faraj, Carla Ellis, Rajni Sharma, Trinity Bivalacqua, Mark Schoenberg, Michael Anthony Carducci, George J. Netto; Johns Hopkins University, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Office of Scientific Investigations, Norte University, Asuncion, Paraguay; Johns Hopkins Hospital, Baltimore, MD; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; The Johns Hopkins University, Baltimore, MD

Background: Insulin-like growth factor-1 receptor (IGF1R) is a transmembrane tyrosine kinase receptor involved in cell proliferation and differentiation. IGF1R is overexpressed in several tumors including UC and is currently under investigation as a target of Rx. We here explore IGF1R expression in UC, its association with clinicopathologic parameters and prognostic role. **Methods:** Five tissue microarrays (TMA) were constructed from 100 cystectomy specimens performed for invasive UC at our institution (1994 to 2007). Formalin-fixed paraffin-embedded paired tumor and benign samples were spotted 3-4 times each. Membranous IGF1R staining was evaluated using immunohistochemistry (G11, Ventana Medical Systems). A scoring method analogous to that of Her2 expression in breast cancer was used and the highest score was assigned to each tumor. IGF1R was considered overexpressed in cases with score 1. Endpoints of the study included overall survival (OS) and disease-specific survival (DSS). Patients were followed-up for a median of 33.5 months (range 1, 141 months). **Results:** IGF1R OE was found in 62% of UC. No differences were noted between normal urothelium and UC regarding IGF1R OE (74% vs. 60%; $P=0.14$). IGF1R OE was more frequent in tumors from African-American patients compared to Caucasians (100% vs. 59%, $P=0.04$). Tumors at stage pT4 overexpressed IGF1R more frequently than tumors at stages pT1-pT3 (71% vs. 29%, $P=0.005$). No association with other analyzed clinicopathologic parameters such as patient's age or gender, muscularis propria invasion, or lymph node metastasis was found. OS and disease-specific survival (DSS) rates were 58% and 69%, respectively. Patients with tumors overexpressing IGF1R had a lower OS and DSS compared to those without IGF1R OE (Mantel-Cox $P=0.0007$ and $P=0.006$, respectively). Using Cox proportional hazards regression, IGF1R OE remained a significant predictor of OS ($HR=3.49$, $P=0.001$) and DSS ($HR=3.54$, $P=0.007$) after adjusting for pathologic stage. **Conclusions:** OE of IGF1R was found in 62% of UC. High stage tumors overexpressed IGF1R more frequently than low stage tumors. Further, IGF1R OE was a significant independent predictor of OS and DSS in invasive UC.

Nomogram to estimate the activity of second-line therapy for advanced urothelial carcinoma (UC).

Guru Sonpavde, Gregory Russell Pond, Neeraj Agarwal, Toni K. Choueiri, Angela Q. Qu, Ronan Fougeray, Yacine Salhi, David J. Vaughn, Nicholas David James, Guenter Niegisch, Peter Albers, Matt D. Galsky, Yu-Ning Wong, Walter Michael Stadler, Peter H. O'Donnell, Nicholas J. Vogelzang, Srikala S. Sridhar, Yoo-Joung Ko, Cora N. Sternberg, Joaquim Bellmunt; University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; McMaster University, Hamilton, ON, Canada; University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; Dana-Farber Cancer Institute, Boston, MA; Institut de Recherche Pierre Fabre, Boulogne, France; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; University of Birmingham, Birmingham, United Kingdom; Department of Urology, Heinrich-Heine-University, Duesseldorf, Germany; The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY; Fox Chase Cancer Center, Philadelphia, PA; The University of Chicago, Chicago, IL; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada; Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada; San Camillo-Forlanini Hospital, Rome, Italy; University Hospital del Mar, Barcelona, Spain

Background: Prognostic factors may impact on endpoints used in phase II trials of second-line therapy for advanced UC. We aimed to study the impact of prognostic factors (liver metastasis [LM], anemia [Hb<10 g/dl], ECOG-performance status [PS] ≥ 1 , time from prior chemotherapy [TFPC]) on PFS6 and RR. **Methods:** Twelve phase II trials evaluating second-line chemotherapy and/or biologics (n=748) in patients with progressive disease were pooled. PFS was defined as tumor progression or death from any cause. PFS6 was defined from the date of registration and calculated using the Kaplan-Meier method. RR was defined using RECIST 1.0. A nomogram predicting PFS6 was constructed using the RMS package in R (www.r-project.org). **Results:** Data regarding progression, Hb, LM, PS and TFPC were available from 570 patients. The mean age was 65.1 years, 45.3% had ECOG-PS ≥ 1 , 30.2% had LM, 14.6% had anemia and TFPC was <6 months (mo) in 60.2%. The overall median PFS was 2.7 mo, PFS6 was 22.2% (95% CI: 18.8-25.9) and RR was 17.5% (95% CI: 14.5%-20.9%). For every unit increase in risk group, the hazard of progression increased by 41% and the odds of response decreased by 48% (Table). A nomogram was constructed to predict PFS6 on an individual patient level. **Conclusions:** PFS6 and RR vary as a function of prognostic factors in patients receiving second-line therapy for advanced UC. A nomogram incorporating prognostic factors might facilitate the evaluation of activity across phase II trials enrolling heterogeneous populations and can help to select and stratify patients for phase III evaluation of suitable agents.

Parameter	N	6-month PFS % (95% CI)	Response rate (95% CI)
No. of risk factors=0	153	34.6 (26.9-42.4)	28.8 (21.7-36.6)
1	205	22.0 (16.4-28.2)	18.5 (13.5-24.5)
2	146	17.0 (11.3-23.8)	10.3 (5.9-16.4)
3-4	66	4.9 (1.3-12.3)	4.6 (1.0-12.7)
Hb ≥ 10 g/dL	487	24.2 (20.4-28.2)	18.9 (15.5-22.7)
Hb <10 g/dL	83	10.5 (4.9-18.4)	9.6 (4.3-18.1)
No liver metastases	398	26.6 (22.3-31.2)	20.6 (16.7-24.9)
Liver metastases	172	11.6 (7.2-17.1)	10.6 (6.3-16.0)
ECOG PS=0	312	25.4 (20.5-30.5)	20.8 (16.5-25.8)
ECOG PS ≥ 1	258	18.5 (13.9-23.6)	13.6 (9.6-18.4)
TFPC<6 months	343	16.6 (12.7-21.0)	11.4 (8.2-15.2)
TFPC ≥ 6 months	227	30.5 (24.5-36.7)	26.9 (21.2-33.1)

4525

Poster Discussion Session (Board #14), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Treatment patterns and outcomes in “real world” patients (pts) with metastatic urothelial cancer (UC).**

Matt D. Galsky, Simon Chowdhury, Joaquim Bellmunt, Yu-Ning Wong, Federica Recine, Sumanta Kumar Pal, Erin L. Moshier, Sylvain Ladoire, Ugo De Giorgi, Evan Y. Yu, Guenter Niegisch, Simon J. Crabb, Mabel A Mardones, Andrea Necchi, Ali Reza Golshayan, Aristotelis Bamias, Roy Mano, Lauren Christine Harshman, Thomas Powles, Jonathan E. Rosenberg, RISC Investigators; Division of Hematology and Medical Oncology, The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY; Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; University Hospital del Mar, Barcelona, Spain; Fox Chase Cancer Center, Philadelphia, PA; San Camillo-Forlanini Hospital, Rome, Italy; City of Hope, Duarte, CA; Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; Georges-François Leclerc Cancer Center, Dijon, France; IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola, Italy; Fred Hutchinson Cancer Research Center, Seattle, WA; Department of Urology, Heinrich-Heine-University, Duesseldorf, Germany; University of Southampton, Faculty of Medicine, Southampton, United Kingdom; Huntsman Cancer Institute, Salt Lake City, UT; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Medical University of South Carolina, Charleston, SC; HECOG and University of Athens, Athens, Greece; Rabin Medical Center, Tel Aviv, Israel; Dana-Farber Cancer Institute, Boston, MA; Barts and the London, London, United Kingdom; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Most studies reporting outcomes of pts with metastatic UC are derived from clinical trial data, potentially limiting the breadth/generalizability of the findings. To explore patterns of care/outcomes in “real world” pts, we initiated an international retrospective cohort study. **Methods:** Data were collected via an electronic data capture platform from 23 centers. Eligible pts had UC (at least muscle-invasive) and were initially evaluated from 1/1/2006-1/1/2011. Parameters were subjected to regression analysis to identify prognostic variables. **Results:** By 12/18/12, 1905 pts were enrolled. Among 1077 with metastatic UC, median age was 67 (IQR 60-75), 80% were male, 87% had bladder primary tumors, and 33% received perioperative chemotherapy. Only 758 (70%) received 1st-line chemotherapy for metastatic UC: cisplatin-based (51%), carboplatin-based (29%), non-platinum single-agent (16%), and non-platinum multi-agent (4%). The median survival from date of diagnosis of metastatic UC was 5.2 months (95% CI 4.4-6.5) and 16.1 months (95% CI 15.1-17.5) for pts who did and did not receive 1st-line chemotherapy, respectively [13.9 months (95% CI 12.78-14.98) from start of chemotherapy for latter group]. Among pts receiving 1st-line chemotherapy, univariable analysis revealed gender, primary tumor site, removal of primary, creatinine clearance, LDH, and hgb were not significantly associated with survival whereas smoking status, performance status, perioperative chemotherapy, metastatic sites, study site and chemotherapy regimen were. The multivariable analysis is shown in the Table. **Conclusions:** The current analysis identifies previously unrecognized prognostic factors in an international cohort of “real world” pts with metastatic UC treated with 1st-line chemotherapy. A large subset of pts with metastatic UC receives no chemotherapy.

Prognostic factors for survival in pts receiving 1st-line chemotherapy.

		HR	95% CI	P
Smoking history	Current vs. never/former	1.48	1.12-1.95	0.006
Perioperative chemotherapy	No vs. yes	0.63	0.46-0.86	0.004
# of visceral metastatic sites	1 vs. 0	1.76	1.25-2.47	0.001
	≥2 vs. 0	2.23	1.56-3.20	<0.001
ECOG PS	1 vs. 0	1.73	1.29-2.32	<0.001
	≥2 vs. 0	2.98	2.02-4.40	<0.001

4526

Poster Discussion Session (Board #15), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Randomized phase III trial of neoadjuvant chemotherapy (NAC) with methotrexate, doxorubicin, vinblastine, and cisplatin (MVAC) followed by radical cystectomy (RC) compared with RC alone for muscle-invasive bladder cancer (MIBC): Japan Clinical Oncology Group study, JCOG0209.**

Hiroshi Kitamura, Taiji Tsukamoto, Naoya Masumori, Taro Shibata, Futoshi Kunieda, Hiroyuki Fujimoto, Yoshihiko Hirao, Yasuo Kitamura, Yoshihiko Tomita, Kenichi Tobisu, Masashi Niwakawa, Seiji Naito, Masatoshi Eto, Yoshiyuki Kakehi; School of Medicine, Sapporo Medical University, Sapporo, Japan; Department of Urologic Surgery and Andrology, Sapporo Medical University School of Medicine, Sapporo, Japan, Sapporo, Japan; JCOG Data Center, National Cancer Center, Tokyo, Japan; JCOG Operations Office, National Cancer Center, Tokyo, Japan; National Cancer Center Hospital, Tokyo, Japan; Nara Medical University, Kashihara, Japan; Niigata Cancer Center Hospital, Niigata, Japan; Yamagata University, Yamagata, Japan; Shizuoka Cancer Center, Shizuoka, Japan; Division of Urology, Shizuoka Cancer Center Hospital, Shizuoka, Japan; Graduate School of Medical Sciences, Kyusyu University, Fukuoka, Japan; Department of Urology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan; Department of Urology, Faculty of Medicine, Kagawa University, Kagawa, Japan

Background: Cisplatin-based NAC for patients (pts) with MIBC is considered to provide a 5–8% overall survival (OS) advantage, although several studies failed to prove the survival benefit of NAC. **Methods:** Eligibility criteria included histologically proven urothelial carcinoma, MIBC (T2-4aN0M0) within 8 weeks from TURBT, PS 0-1, and age 20-75 years old. Patients were randomized to receive 2 cycles of neoadjuvant MVAC followed by RC (NAC arm) or RC alone (RC arm). The primary endpoint was OS. Secondary endpoints were progression-free survival (PFS), surgery-related complications, adverse events during NAC, the percent with no residual tumor in the RC specimens (pT0), and QOL. The sample size was 180 pts in each arm with a one-sided alpha of 5% and a power of 80% to detect a 7% difference in 5-year OS, 45% in the RC arm, and 57% in the NAC arm. **Results:** From March 2003 to March 2009, 130 pts were randomized to the NAC arm (n=64) and RC arm (n=66). Fifty-nine patients in the NAC arm and 65 in the RC arm underwent cystectomy. The patient registration was terminated early because of slow accrual. At the 2nd interim analysis conducted after the completion of patient accrual, OS of the NAC arm was better than that of the RC arm, although the difference was not statistically significant (HR, 0.65; multiplicity adjusted 99.99%CI, 0.19-2.18; one-sided log-rank $p = 0.07$). Considering the current situation in which NAC with gemcitabine and cisplatin (GC) is widely used in clinical practice, the Data and Safety Monitoring Committee recommended early publication of the results. PFS of the NAC arm was better than that of the RC arm (HR, 0.61; 95% CI, 0.35-1.06, one-sided log-rank $p=0.04$). No differences in perioperative complications, other than lymph leakage, were observed between the arms. In the NAC arm and the RC arm, 34% and 9% of the patients had pT0, respectively ($p<0.01$). In subgroup analyses, OS in almost all subgroups was in favor of NAC. **Conclusions:** Although NAC with GC is widely used for MIBC, NAC with MVAC can still be considered promising. Clinical trial information: C000000093.

4527[^]Poster Discussion Session (Board #16), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Preliminary HER2 expression data from NeuACT, the phase II randomized, open-label trial of DN24-02 in patients (pts) with surgically resected HER2+ urothelial cancer (UC) at high risk for recurrence.**

Michael F. Press, Peter H. O'Donnell, Elizabeth R. Plimack, Jean H. Hoffman-Censits, David I. Quinn, Padmanee Sharma, Todd DeVries, Melissa Chen, Michael Locker, Dean F. Bajorin; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; The University of Chicago, Chicago, IL; Fox Chase Cancer Center, Philadelphia, PA; Jefferson Medical College and Kimmel Cancer Center, Philadelphia, PA; The University of Texas MD Anderson Cancer Center, Houston, TX; Dendreon Corporation, Seattle, WA; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: HER2 overexpression may be a prognostic factor for poor outcomes in pts with high-risk UC. Publications report a wide variability of HER2 expression in UC, with $\geq 2+$ HER2 expression by immunohistochemistry (IHC) reported in $<10\%$ to $>50\%$ of cases. DN24-02 is an investigational autologous immunotherapy targeting HER2, based on the same manufacturing platform used for sipuleucel-T. NeuACT (N10-1; NCT01353222) is designed to evaluate whether DN24-02 can prolong survival when given as adjuvant therapy following surgical resection in pts with high risk HER2-expressing UC (Bajorin, et al. ASCO 2012). Here we report preliminary data for HER2 expression on primary tumor and positive lymph node samples, and covariate analyses. **Methods:** Trial eligibility criteria include surgical resection of a primary UC, with either $\geq pT2$ or $pN+$ staging, and HER2 expression $\geq 1+$ IHC. Surgical specimens are screened for HER2 expression by central pathology laboratory review and HER2 positivity is scored using the Dako HercepTest system. **Results:** As of December 2012, tumor specimens from 114 pts have been screened. Of these pts, 84 (74%; 95% CI: 65–82%) had a HER2 expression score $\geq 1+$ in the primary tumor, with 36 (32%) having a 2+ score and 5 (4%) having a 3+ score. Thirty-eight pts also had HER2 expression levels evaluated in lymph node samples. Of these 38 pts, 35 (92%; 95% CI: 79–98%) had a HER2 expression score $\geq 1+$ in the lymph nodes, with 17 (45%) having a 2+ score and 4 (11%) having a 3+ score. Gender, primary tumor site, nodal stage and prior neoadjuvant chemotherapy were not significantly correlated with HER2 expression ($p \geq 0.10$). **Conclusions:** To date, high frequencies ($\geq 74\%$) of HER2 expression $\geq 1+$ in primary tumor and lymph node samples of UC pts have been observed. No baseline variables, including prior neoadjuvant chemotherapy, appear to affect the rate of HER2 expression. Although preliminary, these data are consistent with prior studies that have noted a higher incidence of HER2 expression in UC lymph node tumor vs. primary tumor and suggest that HER2 protein expression is common in high-risk UC. Clinical trial information: NCT01353222.

4528

Poster Discussion Session (Board #17), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Gemcitabine, paclitaxel, and doxorubicin as first-line therapy for patients with advanced urothelial carcinoma and renal insufficiency: A phase II study.**

Lance C. Pagliaro, Mark F. Munsell, Deborah Harris, Robert L. Carolla, Arlene O. Siefker-Radtke; The University of Texas MD Anderson Cancer Center, Houston, TX; Oncology Hematology of Springfield, Springfield, MO

Background: The role of cisplatin-based chemotherapy for the treatment of locally advanced or metastatic urothelial carcinoma is well established. For patients (pts) who cannot receive cisplatin owing to renal insufficiency, substitution with carboplatin was associated with inferior response rate and overall survival (OS). To address this unmet need, we conducted a phase II study of gemcitabine (Gem), paclitaxel (Tax), and doxorubicin (Adria) in this group. **Methods:** The primary endpoint was overall response rate (ORR); secondary endpoints were toxicity, OS, and the safety and efficacy of pegfilgrastim 6 mg (G-CSF) given immediately after chemotherapy on Day 1. A Simon 2-stage design was chosen to detect ORR of 40% and to reject ORR of 25%. Eligible pts had metastatic or unresectable urothelial carcinoma, no prior chemotherapy, performance status ≤ 2 , glomerular filtration < 60 ml/min, and no need for dialysis; all gave informed consent. Brain metastases were excluded, as were clinically significant heart disease, peripheral neuropathy, and liver or bone marrow dysfunction. Treatment consisted of 900 mg/m² Gem (fixed rate of 10 mg/m²/min), 135 mg/m² Tax, and 40 mg/m² Adria administered with same-day G-CSF every 14 d to a maximum of 9 cycles. Tumors were evaluated after every 3 cycles. **Results:** Forty pts were enrolled January 2008 through November 2011, and 39 could be assessed for response. Median age was 72 (range, 51–89) and 11 pts (28.2%) were women. There were 7 complete and 15 partial responses, for an ORR of 56.4% (95% CI 39.6–72.2). Notable grade 3 and 4 nonhematologic toxicities in the first 2 cycles were dyspnea and mucositis (1 pt each). There were no treatment-related deaths and no toxicity attributed to same-day G-CSF. Median OS was 14.4 mo with median follow-up of 12.6 mo for all pts, 15.6 mo for 10 who were alive. **Conclusions:** Gem-Tax-Adria is effective as first-line treatment for metastatic or locally advanced urothelial carcinoma, and it can safely be given to pts with renal insufficiency. Same-day G-CSF also appears to be safe and effective in this setting. Phase III study is warranted. Clinical trial information: NCT00478361.

4529

Poster Discussion Session (Board #18), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Prognostics factors in previously untreated urothelial cancer patients ineligible for cisplatin-based chemotherapy: An external validation of the Bajorin risk groups.**

Sandra Collette, Richard Sylvester, Joaquim Bellmunt, Graham Mead, Jan M. Kerst, Michael Gordon Leahy, Pablo Maroto, Thierry Gil, Sandrine Marreaud, Gedskes Daugaard, Iwona Anna Skoneczna, Ronald De Wit, Maria De Santis, EORTC GU Cancers Group; EORTC Headquarters, Brussels, Belgium; European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium; Department of Medical Oncology, University Hospital del Mar-IMIM, Barcelona, Spain; University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; The Netherlands Cancer Institute-Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium; Department of Oncology, Rigshospitalet, Copenhagen, Denmark; Institute of Oncology, Warsaw, Poland; Erasmus MC, Rotterdam, Netherlands; KFJ Spital Austria, Vienna, Austria

Background: In patients with urothelial cancer who are unfit for Cisplatin chemotherapy, EORTC phase II/III trial 30986 investigated two carboplatin-based chemotherapy regimens: Gemcitabine/Carboplatin (GC) and Methotrexate/Carboplatin/Vinblastine (M-CAVI). The trial did not show any significant differences in efficacy (response rate, OS, PFS) between the treatments; however the incidence of severe acute toxicity was slightly higher on M-CAVI. We now investigate the prognostic factors for survival. **Methods:** 238 patients with impaired renal function (Glomerular Filtration Rate (GF) <60 mL/min) or poor performance status (PS 2) were randomized by 29 institutions between GC and M-CAVI. The median follow-up was 4.5 years and, with 218 deaths reported (progression of malignant disease in 72%), the overall survival median was 9.3 months in the GC arm and 8.1 months in the M-CAVI arm. Univariate and multivariate Cox prognostic factor regression models for overall survival were developed on the whole population stratified by treatment arm. **Results:** In the multivariate analysis, the risk of death significantly increased ($p < 0.10$) with WHO-PS 2, hemoglobin ≤ 12 g/dl (women) or ≤ 13.6 g/dl (men), the presence of visceral metastases and even more with the presence of liver metastases. The risk of death was not influenced by the site of the primary tumour, white blood cell or platelet count. In addition, the prognostic factors had a stronger effect in the M-CAVI arm than in the GC arm. **Conclusions:** This prognostic factors analysis confirms the Bajorin classification based on visceral metastases and performance status. However, we were also able to show the importance of hemoglobin and that in the patients with visceral metastases, the subgroup of patients with liver metastases had a significantly worse prognosis than the patients with only other visceral metastasis. Clinical trial information: NCT00014274.

4530

Poster Discussion Session (Board #19), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Phase II study of neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) chemotherapy in patients with muscle-invasive urothelial cancer (MI-UC): Pathologic and radiologic response, serum tumor markers, and DNA excision repair pathway biomarkers in relation to disease-free survival (DFS).**

Angela Q. Qu, Susanna J. Jacobus, Sabina Signoretti, Edward C. Stack, Katherine Maragaret Krajewski, Jonathan E. Rosenberg, Toni K. Choueiri; Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital/Harvard Medical School, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Neoadjuvant (NA) ddMVAC in patients (pts) with MI-UC is associated with significant pathologic response (PaR) and radiologic response (RaR). We examined the frequency of PaR and RaR as well as the level of serum and tissue biomarkers in correlation with DFS. **Methods:** Pts treated on phase II prospective study of NA ddMVAC (4 cycles) in MI-UC were evaluated for RaR (at least >50% decrease in the primary tumor and nodes after chemotherapy, with delayed enhancement of residual disease) and PaR (p<T1N0M0). Elevated serum tumor markers (CA125, C19-9 and β HCG) at baseline and Day 1 of each cycle were documented. Expression level of baseline DNA ERCC1 protein in tumor biopsy tissues was determined by immunohistochemistry based on H-score <0.1 (negative) vs. >0.1 (positive). Fisher's Exact test was used to evaluate association with response. Post-surgery DFS was estimated by the Kaplan-Meier method and compared between response and biomarker groups using the logrank test. **Results:** Of 39 pts (cT2:42%, cT3:42%, cT4:16%, and cN1:45%), 49% (90% CI 35-63) experienced PaR, and 62% (90% CI 47-75) achieved RaR after ddMVAC chemotherapy. Pts who achieved PaR experienced a DFS advantage, with 18-month DFS of 78% (95% CI 47-92) vs. 48% (95% CI 18-74) in those who did not (p=0.146). Those achieving RaR had a significantly longer DFS (p=0.006), with 18-month DFS of 87% (95% CI 57-97) vs. 29% (95% CI 5-60) in those who did not. Among 10 pts with any elevated serum tumor marker at baseline, only 2 pts showed normalization, both without a PaR. ERCC1(+) tumors were not associated with PaR, pT0 or RaR. DFS by ERCC1status was inconclusive due to limited sample size. 18-month DFS was 91% (95% CI 51-99) in ERCC1(+) tumors vs. 63% (95% CI 29-85) in ERCC1(-) tumors. **Conclusions:** ddMVAC achieves significant PaR and RaR in MI-UC pts that translates into a post-surgery DFS advantage. ERCC1(+) was not associated with response. More effective biomarkers of platinum response are needed to select pts most likely to benefit from NA therapy. Clinical trial information: NCT00808639.

4531

Poster Discussion Session (Board #20), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Phase II study of gemcitabine, oxaliplatin, and paclitaxel (GOT) on a 2-weekly schedule in patients (pts) with refractory germ cell tumor (rGCT): Final results.**

Sarmad Sadeghi, David I. Quinn, Denice D Tsao-Wei, Omid Hamid, James Hu, Anne K. Schuckman, Siamak Daneshmand, Susan G. Groshen, Derek Raghavan, Tanya B. Dorff; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; The Angeles Clinic and Research Institute, Los Angeles, CA; University of Southern California Institute of Urology, Los Angeles, CA; Carolinas Medical Center, Charlotte, NC

Background: Modern therapy (Tx) for GCC has transformed the disease but challenges remain in managing rGCT. **Methods:** 30 men with GCC progression ≤ 4 weeks after a standard (7), salvage (17), or stem cell (6) regimen were enrolled in the trial. PS ≤ 2 , Age > 16 , PD by RECIST/markers (Tm) criteria. Growing teratoma syndrome excluded. Regimen: paclitaxel 170mg/m²/3h; gemcitabine 800mg/m²/80min; oxaliplatin 100mg/m²/90min, increased to 125mg/m² in cycle 2 if no major toxicity. Mg²⁺ and Ca²⁺ infused before oxaliplatin. The regimen was designed to maximize Oxaliplatin density with full dosing of pts with recovering marrow and dose escalation for pts with limited toxicity in cycle 1. Retreatment if ANC ≥ 1000 or 700 with monocytosis, platelets $> 75K$. Pts with normalized Tm had 3 further cycles. Primary endpoint: Response (RR); 2nd: OS, PFS, toxicity. **Results:** Median GOT cycles 6 [1-14]. Dose escalation in 9 pts correlated with improved OS ($p=0.03$). Tm normalized in 23.3%. 5 pts (4 PR, 1 SD) became NED after definitive surgery. No link between ethnicity and RR or OS. **Conclusions:** 2-weekly GOT for rGCC produced high rates of Tm and RECIST response and rendered 5 pts resectable. Dose escalation was associated with better OS and will be explored with GCSF in a trial extension. The median OS of 18.3 mos compares favorably with 6-13.5 mos in other series (Oechsle K Eur Urol 60: 850, 2011). Clinical trial information: NCT00183820.

Pt characteristics (N=30)	
Median age	32 Y
Ethnicity white / Hispanic / Asian	43 / 47 / 10 %
Primary testis / mediastinal	28 / 2
Seminoma / chorio / YST / emb / teratocarcinoma / undiff / mixed NSGCT	1 / 3 / 3 / 1 / 5 / 1 / 16
KPS $\geq 90\%$	66%
FU	40.9 mos (4.6-71.8)
LDH	178 (109-4504)
AFP	26.7 (2-363002)
β hCG	2.6 (0.5-247040)
Prior lines of Tx	2 (1-7)
Prior surgery primary / metastasis	20 / 13
Endpoint	
RR	31% (17-50)
CR / PR / uPR / SD / PD	2 / 7 / 2 / 11 / 5
OS	18.3 mos (12-71.8)
Probability of survival at 2 Y	45 \pm 10 %
PFS	6.5 mos (3.2-27.5)
Time to progression	10.8 mos (3.2-71.8)
Probability of nonPD at 1 Y	47 \pm 9%
Toxicity	
Neutropenia	
G 3-4	17
Febrile	7
Death	1 pneumonia
GI G2-3	12
Neuropathy	
G 3, 4	4, 1
G 1-2	19

G: grade; Y: years, mos: months. Range in []; 95% CI in ().

4532

Poster Discussion Session (Board #21), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Survival and toxicity in patients with disseminated germ-cell cancer above 40 years of age.**

Frederik Birkebæk Thomsen, Mikkel Bandak, Maria Ferløv Thomsen, Jakob Lauritsen, Ib Jarle Christensen, Kirsten Gedske Daugaard; Urology Research Unit, Department of Urology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; Department of Internal Medicine, Amager Hospital, Copenhagen, Denmark; Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; The Finsen Laboratory, Rigshospitalet and Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark; Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Background: The aim was to analyze treatment related toxicity and survival in patients aged 40 years or above (40+) treated with standard chemotherapy for germ-cell cancer (GCC). **Methods:** The study population comprised 135 40+ patients with disseminated GCC treated between 1984 – 2011 with either 3 or 4 cycles bleomycin, etoposide and cisplatin (BEP). A control-group of 135 patients aged 18-35 years was randomly selected matched on year of BEP treatment. All patients were followed until death or October 1st 2011. Cumulated doses of BEP as well as bone-marrow toxicity, renal- and lung functions were recorded before, during and after termination of treatment. The expected mortality was calculated by extracting survival data for each patient matched on the date and age at the time of diagnosis. The cause of death was categorized as GCC, other malignancy or other. **Results:** The cumulated doses of BEP were comparable between the two groups and, generally, BEP was equally well tolerated. 40+ patients had increased cancer specific mortality, HR = 4.8 (P = 0.005). Especially patients with disease progression after first line chemotherapy had increased mortality (P = 0.015). The year of treatment (P = 0.32), histology (P = 0.30), CCI (P = 0.99), tobacco use (P = 0.16), alcohol consumption (P = 0.21), prophylactic G-CSF (P = 0.61), reduced doses of bleomycin (P = 0.11) and decreased renal function (P = 0.18) were not significantly associated with GCC mortality. However, patients with impaired lung function (<80% of expected) prior to treatment had an increased risk of GCC mortality (FVC (P = 0.03), DLCO (P = 0.01) and FEV₁ (P = 0.05)). Moreover, the 5-year overall survival in the 40+ group was 82.5% compared to the expected 5-year survival of the background population of 96.2% (P < 0.001) and the estimated 5-year survival of 97.0% in the control-group (P < 0.001). **Conclusions:** Reduced treatment intensity, or treatment related toxicity could not explain the increased mortality in 40+ GCC patients compared to a younger control-group. The 40+ group has a significantly lower response rate to BEP and a significantly higher mortality in case of disease progression. The worse prognosis could be related to tumor biology or increased co-morbidity.

4533

Poster Discussion Session (Board #22), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM

Germ cell cancer (GCC): Long-term survival after treatment with bleomycin (B), etoposide (E), and cisplatin (P) in a large cohort.

Maria Gry Gundgaard, Jakob Lauritsen, Mette Sakso Mortensen, Mads Agerbaek, Niels Vilstrup Holm, Susanne O. Dalton, Christoffer Johansen, Gedske Daugaard; Survivorship, Danish Cancer Society, Copenhagen, Denmark; Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; Aarhus University Hospital, Aarhus, Denmark; Odense University Hospital, Odense, Denmark

Background: In 1997 the International Germ Cell Cancer Collaborative Group presented a classification dividing patients into a good, intermediate, and poor prognostic group for metastatic GCC with 5-year survival information. However, only a minor part of these patients were treated with today's standard treatment. We present the first nationwide and population based study of overall survival (OS) and disease specific survival (DSS) in a large cohort of GCC patients treated with BEP. **Methods:** A nationwide and population based clinical database covering GCC patients diagnosed 1984-2007 was constructed, including 4,683 GCC cases. Through merging with national administrative registers, information on vital status and cause of death for all patients until November 30, 2012, was obtained. **Results:** The 5-year OS for the whole database cohort was 96%. A total of 1,584 patients were treated with BEP (1,099 patients with primary metastatic disease, 485 patients relapsed from stage I). Until 2001, the standard treatment was 4 cycles of BEP, after 2001 patients with good prognosis had 3 cycles of BEP. Overall survival (OS) and disease specific survival (DSS) with 95% confidence intervals (95% CI) (Table), median observation time was 13.8 years. **Conclusions:** This cohort study showed improved OS for GCC patients across all prognostic groups since 1997, in particular regarding the poor prognostic group. The present result is based on a large number of cases established in a population based fashion, with long follow up time and unbiased information covering all cohort members including detailed clinical information and vital status of all patients.

Histology	Seminoma (n=360)		Non-seminoma (n=1,224)		
	Good	Intermediate	Good	Intermediate	Poor
Prognostic group (%)	95	5	66	20	14
5-year OS (%)	95	82	96	89	67
(95% CI)	(92-97)	(58-93)	(94-97)	(85-93)	(59-74)
5-year DSS (%)	97	85	98	90	71
(95% CI)	(95-98)	(61-95)	(97-99)	(86-93)	(63-77)

4534

Poster Discussion Session (Board #23), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Phase I/II study of paclitaxel plus ifosfamide (TI) followed by high-dose paclitaxel, ifosfamide, and carboplatin (TIC) with autologous stem cell transplant (ASCT) for salvage treatment of germ cell tumors (GCT).**

Xiaoyu Jia, Darren Richard Feldman, Ilya Glezerman, Lindsay Joy Van Alstine, Dean F. Bajorin, Patricia Fischer, Amanda Hughes, Joel Sheinfeld, Manjit S. Bains, Lilian Reich, George J. Bosl, Robert John Motzer, Sujata Patil; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: High-dose chemotherapy (HDCT) can achieve durable remissions in 30-60% of GCT patients (pts) requiring salvage treatment. This Phase I/II study investigated safety and efficacy of a novel high-dose regimen (TI-TIC) in this population. **Methods:** Pts age ≥ 18 with GCT and progression after ≥ 1 cisplatin-based regimen were eligible. TI-TIC consists of 1-2 cycles of conventional-dose paclitaxel plus ifosfamide (TI) q14-21 days followed by 3 cycles of high-dose TIC with ASCT q21-28 days. TI dosing was constant. In Phase I, high-dose TIC was administered in 1 of 5 cohorts (I: 6, 8 or 10g/m²; T: 200 or 250mg/m²; C: AUC=21 or 24) using a standard 3+3 dose escalation design to determine the maximal tolerated dose (MTD). In Phase II, Simon's 2-stage optimal design was used to estimate the complete response (CR) rate at MTD. **Results:** Of 26 pts (25 male; median age 31; 21 nonseminoma, 5 seminoma) enrolled, 23 received ≥ 1 cycle of high-dose TIC. Primary sites included testis (n=15), mediastinum (n=6), other (5). In Phase I, 0/18 pts had dose-limiting toxicity (DLT) during TIC cycle 1, making cohort 5 (T 250mg/m², I 10g/m², C AUC=24) the MTD. Toxicities were similar to those reported with TI-CE (Feldman JCO 2010) with little variation across cohorts. However, 2/18 pts in Phase I (1 in cohort 4, 1 in cohort 5) developed grade 3 acute renal insufficiency after cycles 1 and 2 (cycle 3 not given). Both later developed chronic renal insufficiency with 1 pt requiring dialysis 10 months after TI-TIC. A third pt treated in Phase II developed a similar acute and then chronic renal insufficiency pattern with TIC cycles 1 and 2. In Phase II, 7/11 evaluable pts (64%, 90% one-sided CI 40%-100%) achieved a CR, 1 had a partial response with negative markers, and 3 had incomplete responses. Although the CR rate was sufficient to move to the second Simon's stage, renal toxicity led to premature trial closure. **Conclusions:** Although there was preliminary evidence of efficacy, high dose TI-TIC was associated with acute and chronic renal insufficiency. TI-CE remains the standard high dose regimen for salvage treatment of GCT at MSKCC. Clinical trial information: NCT00423852.

4535

Poster Discussion Session (Board #24), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**A randomized trial of 72-hour infusional bleomycin in BEP (cisplatin, etoposide, and bleomycin) versus conventional weekly bleomycin in patients with metastatic IGC-CCG good prognosis disease.**

Sarah Vinnicombe, Stephen John Harland, Johnathan K. Joffe, Robert Huddart, Danish Mazhar, Alison J. Birtle, Jeff D. White, Peter Wilson, Marita Marshall, Shah-Jalal Sarker, Jonathan Shamash; University of Dundee, Dundee, United Kingdom; University College London Cancer Institute, London, United Kingdom; St. James University Hospital, Institute of Oncology, Leeds, United Kingdom; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Addenbrooke's Hospital, Cambridge, United Kingdom; Rosemere Cancer Centre, Royal Preston Hospital, Preston, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; St Bartholomew's Hospital, London, United Kingdom; Barts Cancer Institute, London, United Kingdom; St. Bartholomew's Hospital, London, United Kingdom

Background: Bleomycin is an integral part of combination chemotherapy in germ cell tumours. Pulmonary symptoms often dictate drug cessation and death occurs in 1-2% of patients. Circumstantial evidence suggests that continuous infusion may be less toxic. **Methods:** We conducted a randomized phase 3 study to see whether infusional bleomycin was associated with less pulmonary toxicity. Patients were stratified for smoking, renal dysfunction and age and were randomized to receive either conventional BEP with weekly bleomycin (3,000 units /week iv over 30min) or the same doses but administered as a 90,000 unit infusion on day 1 over 72 hours. The primary endpoint was CT proven lung toxicity, secondary endpoints included PFS and changes in lung function testing. CT scans and lung function testing were conducted after 1 cycle, end of treatment and 1 year post treatment. Sample size of 210 was calculated to detect a difference of 16% Bleomycin damage with 80% power at the 5% level of significance using 2-sided test. **Results:** The median follow-up was 2.5 years. At day 21 of the treatment, 52% patients in the infusional arm had grade 1 or above toxicity compared to 55% in the conventional. At the end of treatment the results were 84% vs. 60% and at one year it was 65% vs. 59%. Repeated measures mixed effects model shows no significant difference in percentage of grade 1 and above toxicity between the two arms (Difference=1.63, P=0.09, 95% CI: -0.28, 3.54). However, there was a significantly higher level of grade 2 and above toxicity in patients in the infusion arm (difference=0.8; 95% CI 0.11 to 1.49). Toxicity level was the highest at the end of treatment and in older patients (Age>30). Lung function testing between the two arms failed to show any differences. Two-years PFS rate was 93% in both arms (hazard ratio infusion vs conventional was 0.91; 95% CI 0.33 to 2.52). There was an association between toxicity after 1 cycle and subsequent toxicity at end of treatment and at 1 year (p=0.003). **Conclusions:** Infusional bleomycin has no advantage over standard administration of bleomycin. Clinical trial information: 08648791.

4536

Poster Discussion Session (Board #25), Tue, 8:00 AM-12:00 PM and
11:30 AM-12:30 PM**Stomach cancer risk following radiotherapy for testicular cancer.**

Lindsay M Morton, Sophie D. Fossa, Marilyn Stovall, Flora E. van Leeuwen, Tom B. Johannesen, Preetha Rajaraman, Berthe M Aleman, Graca Dore, Ethel S. Gilbert, Per Hall, Eric J. Holowaty, Heikki Joensuu, Magnus Kaijser, Charles Lynch, Eero Pukkala, Hans H Storm, Susan A Smith, Joseph F Fraumeni, Lois B. Travis, Michael Hauptmann; Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Rockville, MD; Department of Oncology, Oslo University Hospital and University of Oslo, Oslo, Norway; The University of Texas MD Anderson Cancer Center, Houston, TX; Netherlands Cancer Institute, Amsterdam, Netherlands; Cancer Registry of Norway, Oslo, Norway; The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; Department of Veterans Affairs Medical Center, Oklahoma City, OK; Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland; Clinical Epidemiology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden; University of Iowa, Iowa City, IA; The Finnish Cancer Registry, Helsinki, Finland; Cancer Prevention and Documentation, Danish Cancer Society, Copenhagen, Denmark; Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Rochester School of Medicine and Dentistry, Rochester, NY; Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

Background: Testicular cancer (TC) is a highly curable malignancy occurring most commonly among men aged 15-34 years. Survivors are at increased risk for adverse late effects of therapy. Previous studies have reported more than 4-fold risks of stomach cancer after TC, although the potential role of radiotherapy and chemotherapy for TC in these associations is unclear. **Methods:** We evaluated stomach cancer risk in an international cohort of 23,982 men diagnosed with TC during 1959-1987. Using detailed radiotherapy records, doses to the stomach tumor location were estimated for 92 stomach cancer patients and 180 individually matched controls. Chemotherapy drugs and doses also were recorded. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression. **Results:** Fifty-seven percent of patients with stomach cancer were diagnosed with TC before age 40 years, 65% had seminoma, 95% had stage I or II disease, and 37% were diagnosed with stomach cancer ≥ 20 years after TC diagnosis. Patients who received radiotherapy [87 (95%) cases, 151 (84%) controls] had a 5.9-fold (95%CI 1.6-21.3) increased risk of stomach cancer compared with patients who did not receive radiotherapy. Risk increased with increasing radiation dose to the stomach (P-trend <0.001), with ORs of 3.6 (95%CI 1.3-10.6), 4.4 (1.2-16.4) and 13.3 (2.5-70.0) after 20-39.9 Gy, 40-49.9 Gy, and ≥ 50 Gy radiation to the stomach, respectively, compared with <10 Gy. Radiation-related stomach cancer risk did not vary by calendar year of treatment, age at exposure, or TC histology. The OR for having received any chemotherapy was 1.3 (14 cases, 23 controls, 95% CI 0.6-2.8). Stomach cancer risk was not significantly elevated among patients given cisplatin-based chemotherapy (7 cases, 10 controls, OR=1.7, 95% CI 0.6-5.1). **Conclusions:** Patients administered radiotherapy for TC in the past are at increased risk of developing stomach cancer, particularly those who received ≥ 20 Gy to the stomach. The study results warrant consideration in radiation risk assessment and long-term follow-up. Future studies should further investigate a possible role for chemotherapy in stomach cancer risk.

4537

General Poster Session (Board #25A), Mon, 8:00 AM-11:45 AM

Low-dose versus standard-dose gemcitabine infusion and cisplatin for patients with advanced bladder cancer: A randomized phase II trial: An update.

Rasha Mohamed Haggag, Kamel Farag, Fouad Abu-Taleb, Sameh Shamaa, Abdel-Rahman Zekri, Tarek ELBolkainy, Hussein Mustafa Khaled; Department of Medical Oncology and Hematology, Faculty of Medicine, Zagazig University, Zagazig, Egypt; Oncology Center, faculty of Medicine, Mansoura University, Mansoura, Egypt; Center, Faculty of Medicine Mansoura University, Mansoura, Egypt; Department of Cancer Biology, National Cancer Institute, Cairo University, Cairo, Egypt; Department of Pathology, National Cancer Institute, Cairo University, Cairo, Egypt; Department of Medical Oncology, National Cancer Institute, Cairo University, Cairo, Egypt

Background: Bladder carcinoma is still one of the foremost oncologic problems in Egypt. In previous single-arm and double-arm phase II studies, prolonged infusion of low dose gemcitabine and cisplatin proved to be an effective treatment for such patients with advanced disease. **Methods:** To compare efficacy and safety of both prolonged infusion and standard gemcitabine-cisplatin combination, we updated the data and duplicated the number of patients of our previously published phase II randomized study to 120 untreated patients with stage III/IV bladder cancer. Patients were randomized to receive either gemcitabine (250 mg/m²) 6-hour infusion on days 1 and 8, and cisplatin (70 mg/ m²) on day 2 every 21-day cycle (Arm1) or gemcitabine (1,250 mg/ m²) 30-min infusion on days 1 and 8, and cisplatin (70 mg/ m²) on day 2 every 21-day cycle (Arm 2). **Results:** The 92 males and 28 females had a median age of 62 years (range 40-85 years). A total of 87 patients had transitional cell, 28 had squamous cell, and 5 had undifferentiated cell carcinoma. Among the 105 evaluable patients (52patients in arm1 and 53patients in arm 2), complete response rate was achieved in 13.5% (7/52 patients of arm 1) and 5.7% (3/53 patients of arm 2). Eighteen patients in arm 1 (34.6%) and 17 patients (32.1%) in arm 2 had partial response on therapy. Thus the overall response rate of patients in arm1 and arm 2 was 48% (25/52 patients) and 37.7% (20/53patients), respectively (p = 0.26). No significant difference in median time to disease progression (26 months versus 24 months, p =0.4), median survival (12 months versus 16 months, p =0.8), and 1-year survival (49.9 % versus 54.7%, p = 0.8) was detected between arms 1 and 2, respectively. No treatment- related deaths occurred. Main hematologic and nonhematologic toxicities were similar in both arms with no statistically significant differences. **Conclusions:** In the treatment of advanced bladder cancer, gemcitabine in low dose and prolonged infusion in combination with cisplatin is not inferior to high-dose short infusion gemcitabine and cisplatin in terms of overall survival, time to disease progression, and response rates with favorable toxicity profile and less financial costs.

4538

General Poster Session (Board #25B), Mon, 8:00 AM-11:45 AM

A STAT3- and p63-dependent transcriptional network to define a lethal basal subset of human bladder cancers.

Colin P.N. Dinney, Woonyoung Choi, Sima P. Porten, Beat Roth, Tiewei Cheng, Daniel Levi Willis, Mai Ngoc-Ahn Tran, I-Ling C. Lee, Jolanta E. Bondaruk, Tadeusz Majewski, Shizhen Zhang, Shanna M. Pretzsch, Keith A. Baggerly, Arlene O. Siefker-Radtke, Bogdan Czerniak, David James McConkey; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Muscle-invasive bladder cancers (MIBCs) are a heterogeneous group of tumors that display widely variable clinical outcomes and responses to conventional chemotherapy. **Methods:** We used whole genome mRNA expression profiling and unsupervised hierarchical cluster analyses on a cohort of 73 flash frozen primary tumors to identify 3 distinct subsets of muscle-invasive bladder cancer (MIBC). We confirmed the existence of these 3 subsets in a second cohort of 57 formalin-fixed, paraffin-embedded (FFPE) MIBCs and in 2 other public datasets. Analysis of primary tumors and mechanistic studies in human bladder cancer cell lines identified tumors that respond to FGFR inhibitors or chemotherapy. **Results:** The first subset was driven by an active "basal" EGFR-STAT3-p63 transcriptional network, and was associated with poor clinical outcomes. High miR-200c expression stratified the survival of these basal tumors. The second subset was characterized by active p53 pathway activation, and tumors and cell lines with these features were resistant to cis-platinum based chemotherapy. The third subset expressed "luminal" markers and active estrogen receptor (ER) and PPAR γ signaling, and luminal cell lines were sensitive to fibroblast growth factor receptor (FGFR) inhibition. **Conclusions:** Molecular subtyping of MIBCs can be used to identify lethal cancers and enrich for tumors that will respond to FGFR inhibitors or conventional chemotherapy.

4539

General Poster Session (Board #25C), Mon, 8:00 AM-11:45 AM

Impact of response to prior chemotherapy (RTPC) on outcomes in second-line therapy for advanced urothelial carcinoma (UC): Implications for trial design.

Gregory Russell Pond, Joaquim Bellmunt, Ronan Fougeray, Toni K. Choueiri, Angela Q. Qu, Yacine Salhi, Guenter Niegisch, Peter Albers, Giuseppe Di Lorenzo, Matt D. Galsky, Andrea Necchi, Guru Sonpavde; McMaster University, Hamilton, ON, Canada; University Hospital del Mar, Barcelona, Spain; Institut de Recherche Pierre Fabre, Boulogne, France; Dana-Farber Cancer Institute, Boston, MA; Department of Urology, Heinrich-Heine-University, Duesseldorf, Germany; Heinrich Heine University, Duesseldorf, Germany; Department of Clinical Oncology and Endocrinology and Rare Tumors Reference Center Campania Region, University Federico II, Napoli, Italy; The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL

Background: Performance status (PS), hemoglobin (Hb), liver metastasis (LM), and time from prior chemotherapy (TFPC) are significant prognostic factors in second-line therapy for advanced UC. Setting of prior chemotherapy, i.e., metastatic or perioperative, has not appeared significant. However, the impact of prior chemosensitivity is unclear, which may confound trial interpretation. Hence, we examined the prognostic impact of RTPC, when prior therapy was given for metastatic disease. **Methods:** Six phase II trials evaluating second-line chemotherapy and/or biologics (n=504) were pooled. Patients who received prior therapy for metastatic disease were eligible for analysis if data regarding Hb, LM, PS, and TFPC were available. Response by RECIST to first-line therapy was recorded. Progression-Free Survival (PFS) and overall survival (OS) were calculated from the date of registration using the Kaplan-Meier method. **Results:** 275 pts were evaluable for analysis. Patients received gemcitabine-paclitaxel, cyclophosphamide-paclitaxel, pazopanib, docetaxel plus vandetanib/placebo or vinflunine (2 trials). Those with prior response (n=111) had a median (95% CI) OS of 8.0 (6.8-9.4) months (mo) and PFS of 3.0 (2.6-4.0), compared with OS and PFS of 5.9 (5.0-6.6) mo and 2.6 (2.0-2.8) for those without prior response (n=164). Multivariable analysis did not reveal an independent impact of RTPC on PFS or OS (Table). **Conclusions:** RTPC in patients receiving prior chemotherapy for metastatic disease did not confer an independent prognostic impact with second-line therapy for advanced UC. Patients who received prior chemotherapy in peri-operative or metastatic settings may be enrolled in the same second-line trial stratified for PS, anemia, LM and TFPC.

	Progression-free survival		Overall survival	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Liver disease	1.46 (1.09-1.95)	0.012	1.33 (0.98-1.81)	0.068
ECOG PS	1.23 (0.99-1.61)	0.14	1.73 (1.29-2.32)	<0.001
Anemia	1.48 (1.03-2.11)	0.032	1.65 (1.15-2.38)	0.007
≥3 months from chemo	0.79 (0.59-1.05)	0.11	0.75 (0.55-1.03)	0.078
Prior response (yes/no)	1.05 (0.78-1.42)	0.73	0.77 (0.56-1.05)	0.099

4540

General Poster Session (Board #26A), Mon, 8:00 AM-11:45 AM

Introduction of a tobacco-screening initiative for those at risk for bladder cancer in a high volume urology clinic.

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Background: Tobacco use is causal or contributory in 50% of bladder cancer diagnoses. Continued use after diagnosis may negatively impact recurrence, progression, and mortality. Despite its relevance, tobacco screening was infrequently occurring in a regional urology clinic. We hypothesized that the clinic was fertile ground for a tobacco-screening initiative given the number of referrals for bladder cancer, hematuria, and other tobacco-related urologic conditions. **Methods:** An EMR-based tobacco-screening prompt was designed using the same informatics architecture and clinical reporting system used in primary care. The prompt was introduced for all new patient encounters beginning January 2010. We prospectively collected the proportion of patients asked about tobacco use, advised to quit, and assisted with smoking cessation. **Results:** For the two years ending December 2011, 4,617 patients were seen in urologic consultation; 31% (n = 1,444) were referred for tobacco-related urologic diagnoses, 36% (n = 518) of whom were referred for bladder cancer or hematuria. The tobacco-screening prompt was used 57% (n = 2,626) of the time. Attending physicians utilized the template in 17% of their encounters, resident physicians in 71%, and nurse practitioners in 97% (p < 0.001). 49% (n = 255) of those referred for bladder cancer or hematuria were screened for tobacco use. Active smokers comprised 21% (n = 558) of screened patients. Relative to former and never smokers, active smokers were more likely referred for bladder cancer or hematuria (p = 0.005). 40% (n = 225) of active smokers desired to quit. Those counseled by an attending physician were more likely ready to quit and trended toward a more intensive cessation program (p = 0.004 and p = 0.07, respectively). **Conclusions:** Our data suggest that urology clinics may be important sites for tobacco-screening initiatives, particularly for those with tobacco-related urologic diagnoses. Screening patients referred for bladder cancer or hematuria is likely high yield due to the increased proportion of active smokers. Given the disparate utilization of the prompt, identification of provider-level facilitators and barriers to tobacco screening is worthy of study.

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General Poster Session (Board #26B), Mon, 8:00 AM-11:45 AM

Expression of PD-L1 in primary urothelial carcinoma (UC).

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Background: Engagement of programmed cell death-1 (PD-1), expressed on CD8+ T cells, with its ligand PD-L1(B7H1), expressed on tumor cells, results in T cell suppression and tumor protection. Antibodies against PD-1 or PD-L1 have reported impressive anti-tumor activities in phase I/II trials and are being tested in the phase 3 setting. Exploratory analysis indicated that expression of PD-L1 could be a predictive marker for response. Of note, urothelial carcinoma (UC) was not included in the early phase anti-PD1 or anti-PD-L1 studies. To explore anti-PD-L1 as a new treatment for this lethal disease, we assessed PD-L1 expression in UC. **Methods:** The relative mRNA abundance of PD-L1 mRNA in UC was studied in the Oncomine Bittner Multi-cancer dataset, which included a total of 1911 tumor samples. PD-L1 immunohistochemistry (IHC) was performed with rabbit monoclonal antibody against human PD-L1 on tissue microarrays with 83 formalin fixed paraffin embedded T1, T2 and T3 UC. IHC slides were reviewed by a genitourinary pathologist. A positive staining is defined when $\geq 5\%$ of cancer cells had positive PD-L1 membrane and/or cytoplasmic staining. The IHC slides were scanned with the Aperio ScanScope XT and the immunopositivity of PD-L1 was quantitatively scored using commercial algorithms from the Aperio Toolbox and TissueStudio. The 1+, 2+, and 3+ score of each core was based on the dominant IHC staining intensity. **Results:** In the Bittner multi-cancer dataset, the log2 median mRNA intensities of PD-L1 in prostate cancer, clear cell renal cell carcinoma, colon cancer, UC of the bladder, ureter and squamous cell carcinoma of the bladder were 0.245, 0.528, 0.61, 0.81, 0.802, and 1.202 respectively. The overall PD-L1 IHC staining positivity was 45% in 83 primary UC samples. All six 3+ PD-L1 staining cores were grade 3 urothelial carcinomas and each core had more than 60% of cancer cells with 3+ PD-L1 membrane staining. Grade 3 cores also had the highest percentage of 2+ and 3+ PD-L1 positivity. No association was observed between T staging and PD-L1 staining intensity. **Conclusions:** PD-L1 is expressed in primary UC. We have obtained additional UC samples to correlate its expression with survival and its expression pattern with the pattern of tumor infiltrating lymphocytes.

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General Poster Session (Board #26C), Mon, 8:00 AM-11:45 AM

Development of a genomic-clinical classifier for predicting progression after radical cystectomy in patients with muscle invasive bladder cancer.

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Background: The mainstay of muscle-invasive bladder cancer treatment is surgical resection with/without multi-agent chemotherapy. Management decisions are based on a small number of clinical and pathologic parameters with poor prognostic and predictive power. There is an urgent need for enhanced biomarkers to guide therapy of this lethal disease. Here we have developed a genomic signature of bladder cancer progression using whole transcriptome profiling technology. **Methods:** 251 FFPE bladder cancer specimens were obtained from patients undergoing radical cystectomy at the University of Southern California (1998-2004). All patients had pT2-T4a,N0 urothelial carcinoma in the absence of pre-operative chemotherapy. Median follow-up was 5 years. RNA expression levels were measured with 1.4 million feature oligonucleotide microarrays. Patients were divided into a training set (2/3 of cohort) to develop a genomic classifier for risk of progression (defined as any type of bladder cancer recurrence), and a validation set (1/3 of cohort). In parallel, multivariable analysis was used to develop a clinical classifier using typical clinical and pathologic variables. Finally, a genomic-clinical classifier was built combining the genomic classifier with clinical variables using logistic regression. The receiver-operator characteristic (ROC) area under the curve (AUC) metric was used to evaluate each classifier in the validation set. **Results:** The genomic classifier consisted of 89 features corresponding to 80 genes that were combined in a k-nearest neighbor model (KNN89). KNN89 showed an AUC of 0.77 in ROC analysis on the validation set. The best clinical classifier showed an AUC of 0.72. The genomic-clinical classifier demonstrated an AUC of 0.81. Multivariable analysis incorporating all clinical parameters and KNN89 further revealed that KNN89 was the only significant predictor of bladder cancer progression ($p=0.0077$). **Conclusions:** We have developed a combined genomic-clinical classifier that shows improved performance over clinical models alone for prediction of progression after radical cystectomy. External validation of this classifier is ongoing.

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General Poster Session (Board #27A), Mon, 8:00 AM-11:45 AM

Preclinical and correlative studies of cabozantinib (XL184) in urothelial cancer (UC).

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Background: Mounting evidence supports Met as a therapeutic target in urothelial cancer (UC). Activated Met can promote angiogenesis and tumor growth by upregulating VEGF and may play a role in UC pathogenesis. Cabozantinib inhibits VEGFR2 and Met pathways. In this study, we assessed shed Met (sMet) levels in the urine and serum of UC patients (pts) and cabozantinib's effects on HGF-driven UC cell growth and invasion. **Methods:** sMet levels in serum and urine samples from 31 pts with UC (23 metastatic, 8 muscle-invasive) were correlated with stage, presence of visceral metastases and urinary source. The effects of cabozantinib on 4 human UC-derived cell lines were studied in vitro. Intact RT4, TCC-SUP, T24M2 and T24M3 cells at 80% confluence were serum deprived 16 h, then left untreated or treated with hepatocyte growth factor (HGF) and/or cabozantinib prior to analysis of Met, phospho- (p)Met, pAkt, Akt, pMAPK and MAPK by immunoassay or immunoblotting. Cabozantinib effects on basal and HGF-induced UC cell invasion, proliferation and soft agar growth were measured. **Results:** Median serum Met levels were modestly higher in pts with metastatic versus muscle-invasive disease. Urinary Met levels were clearly higher in pts with visceral metastasis ($P=0.0111$) and in urine from ileal conduits and neobladders compared to normally voided urine, regardless of stage ($P=0.0489$). Met content in UC cell lines was low in RT4 and higher in T24M2, T24M3 and TCC-SUP. Basal pMet content was universally low, increased significantly by HGF and this was reversed by cabozantinib. HGF-driven increases in pAkt/Akt and pMAPK/MAPK in all 4 cell lines were reversed by cabozantinib, as were HGF-enhanced UC cell invasion, proliferation and anchorage independent growth. **Conclusions:** Median urinary sMet is significantly higher in pts with visceral metastasis and in specimens from ileal conduits and neobladders relative to normally voided urine. UC cell Met content in culture increased with disease grade; HGF stimulated activation of Met and known effectors, and enhanced invasion, growth rate and anchorage-independent growth; cabozantinib effectively reversed these HGF-driven effects. These data support evaluation of cabozantinib in pts with metastatic UC.

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General Poster Session (Board #27B), Mon, 8:00 AM-11:45 AM

Does chemotherapy improve survival in muscle-invasive bladder cancer (MIBC)? A systematic review and meta-analysis (MA) of randomized controlled trials (RCT).

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Background: There is strong evidence that neoadjuvant chemotherapy improves survival in MIBC but its uptake in clinical practice is variable. The benefits of adjuvant chemotherapy are controversial, especially with the recent presentation of 3 RCTs not included in previous MA. We sought to summarise the effects of chemotherapy, both neoadjuvant and adjuvant, on survival in MIBC. **Methods:** We included published summary data from recent MA and RCTs. Eligible RCTs compared the addition of chemotherapy, neoadjuvant or adjuvant, to local treatment versus local treatment alone. We searched CENTRAL, PubMed, MEDLINE, proceedings of ASCO and clinicaltrials.gov from 2004 to August 2012. The primary outcome was overall survival (OS). Disease-free survival (DFS) and adverse events (AE) were secondary outcomes. Pooled hazard ratios (HR), confidence intervals (CI) and p-values (p) were estimated with fixed effects model. Heterogeneity and subgroup effects were assessed with p-values for interaction. **Results:** We included 21 RCTs (n=3986), 12 of neoadjuvant (n=3047) and 9 adjuvant chemotherapy (n=939). The addition of chemotherapy significantly improved OS (HR 0.86, 95% CI 0.79 to 0.93, p=0.0004). Separate analyses of neoadjuvant therapy and adjuvant therapy yielded significant results in both subgroups (HR 0.89, 95% CI 0.81 to 0.98, p=0.02; HR 0.75, 95% CI 0.63 to 0.90, p=0.002; respectively; p-value for interaction 0.11). There were larger benefits in DFS (HR 0.77, 95% CI 0.71 to 0.84, p<0.000001), which were also noted with the addition of neoadjuvant and adjuvant therapy (HR 0.80 95% CI 0.73 to 0.88, p<0.00001; HR 0.67 95% CI 0.55 to 0.81, p<0.0001; respectively; p-value for interaction 0.10). The most common AE of grade 3 or 4 were haematological, gastrointestinal and renal impairment with median frequencies of 33%, 15% and 2% respectively in neoadjuvant; and 15%, 21% and 27% in adjuvant trials. **Conclusions:** Meta-analysis of available randomized trials indicates that chemotherapy, both adjuvant and neoadjuvant, improves survival in MIBC. A direct comparison of these two strategies in a large scale randomised trial is needed to determine which is optimal.

4545

General Poster Session (Board #27C), Mon, 8:00 AM-11:45 AM

Investigation of a novel irreversible pan-HER inhibitor combined with chemotherapy in bladder cancer models.

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Background: Human Epidermal Receptors (HER) play an important role in bladder cancer (BCa) progression and may mediate chemotherapy resistance. Dacomitinib (Dac) is a novel, potent, irreversible pan-HER inhibitor with activity in several solid tumors, currently in phase III trials in NSCLC. We showed that Dac has single agent anti-tumor activity in human BCa models in vitro and in vivo, inducing apoptosis and G1 arrest. We hypothesized that Dac has additive effects with Gemcitabine (G) and Cisplatin (C) in BCa xenografts. **Methods:** UM-UC-6 (UC6) or UM-UC-9 (UC9) xenografts were established in age-matched NOD/SCID mice. A week after injection, mice had small tumors, were randomized and treated with i. G 50mg/kg + C 2mg/kg via 3 weekly intra-peritoneal injections (IPI) + daily p.o. buffer for 3 weeks; ii. Dac 6mg/kg p.o. daily for 3 weeks + 3 weekly IPI (saline); iii. GC (same dose/schedule) + Dac starting 1 day after GC (based on cell cycle effect and kinetics); iv. no treatment (control). Mice were monitored daily, weighed weekly, sacrificed at 4 weeks and tumors were weighed. 3 tumors/group were stained for EGFR, HER2, Ki67, E-cadherin, ALDH, p-EGFR, p-ERK, p-Akt. 3rd GC dose in UC6 model was given at 50% due to weight loss; all GC doses were given at 50% in UC9 model. Mann-Whitney test with multiple comparison adjustments was used for analysis. **Results:** Dac- and GC+Dac-treated mice had no significant weight loss. UC6 tumor weights were significantly lower in Dac and GC+Dac vs control ($p<0.0001$) or GC ($p<0.0001$), corresponding to decreased p-ERK %cell expression and staining intensity. GC and control had similar tumor weights ($p=0.19$). 5 Dac and 3 GC+Dac UC6-injected mice had no tumor at 4 weeks. UC9 tumor weights were significantly lower in Dac ($p=0.002$, 6x reduction) or GC ($p=0.0006$; 7x reduction) vs control. GC+Dac had significantly lower tumor weights vs GC ($p=0.005$), Dac ($p=0.06$) or control ($p<0.0001$; 17x reduction). **Conclusions:** Dac had dramatic single-agent activity in UC6 xenograft that was GC-resistant. Dac+GC was superior to GC in UC9 xenograft, supporting clinical evaluation. Further investigation of Dac anti-tumor activity and predictive biomarker discovery in additional bladder cancer models is pursued.

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General Poster Session (Board #28A), Mon, 8:00 AM-11:45 AM

Association between pioglitazone (PZD) therapy and bladder cancer (BC): A meta-analysis of epidemiologic evidence.

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Background: There is evidence suggesting that PZD use may be a risk factor for BC, yet these reports are controversial. The aim of this meta-analysis is to review available data and evaluate the association between PZD and BC. **Methods:** Two independent reviewers conducted a systematic search of the Cochrane Library, OvidSP and PubMed for articles published January 1970 to April 2012. MeSH search terms included PZD, Actos, thiazolidinediones, diabetes mellitus (DM), and BC. Only studies reporting an effect measure for the association between PZD and BC were included. Subgroup analyses by study design and country were performed. Analysis was done using a random effect model after a preliminary review showed evidence of study heterogeneity. This was then assessed using the Cochrane's Q and I² statistics. Publication bias was evaluated using the Begg's and Egger's tests, and funnel plots. All analyses were performed using REVMAN 5.1. **Results:** A total of 6 studies (3 cohort and 3 case control) met the inclusion criteria. The overall pooled risk ratio (RR) for the association between PZD and BC was 1.12 (95% CI 1.09, 1.15; P <0.001). The summary RR for cohort and case control studies were 1.13(95% CI 1.07, 1.19; P <0.001) and 1.11(95% CI 1.07, 1.15; P <0.001), respectively. The subgroup analysis showed a significant association with BC in the USA and Europe, but not in Asia (RR 0.98, 95% CI 0.71, 1.34; P = 0.88). The association of PZD and BC was more sensitive for treatment duration (>12 month). **Conclusions:** Our study analyzed 1,214,071 patients, demonstrating a weak association between PZD and BC. The results were significant with increase in treatment duration, which corresponds to previous studies. This meta-analysis has limitations. Not all studies reported known variables associated with BC, such as smoking or occupational exposure. They did not address patient BMI, time from DM diagnosis or previous drug therapy. These parameters reflect severity of disease and level of insulin-resistance. Future studies should evaluate markers of insulin-resistance with PZD use and correlate with BC. Understanding the link between PZD and BC in the context of DM may allow physicians to determine a more accurate risk of PZD use.

4547[^]

General Poster Session (Board #28B), Mon, 8:00 AM-11:45 AM

Preliminary safety, product parameters, and immune response assessments from a phase II randomized, open-label trial of DN24-02, an autologous cellular immunotherapy (ACI), in patients (pts) with surgically resected HER2+ urothelial cancer (UC) at high risk for recurrence.

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Background: DN24-02 is a HER2-targeted ACI, consisting of antigen presenting cells (APC) cultured with BA7072, a recombinant HER2-derived antigen (HER500) linked to GM-CSF; DN24-02 is based on the same manufacturing platform as sipuleucel-T, approved for asymptomatic/minimally symptomatic metastatic castrate resistant prostate cancer. NeuACT (N10E1; NCT01353222) is an open-label, randomized phase 2 trial comparing adjuvant DN24E02 to surveillance in HER2+ UC pts at high risk of relapse following cystectomy or nephroureterectomy. The primary endpoint is overall survival. Here we report preliminary evaluation of adverse events (AE), product potency, and immune response. **Methods:** Pts randomized to DN24-02 underwent leukapheresis followed by infusion of DN24-02 (total of 3 infusions with 2 wk intervals). AEs were assessed at each visit. Product potency was assessed for each infusion by measuring CD54 upregulation on APCs, a marker of APC activation. Antigen-specific immune responses were evaluated by ELISA to HER500 and BA7072. **Results:** As of November 2012, 13 pts had received ≥ 1 DN24-02 infusion. The most commonly reported AEs within 1 day after DN24-02 infusion were mild-moderate chills (54%), nausea (31%) and fatigue (23%). Ten pts completed all DN24-02 infusions and were assessed for product potency. Increased median APC activation at infusions 2 and 3 compared with infusion 1 was indicative of an immunological prime-boost effect; this effect was also seen in the 7/10 pts with prior neoadjuvant chemotherapy. Median anti-BA7072 and anti-HER500 titers (IgM) were 128- and 256-fold higher at week 6 vs baseline, respectively. The emergence of IgG indicated a memory antibody phenotype. **Conclusions:** Preliminary data indicate that DN24-02 product potency (CD54 upregulation) is comparable to sipuleucel-T. DN24-02 appears to be well tolerated in UC. Favorable immune responses were observed, including in pts with prior neoadjuvant chemotherapy. Updated results, including preliminary T-cell immune response data, will be presented. Clinical trial information: NCT01353222.

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General Poster Session (Board #28C), Mon, 8:00 AM-11:45 AM

A novel phase I trial design featuring a two-dimensional dose-finding algorithm optimizing the dose of gemcitabine and doxorubicin with bortezomib in metastatic urothelial carcinoma (UC).

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Background: Preclinical studies suggested that bortezomib (B) enhanced the activity of gemcitabine and doxorubicin (GA) in UC; thus we sought to define possible combinations of bortezomib with this doublet. We employed a novel phase I trial design systematically exploring doses in 2 dimensions. The method estimates an isotoxic curve allowing not only a combination with approximately equal (with respect to single component MTD) contributions of the two components to be found, but also combinations emphasizing one component or the other. **Methods:** Since 11/06, 74 patients with previously treated metastatic cancer were enrolled (70 UC, 3 prostate, 1 renal). GA was treated as a single component and given in a fixed ratio to a maximum of 900 and 50 mg/m², and B to a maximal dose of 1.6 mg/m² IV, with dosing every 14 days. After determining the MTD along the diagonal, we then decreased the dose of B, increasing GA, and vice versa, exploring doses along an isotoxic curve aiming for $\leq 30\%$ dose limiting toxicity (DLT) in cycle 1. The objective response rate (ORR) includes PR or CR, and excludes SD. **Results:** The MTD along the diagonal for GAB was 756, 42, and 1.4 mg/m², respectively. Doses maximizing the GA (900, 50) required reduction of B to 1.2 mg/m². Likewise, doses maximizing B (1.6) required reduction of GA to 559 and 33 mg/m². The most common DLT were thrombocytopenia 14%, neutropenic fever 5%, and mucositis 1%. There was minimal activity at the on-diagonal MTD with an ORR 1/10. Of the tolerable doses along the isotoxic curve, the greatest activity was seen when maximizing B (1.5-1.6 mg/m², ORR 7/12 (58%)). The ORR when maximizing GA was 4/10. The most frequent \geq G3 toxicities include: thrombocytopenia (26%), neutropenia (26%), anemia (24%), fatigue (8%), and neutropenic fever or infection (12%). Treatment was tolerable in poor renal function; 36 patients (49%) had a GFR < 50 ml/min. **Conclusions:** The combination of GAB has promising activity at doses maximizing proteasome inhibition, despite relatively low doses of GA. Traditional phase 1 design dosing to the MTD "along the diagonal" would have lead to the incorrect conclusion that there was minimal activity. Clinical trial information: NCT00479128.

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General Poster Session (Board #29A), Mon, 8:00 AM-11:45 AM

Investigating serum β -HCG as an independent prognostic factor in patients (pts) receiving chemotherapy (Ct) for transitional cell carcinoma (TCC) of the urothelial tract.

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Background: Serum human chorionic gonadotrophin β subunit (β -HCG) has prognostic value in TCC but has not been investigated in pts receiving Ct for this disease. Furthermore prior studies lacked statistical power to test independence from other prognostic variables. **Methods:** A single institution retrospective clinical database was constructed of pts receiving Ct between 2005 and 2011 for cancer of the urothelial tract. Eligible pts had pure or a component of TCC. Prognostic variables were tested by univariate Kaplan Meier analyses. Statistically significant variables were then assessed by multivariate cox regression analysis. A prospectively defined β -HCG cut-point of $<$ versus ≥ 2 iu/L, either prior to (β -HCGp), or on completion of (β -HCGc) Ct was used. **Results:** 235 pts were eligible (72% male, 55% ≤ 70 years, 83% bladder primary). Initial Ct was perioperative (CtPeri) in 46% (7% adjuvant, 39% neoadjuvant). 63% had first line palliative Ct for metastatic disease (CtMet). For CtPeri, ECOG performance status (PS), haemoglobin (Hb), CtPeri regimen and T stage were statistically significant prognostic factors in univariate analyses for overall survival (OS), as were β -HCGp (median OS (mOS) 8.50 v. 1.86 years, $p < 0.001$) and β -HCGc (mOS 4.27 v. 0.66 years, $p = 0.003$). β -HCGp and β -HCGc after CtPeri were also prognostic for relapse free survival and in multivariable analysis remained statistically significant as a prognostic factor for OS (β -HCGp: hazard ratio (HR) 3.13, $p = 0.001$; β -HCGc: HR 4.26, $p = 0.007$). In pts treated with CtMet, PS, alkaline phosphatase, prior CtPeri, visceral metastases, CtMet regimen and β -HCGc (mOS 1.70 v. 1.07 years, $p = 0.005$) were prognostic in univariate analyses for OS. β -HCGc after CtMet was also prognostic for progression free survival and in multivariable analysis remained statistically significant as a prognostic factor for OS (HR 3.47, $p < 0.001$). **Conclusions:** β -HCG, and specifically its post-Ct level, is an independent prognostic factor for TCC treated with Ct in both curative and palliative settings. Prospective evaluation is warranted for incorporation into treatment selection strategies.

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General Poster Session (Board #29B), Mon, 8:00 AM-11:45 AM

Phase I/II study of biweekly pemetrexed plus cisplatin in patients with locally advanced, nonresectable or metastatic urothelial cancer: Safety and efficacy results from phase II.

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Background: Pemetrexed (P) plus cisplatin (C) combination is effective against several malignant tumors. Single-agent P has shown antitumor activity in advanced urothelial cancer; we performed a phase I/II study to define the maximum tolerated dose of biweekly P plus C combination. Here, we report the final results of the phase II study. **Methods:** Eligible patients (pts) had locally advanced or metastatic transitional cell carcinoma of the urothelium not suitable for curative therapy, performance status (PS) 0-2, estimated life expectancy of at least 12 weeks, and adequate organ function. P and C were administered on days 1 and 15 of each 28-day cycle, up to a maximum of 6 cycles. Pts received the recommended dose from phase I, with P at 400 mg/m² plus C at 50 mg/m² (folic acid and vitamin B₁₂ supplementation were also administered). Primary objective was overall response rate (ORR) according to RECIST 1.0. **Results:** Thirty-eight pts were recruited, 32 (84.2%) pts had bladder cancer with a mean diagnosis time of 1 (range 0-7) year and 30 (78.9%) had metastatic disease; 19 (50%) pts had visceral metastasis and 2 (5.3%) pts had a PS 2. Only 2 pts did receive adjuvant systemic therapy. Median number of cycles was 3 (range 0-7). Twelve (31.6%) pts discontinued the study treatment due to toxicity. The most common treatment-related AEs (> 20%) were asthenia (n=27 pts), nausea and vomiting (n=21, respectively), diarrhea (n=18), anorexia (n=17), mucosal inflammation (n=14), and constipation (n=8). Most treatment-related AEs were of mild or moderate severity. Neutropenia (n=5) and asthenia (n=3) were the most frequent Grade 3 or 4 treatment-related AEs. Serious related AEs were observed in 8 (21.1%) pts. ORR was 39.5% (95% CI 24.0-56.6); 2 (5.3%) pts achieved complete response and 13 (34.2%) pts, partial response. Median progression free survival was 6.7 months, and median overall survival was 10.5 months. **Conclusions:** In this study, biweekly P (400 mg/m²) plus C (50 mg/m²) combination showed anti-tumor activity in pts with advanced urothelial cancer, with an acceptable safety profile. Clinical trial information: NCT00374868.

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General Poster Session (Board #29C), Mon, 8:00 AM-11:45 AM

Patterns of chemotherapy and survival in elderly patients with advanced bladder cancer: A large Medicare database study.

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Background: The frequency of employment of cisplatin-based chemotherapy in elderly patients (≥ 66 years) presenting with advanced (unresectable or metastatic) bladder cancer is unclear. We examined the use of and overall survival (OS) with chemotherapy regimens employed in elderly patients with newly diagnosed advanced bladder cancer (ABC). **Methods:** SEER-Medicare linked data were used to identify incident ABC patients presenting with the following stages of bladder cancer: T4bN0M0; Any TN1–N3M0; Any T, Any N, M1 between 2004 and 2007, with claims data until 2009. Outpatient and inpatient Medicare claims data were queried for receipt and type of chemotherapy used. The descriptive analyses were performed to examine associations between chemotherapy regimen, clinical characteristics and OS. **Results:** A total of 1,031 patients with ABC met inclusion criteria. The median age was 74 years, 69.8% were men. 4.6% (n=47) were T4bN0M0, 55.3% (n=570) were anyT,N1-3M0 and 40.1% (n=414) were any T, any N, M1. Overall, 20.5% (n=211) received cisplatin, 26.1% (n=269) received carboplatin, 5% (n=52) received no platinum and 48.4% (n=499) received no chemotherapy. There were no differences in regimen according to gender, race, stage and age. The median OS for cisplatin, carboplatin, no platinum and no chemotherapy groups were 1.67, 1.41, 1.5 and 1.41 years, respectively (F=5.36, $p<0.001$). Patients with Any TN1–N3M0; Any T, Any N, M1 receiving cisplatin had better OS compared to carboplatin. T4bN0M0 patients receiving carboplatin exhibited better OS relative to those receiving cisplatin, but this finding is limited by the small number of patients. **Conclusions:** Among patients presenting with ABC in the Medicare database aged ≥ 66 years, only 20.5% received cisplatin and 48.4% received no chemotherapy. Those with distant and nodal metastasis displayed better OS with cisplatin. Further analysis will control for baseline prognostic factors and comorbidities. Drug development in the ABC population, especially the elderly, should focus on chemotherapy-ineligible and cisplatin-ineligible patients.

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General Poster Session (Board #29D), Mon, 8:00 AM-11:45 AM

The impact of clinically significant discrepancies from primary pathological review of transurethral bladder resection specimens upon repeat review at a tertiary care center.

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Background: Internal review of outside pathology slides is a common practice among urologic oncologists at tertiary care facilities, and discrepancies have a potential to directly affect the choice of treatment. While repeat prostate biopsy review has been extensively studied, there is little data available on the impact of repeat reviews of bladder biopsies. The purpose of the current study is to perform a standardized comparison of original and internal pathology reviews of identical bladder specimens to characterize the impact of repeat review on treatment decisions. **Methods:** Using the Columbia Urologic Oncology Database, a retrospective analysis of 91 consecutive patients who underwent bladder resections at outside institutions from 2008-2012 with secondary referral to a single urologist and internal review at our institution was conducted. Characteristics of both original pathology reports and internal reviews were collected and compared by blinded reviewers. A discrepancy in one of the following characteristics was considered treatment-altering: presence of muscularis in specimen or tumor involvement in muscularis. Additional clinically-significant discrepancies including presence of secondary histology, carcinoma in situ, lymphovascular invasion, micropapillary features, tumor stage, and overall accumulative discrepancy rate were also analyzed. **Results:** Median time from original procedure to internal review was 34 days (range: 9-368). 56/91 (62%) patients had at least one of the predefined clinically-significant discrepancies. 27/91 (30%) patients had at least one treatment-altering discrepancy, including 25 with discrepant muscle in specimen and 11 with discrepant muscle invasion. Regarding tumor stage, 8 patients were upstaged, 71 were unchanged, and 12 were downstaged on internal review. **Conclusions:** Repeat pathologic review of primary bladder specimens at a tertiary care center has the potential to alter clinical care for the majority of patients. Further studies are needed to determine if these discrepancies and the decisions they influence have a significant impact on patient outcomes.

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General Poster Session (Board #29E), Mon, 8:00 AM-11:45 AM

One course of adjuvant BEP in clinical stage I, nonseminoma: Mature and expanded results from the SWENOTECA group.

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Background: The SWENOTECA group has since 1998 offered patients with clinical stage I (CSI) nonseminoma (NSGCT) treatment based on a risk-adapted approach. Patients with lymphovascular invasion (VASC+) were recommended one course of adjuvant chemotherapy (ACT) with bleomycin, etoposide and cisplatin (BEP). Patients without lymphovascular invasion (VASC-) had the choice between one course of adjuvant BEP or active surveillance. **Methods:** From 1998-2010, 491 patients with CSI NSGCT received one course of adjuvant BEP. Following histopathological evaluation 247 patients were classified as VASC+, 239 as VASC- and five patients had uncertain VASC status. All patients were included into a prospective, community-based, multicenter SWENOTECA management program. Initial results from patients treated during 1998-2005 have earlier been reported. We now report the mature data, expanded with patients treated during 2005-2010. **Results:** The median follow-up was 8.0 years. Eleven relapses were observed. After one course of adjuvant BEP 2.3% of patients relapsed. In regard to VASC status 3.4% of VASC+ and 1.3% of VASC- patients relapsed. The latest relapse was detected 3.3 years after ACT. Ten patients have died, only one due to testicular cancer. The 5 and 10-year overall survival rates were 98.9% and 96.8%, respectively. The 5 and 10-year disease-specific survival rates were 100% and 99.6% respectively. **Conclusions:** One course of adjuvant BEP reduces the risk of relapse in CSI NSGCT with over 90%. These mature results confirm our earlier results on one course of adjuvant BEP. There is no evidence of late relapses, or chemotherapy-resistance in relapses following ACT. To detect relapses, a follow-up of five years is sufficient.

4554

General Poster Session (Board #29F), Mon, 8:00 AM-11:45 AM

Aggressive surgical management of germ cell tumors with somatic-type malignancy: Pathologic features, prognostic factors, and survival outcomes.

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Background: Germ cell tumors (GCT) with somatic-type malignancy (SM) are rare occurring in approximately 3-8% of GCT cases. Prognostic factors and optimal management remain poorly-defined. **Methods:** The Indiana University (IU) testis cancer database was queried from 1979 to 2011 for patients demonstrating atypical histology at orchiectomy or subsequent resection of metastatic disease. Patients with transformation to PNET only were excluded due to distinct management. Chart review, pathologic review, and survival analysis were performed. **Results:** 122 patients met study inclusion criteria. Primary tumor site was testis in 112, retroperitoneum in 8, groin in 1, and pineal gland in 1. The most common SM histologies were sarcoma (71) and carcinoma (32). At GCT diagnosis, 24, 44, 45 patients had stage I, II, and III disease, respectively. Stage was unknown in 9. Median time from GCT diagnosis to SM was 13 months (Range, 0-397). This interval was longest for carcinomas (94.5 months) and sarcomatoid yolk sac tumors (113 months). Only 11 of 83 patients (13.3%) receiving cisplatin-based chemotherapy for measurable disease demonstrated an initial complete response. First resection at IU was reoperative in 45 patients (36.9%). 69 patients (56.6%) required extirpation of abdominal viscera/vascular structures or distant metastases. At a median follow-up of 71 months, the 5-year cancer specific survival (CSS) was 63%. Predictors of poorer CSS included SM diagnosed at late relapse ($p = 0.014$), referral to IU for reoperative RPLND ($p = 0.022$), and tumor grade ($p = 0.043$). SM histology subtype, stage, risk category, and number of resections for SM were not predictive of CSS. **Conclusions:** GCT with SM is associated with poorer CSS than traditional GCT. Established prognostic factors for GCT lose their predictive value in the setting of SM. SM can occur at any point in the course of GCT, but has a propensity for delayed presentation with later onset being associated with poorer CSS. Aggressive and serial surgical resections are often necessary to optimize CSS. Tumor grade is an important prognostic factor, particularly in sarcoma cases.

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General Poster Session (Board #29G), Mon, 8:00 AM-11:45 AM

Association between *ERCC1* and *XPA* expression and polymorphisms and the response to cisplatin in patients with non-seminomatous testicular germ cell tumors.

Julia Mendoza, Jorge Martinez-Cedillo, Carlos Alberto Hernández, Delia Pérez-Montiel, Clementina Castro, Eunice Fabián-Morales, Miguel Santibañez, Rodrigo González-Barrios, José Díaz-Chávez, Marco Alonso Andonegui, Luis F. Onate-Ocana, Miguel Jimenez, Nancy Reynoso, Marlene Núñez, Richard Dyer, Luis A. Herrera; Instituto Nacional de Cancerología, Mexico City, Mexico; Instituto Nacional de Cancerología, Mexico City, Mexico; Hospital Regional Presidente Juárez, Oaxaca, Mexico; Instituto de Investigaciones Biomedicas/UNAM, Mexico City, Mexico; Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru

Background: Cisplatin-based chemotherapy cures over 80% of testicular germ cell tumors (TGCTs); nucleotide-excision repair (NER) modifies the sensitivity to cisplatin. In this work we explored the association between NER-proteins and their polymorphisms (SNPs) with cisplatin-sensitivity (CPS) and overall survival (OS) of patients with advanced non-seminomatous (ns)-TGCTs treated with bleomycin-etoposide-cisplatin (BEP). **Methods:** *ERCC1*, *XPA*-expression and gammaH2AX-presence, were tested in cisplatin-treated cancer cell lines. *ERCC1* and *XPA*-expression were also analyzed in ns-TGCTs by qPCR. Immunohistochemistry was performed to detect *ERCC1* protein in ns-TGCTs specimens. The SNPs were genotyped by PCR-RFLPs technique. **Results:** High basal *ERCC1*-expression was observed in non-CPS cancer cell lines; *ERCC1*-expression augmented further, as well as gammaH2AX, after cisplatin-treatment. Basal *ERCC1* expression increases in the non-CPS patients in Mexican and Peruvian populations compared to CPS patients ($p<0.001$; $p=0.002$). *XPA*-expression levels weren't different. These polymorphisms weren't associated with CPS or OS. *ERCC1*-positive immunostaining was observed in 30/108 patients (27.8%). From 76 patients that were CPS, 59 (77.6%) were *ERCC1*-negative, compared with 17 (22.4%) that were *ERCC1*-positive ($p=0.05$). 5-year OS probability was smaller for those patients *ERCC1*-positive and non-CPS (15.38%) than tumor *ERCC1*-negative and CPS (89.3%) ($p<0.001$). Using the Cox Model, adjusted on the prognosis groups, the hazard ratio (HR) of death in patients with *ERCC1*-negative and non-CPS was >14.43 and in patients *ERCC1*-positive and non-CPS the HR was >11.86 ($p<0.001$). **Conclusions:** High-levels of *ERCC1*-expression and *ERCC1*-protein are associated with non-CPS, suggesting the use of *ERCC1* as a potential indicator of response to cisplatin-based chemotherapy and the prognosis in patients with ns-TGCTs. Moreover, it's important to identify patients potentially non-CPS in order to diminish the toxicity of cisplatin and improved quality of life avoiding adverse effects due to this agent. Work supported by CONACYT 83959 and PAPIIT IN213311-3.

4556

General Poster Session (Board #29H), Mon, 8:00 AM-11:45 AM

Expression profiling of peripheral blood (PB) enriched for circulating tumor cells (CTCs) in testicular germ cell tumors (TGCTs).

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Background: CTCs are prognostic in several types of tumors and are easily accessible for repeat examination. TGCTs represent a model for the cure of cancer. Nonetheless, a small proportion of patients develop disease recurrence. We investigated expression profiling of PB enriched for CTCs in TGCTs aimed to identify expression signature associated with treatment resistance. **Methods:** This prospective study included 30 patients (pt) treated with first line (27 pt) or salvage (3 pt) chemotherapy. CD45⁺ peripheral mononuclear cells (PBMCs) were isolated from 10mL of PB on day 1 and on day 22 of first cycle of chemotherapy. Isolated PBMC were depleted of cells of hematopoietic origin (CD45⁺) using RosetteSep kit negative selection with anti-CD45 antibody. CD45-depleted PBMC represent compartment enriched for CTCs, as showed previously. RNA was extracted from CD45⁺PBMCs and the expression profiles were obtained using Roche NimbleGen microarrays. Data analysis was processed in R using a limma package followed by GO analysis and MetaCore pathway analysis. **Results:** Six patients achieved unfavorable response to chemotherapy (other than CR or PR with negative serum markers). We identified 1,506 and 211 genes that were expressed at significantly different levels (FDR<0.05) on day 1 and day 22 of chemotherapy, respectively, with 108 overlapping genes. Cluster analysis using principal component analysis showed, that 5 of 6 samples from patients with unfavourable response to chemotherapy form clearly defined cluster opposed to samples from patients with favourable response. Based on pretreatment expression profiling using MetaCore pathway analysis software, we further identified 758 genes, belonging to several critical functional groups such as immune response, signal transduction, cell proliferation, cell cycle progression, or apoptosis, to be significantly differentially expressed in patients with favourable vs. unfavourable response. **Conclusions:** Our data suggests that expression profiling of PB enriched for CTCs in TGCTs is feasible, and show great promise in identifying new therapeutic targets and gene expression signature associated with treatment resistance.

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General Poster Session (Board #30A), Mon, 8:00 AM-11:45 AM

A retrospective analysis of patients with poor-risk germ cell tumor (PRGCT) treated at Indiana University from 2000 to 2010.

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Background: PRGCT represents 14% of germ cell tumors, with 2-year PFS of 50%. PRGCT is defined by primary mediastinal non-seminomatous germ cell tumor (PMNSGCT), non-pulmonary visceral metastasis (NPVM), AFP > 10,000 or hCG > 50,000. This analysis attempts to identify subsets of patients with more or less favorable outcomes among the poor risk groups. **Methods:** Retrospective analysis of all patients with testicular cancer seen at Indiana University (IU) from 2000-2010. 291 patients with PRGCT identified of whom 79 received initial therapy at IU. We analyzed the following variables: primary site testis/retroperitoneal (T/RP) vs. PMNSGCT, pulmonary vs. NPVM, and the amplitude of serum tumor markers. We identified groups of patients according to the level of tumor marker elevation with cutoff points of AFP 20,000 and hCG 200,000. **Results:** Mean age 29, mean AFP 8,283, mean hCG 185,667. 24% had PMNSGCT, 48% NPVM, 11% AFP>20,000, and 25% hCG>200,000. When hCG was analyzed as a continuous variable, every 10,000 unit increase in hCG caused the hazard of progression to increase by 1% (p value 0.01). Patients with NPVM had significantly worse PFS. NPVM with elevated hCG had worse outcome than NPVM with normal hCG. This did not correlate as well with AFP. PFS was worse with NPVM than elevated pre-chemotherapy tumor markers. Multiple different criteria for poor risk disease carried significantly worse impact on PFS and OS when compared to having a single criterion for poor risk disease. **Conclusions:** Our data indicate that patients with NPVM or more than one criteria for PRGCT have a worse outcome compared to other PRGCT subgroups.

	2 y PFS	5 y PFS	5 y OS	P value
AFP < 20,000 vs AFP > 20,000	61% vs 57%	56% vs 57%	79% vs 83%	PFS 0.98; OS 0.80
hCG < 200,000 vs hCG > 200,000	63% vs 52%	57% vs 52%	80% vs 79%	PFS 0.28; OS 0.50
No NPVM vs NPVM	65% vs 54%	61% vs 50%	83% vs 75%	PFS 0.05; OS 0.18
PMNSGCT vs T/RP	67% vs 58%	59% vs 55%	66% vs 84%	PFS 0.36; OS 0.34
No NPVM with AFP<20,000 vs No NPVM with AFP>20,000	68% vs 50%	63% vs 50%	85% vs 75%	PFS 0.17; OS 0.49
NPVM with hCG<200,000 vs NPVM with hCG>200,000	62% vs 39%	55% vs 39%	75% vs 75%	PFS 0.11; OS 0.47
Single criterion vs Multiple criteria for poor-risk disease	71% vs 47%	71% vs 37%	84% vs 73%	PFS 0.003; OS 0.07

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General Poster Session (Board #30B), Mon, 8:00 AM-11:45 AM

Two cycles of carboplatin as adjuvant therapy in stage I seminoma: 8-year experience by the Hellenic Co-operative Oncology Group (HECOG).

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Background: Adjuvant chemotherapy is used in stage I testicular seminoma. We have reported a risk-adapted strategy of 2 cycles of cisplatin/etoposide (EP) in 64 patients with age < 34 and/or tumor diameter > 4cm (Bamias et al, Urology 2007), resulting in no relapses over a median follow up of 5 years. Following the establishment of adjuvant carboplatin as a standard, we adopted this treatment for all patients with stage I seminoma. We report our 8-year experience and compare these results with our previous EP strategy. **Methods:** Patients with stage I seminoma, treated with 2 cycles of carboplatin AUC 6 and a minimum follow up of 1 year after chemotherapy were selected. All patients consented for the use of their medical information and the analysis was approved by the centers involved. Survival functions were presented using Kaplan-Meier curves. The log-rank test was used to test for survival differences across different categories. **Results:** 137 patients (Median age: 34; Age<34: 49%, tumor diameter>4cm: 42%; rete testis invasion: 24%), treated between 11/2003-12/2011 were selected. During a median follow up of 4 years, there were 5 relapses (5-y relapse rate [RR]: 97% [SE: 2%]): retroperitoneal lymph nodes (n=4) and isolated brain (n=1). All patients with relapse had tumor diameter > 4cm and/or age < 34. No relapse was associated with rete testis invasion. Patients with at least 1 of the above risk factors (n=94) had a significantly higher relapse rate compared with a similar population (n=64) treated with 2 cycles of adjuvant EP: 5-y RR was 95% (SE: 2%) vs.100% (SE 0%), (p=0.033). All relapsed patients were treated with BEP chemotherapy and are currently alive with no evidence of relapse. Neutropenia and nausea/vomiting were less frequent with carboplatin than with EP (11% vs. 36% and 15% vs. 65%). **Conclusions:** Our analysis confirms the association of age and tumor diameter with relapse in stage I seminoma treated with adjuvant carboplatin. Although adjuvant carboplatin in patients with age<34 and/or tumor diameter> 4 cm is associated with higher RR than EP, the prognosis of these patients is excellent with salvage chemotherapy and, therefore, the use of less toxic treatment is justified.

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General Poster Session (Board #30C), Mon, 8:00 AM-11:45 AM

First-salvage treatment in patients with recurrent or refractory advanced germ-cell cancer after cisplatin-based chemotherapy: A database of the German Testicular Cancer Study Group.

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Background: About 20-30% of patients (pts) with advanced germ-cell cancer (GCC) relapse after cisplatin-based chemotherapy. This database evaluates first salvage treatment and the prognostic categories at first relapse according to the International Prognostic Factors Study Group (= IPFSG; JCO 2010). **Methods:** A total of 144 pts (78% nonseminoma) with relapsed or refractory GCC undergoing 1st salvage treatment with either conventional (CD-CX) or high-dose chemotherapy with autologous stem cell support (HD-CX) from 16 German centers were retrospectively analysed. **Results:** Subgroups according to the IPFSG prognostic categories, were: very low risk in 9/144 (6%), low risk in 26/144 (18%), intermediate risk in 78/144 (54%), high risk in 27/144 (19%), and very high risk in 4/144 pts (3%). 1st salvage treatment consisted of HD-CX in 96 (67%) and CD-CX in 48 pts (33%). Treatment response was CR/PR- in 60%, PR+/SD in 33%, and PD in 7%. After a median follow-up (mFU) of 21 months (mos) (range, 0 – 193), 53% of all pts had relapsed and 30% had died resulting in a median progression-free survival (PFS) of 7 mos (^{95%}CI 0-16) and overall survival (OS) of 47 mos (^{95%}CI 21-73). At subsequent relapses, 25/48 pts (52%) received HD-CX as > 2nd-salvage treatment. For the total cohort, PFS rate after 2 years was 35%, and OS rate after 5 years was 53%. Stratification according to IPFSG prognostic categories significantly correlated with PFS (p=0.001) and OS (p=0.004) after 1st salvage treatment. Even among high-risk and very high risk (n=31, mFU 12 mos) a PFS of 37 % at 2 years and an OS of 60 % at 2 years was observed, after 1st or 2nd salvage treatment, which might be due to patient selection and short follow-up. **Conclusions:** IPFSG prognostic categories highly correlated with observed PFS and OS after first salvage treatment in this cohort of pts with refractory or relapsed GCC. First salvage treatment with CD- or HD-CX resulted in overall 5 year-OS rates of about 50% across all prognostic categories. Even pts with high and very high risk achieved 2 year-OS rates of about 60% with salvage HD-CX at first or subsequent relapses.

Comparing diagnosis, management, and outcomes of synchronous versus metachronous brain metastases from testicular germ cell tumors (TGCT): Multinstitutional experience from the Spanish Germ Cell Cancer Group (SGCCG).

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Background: Metastases of testicular germ cell tumors (TGCT) to brain are a rare event. Prognostic is poor and there is little evidence on optimal management of these patients. **Methods:** A retrospective review of case records of germ cell tumor patients within the Spanish Germ Cell Cancer Group from 1994 to 2012 was conducted. **Results:** Thirty-three cases of testicular germ cell tumors from 17 institutions were reported. Nineteen patients (57%) presented with brain metastases at primary diagnosis (group 1: synchronous), thirteen (40%) developed brain metastases at relapse (group 2: metachronous) and only one patient developed brain metastasis during cisplatin based-chemotherapy (3%) (excluded from the analysis). Main demographics and comparison between series are shown on table. Median serum BHCG levels at initial diagnosis were higher in group 1 (279.083 versus 175.873), whereas those of AFP were higher in group 2 (1320 versus 4181). The most common histology in the primary tumor was choriocarcinoma for group; versus embryonal carcinoma for group 2. Patients had neurological symptoms at diagnosis of brain metastases (63% synchronic/93% metachronus). Performance status was also poor (PS 2-3: 52,6% group 1-62,2% group 2). Four patients (21%) in group 1 had a solitary brain lesion vs seven (54%) on group 2. Median time since last dose of cisplatin to development of brain metastases on group 2 was 6 months (3-22). Median overall survival was 16 months (95% CI 5,3-26,6): group 1: 16 (95% CI 13,9-18); 23 group 2 (95% CI 0-165). We have not found significant differences in survival between both groups. Overall 37,5% of patients achieved long-term survival (38,9% in group 1 versus 38,5% in group 2). Patients achieving complete response of brain metastases had a better survival (log rank p:0,003). **Conclusions:** Long term survival can be achieved in approximately 1/3 of patients with brain metastases. Chemotherapy remains the cornerstone of treatment. Selection bias because of the retrospective nature of review should make us be careful with the conclusions.

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General Poster Session (Board #30E), Mon, 8:00 AM-11:45 AM

Smoking history and disease outcomes in patients with malignant germ cell tumors.

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Background: In 2011, of 8260 cases of Germ Cell Tumor (GCT) in the US, about 350 (4%) died of disease. The impact of smoking on disease outcomes of relapse and death is unknown. **Methods:** Retrospective review of 891 GCT pts treated at Dana-Farber Cancer Institute (DFCI) between 1997 and 2010 was conducted. Inclusion criteria were men age >18 yrs treated for GCT with a quantified smoking history in an electronic medical record. The outcomes of interest were relapse after first-line chemotherapy and death from the disease. A Chi-square or Fisher's exact test assessed the association of the disease outcomes and the smoking history (heavy smoker vs. less), and a Wilcoxon test for ordered categories assessed the association of the outcomes with the IGCCCG risk groups (good, intermediate, and poor), stratified by histology (seminoma vs non-seminoma (NS)). **Results:** 327 men with metastatic disease were identified. Median age was 31.5 years. 47(14%) had a history of smoking >10 pack-years (pyrs). Of the 256 NSGCT pts with metastases at time of chemotherapy, pts who smoked >10 pyrs constituted 27% of the 64 relapses vs. 11% of the 192 non-relapses (Odds Ratio (OR) 2.9, $p=0.003$). Of the 71 metastatic seminoma pts, 40% of the 10 relapses had smoked >10 pyrs compared with 8% of the 61 pts who did not relapse (OR 7.5, $p=0.01$). Smoking >10 pyrs was associated with (i) higher IGCCCG risk at time of metastatic disease [24% of poor-risk pts had a >10 pyr history compared with 12% who had good-risk or 19% who had intermediate-risk ($p=0.01$)] and (ii) higher staging at initial diagnosis, 23% of poor-risk pts were heavy smokers compared with 9% who were CS1 and 12% good-risk ($p=0.002$). Of the 50 pts who died of metastatic disease, 36% had smoked >10 pyrs compared to 9% who were cured, Pts who smoked >10 pyrs had significantly increased odds of death compared to those who smoked 0-10 pyrs (OR=5.5, $p<0.0001$). 3 out of 30 pts who smoked >10 pyrs received suboptimal bleomycin, and only 1 relapsed. **Conclusions:** Greater than 10 pack-year smoking history is a modifiable risk factor associated with a higher IGCCCG risk at diagnosis of metastatic disease, higher risk of relapse after 1st-line chemotherapy and higher risk of death from germ cell tumor.

Testosterone (T), luteinizing hormone (LH), and follicle stimulating hormone (FSH) levels in testicular cancer survivors (TCSs) 11 and 19 years after orchiectomy.

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Background: Hypogonadism, i.e., low T-, high LH- and/or FSH-levels, is frequently observed in TCSs and is associated with cardiovascular disease, osteoporosis and reduced quality of life. Little is known about the impact of aging on hypogonadism in TCSs. **Methods:** T, LH, and FSH levels were retrieved twice from 874 TCSs median 11 (S11) and 19 (S19) years after orchiectomy and categorized based on cut-offs calculated from 570 healthy controls (C), separately for each decadal age group. Treatment was categorized into surgery (S), radiotherapy (RT) or cisplatin-based chemotherapy (CT). Impact of treatment and aging on T, LH and FSH levels was assessed by comparing proportions of TCSs grouped into the C quartiles by ordinal logistic regression and expressed with odds ratios (OR) and 95% confidence interval (CI). **Results:** TCSs had lower T and higher LH and FSH levels than C at S11 and S19 ($p < 0.05$, except for LH after S at S11) (Table). Approximately 50% of TCSs had T levels in the lowest quartile at S11 and S19. The proportion of TCSs with T below the 2.5% cut-off threshold for C increased from S11 to S19, for the S (9.7 - 12.5%), RT (9.4 - 16.3%) and CT group (12.5- 19.9%). **Conclusions:** TCSs had lower T and higher LH and FSH levels than C of similar age indicating an impact of treatment. Importantly, proportions of TCSs in the highest LH quartile and below the 2.5% cut-off for T-level increased from S11 to S19, indicating an accelerated hormonal aging. Continued follow-up of hormone levels is important.

	TCSs: n=874	S: n=176, (100%)	RT: n=362, (100%)	CT: n=336, (100%)
S11				
T in lowest quartile	80 (46)		190 (53)	184 (55)
OR(95%CI)	2.6 (1.9- 3.5)		3.3 (2.6- 4.3)	3.6 (2.8- 4.7)
LH in highest quartile	58 (33)		150 (41)	173 (52)
OR(95%CI)	1.2 (0.9- 1.6)		2.0 (1.6- 2.5)	2.7 (2.1- 3.4)
FSH in highest quartile	146 (83)		293 (81)	292 (87)
OR(95%CI)	15.6 (10.1 - 24.0)		13.5 (9.8- 18.5)	21.1 (14.7- 30.4)
S19				
T in lowest quartile	81 (46)		201 (56)	193 (57)
OR(95%CI)	2.5 (1.8- 3.4)		3.9 (3.0- 5.0)	3.8 (3.0- 5.0)
LH in highest quartile	90 (51)		207 (57)	200 (60)
OR(95%CI)	3.2 (2.3- 4.4)		4.0 (3.1- 5.2)	4.5 (3.5- 5.9)
FSH in highest quartile	149 (85)		296 (82)	293 (87)
OR(95%CI)	17.4 (11.1 - 27.1)		14.4 (10.4 - 19.7)	21.4 (14.8 - 30.7)

4563

General Poster Session (Board #30G), Mon, 8:00 AM-11:45 AM

A phase I/II trial of BNC105P with everolimus in metastatic renal cell carcinoma (mRCC) patients: Updated phase I results of the Disruptor-1 trial.

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Background: BNC105P is an inhibitor of tubulin polymerization. In vivo exposure to BNC105P leads to selective damage of tumor vasculature in both primary and metastatic lesions, causing disruption of blood flow to tumors, hypoxia and associated tumor necrosis. BNC105P also has a direct anti-proliferative action on cancer cells. Up regulation of the mTOR pathway has been identified as a cellular response to hypoxic stress. 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. The phase I component enrolled 12 subjects at 4 dose levels of BNC105P (4.2, 8.4, 12.6, 16 mg/m²; IV infusion Days 1 & 8, 21-day repeating cycle). Everolimus was administered concurrently (10 mg p.o.). PK analysis was performed during Cycle 1. Biomarker samples (pre- and post-dose during Cycle 1) were analyzed for 70 plasma analytes including VEGF, PDGF and other markers associated with angiogenesis and vascular responses. **Results:** Updated results from the completed phase I component confirm 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 of fatigue, anemia and oral mucositis were also observed. Eight of the 12 phase I subjects achieved disease stabilization. Across all subjects a median of 6 cycles (range: 1-24) was administered, with removal from study predominantly due to disease progression. PK analysis confirmed no drug-drug interaction. The randomized phase II component of the study continues and will compare everolimus given concomitantly with BNC105P to a sequential approach (everolimus followed by BNC105P). **Conclusions:** Full dose BNC105P (16 mg/m²) can be combined with full dose everolimus (10 mg) and is being further evaluated in a randomized phase II study. Clinical trial information: NCT01034631.

4564

General Poster Session (Board #30H), Mon, 8:00 AM-11:45 AM

Rates of dose adjustment in patients treated with tivozanib versus sorafenib in the phase III TIVO-1 study.

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Background: Tivozanib hydrochloride (tivozanib) is a potent, selective, tyrosine kinase inhibitor of all three vascular endothelial growth factor receptors, with a long half-life. Superior progression-free survival (PFS) and overall response rate (ORR) with tivozanib versus sorafenib were demonstrated in a phase III trial (TIVO-1) in patients with advanced renal cell carcinoma (PFS: 11.9 vs 9.1 months in ITT population, 12.7 vs 9.1 months in patients who received no prior systemic treatment for mRCC; ORR: 33% vs 23% in ITT population). Hypertension was more common with tivozanib, while lower rates of certain off-target adverse events (AEs) relative to sorafenib were reported (*J Clin Oncol* 2012;30[suppl]:Abstract 4501). Here we present detailed dose adjustment data. **Methods:** In total, 517 patients were enrolled and randomized 1:1 to tivozanib 1.5 mg/d (once daily 3 weeks on, 1 week off) or sorafenib 400 mg/d (twice daily, continuously). Treatment duration and AEs leading to discontinuation and dose adjustment were assessed in these patients. **Results:** Median duration of treatment with tivozanib was 12.7 months vs 9.5 months with sorafenib; fewer patients in the tivozanib arm experienced drug reduction or dose interruption due to AEs (see Table). Treatment-related AEs, as defined by the investigator, led to drug discontinuation in 3.9% of tivozanib patients and 5.4% sorafenib patients. **Conclusions:** Lower rates of dose adjustment due to related AEs were observed in patients with metastatic RCC who received tivozanib compared to sorafenib. Clinical trial information: NCT01030783.

Related AEs leading to dose reduction or dose interruption.

Adverse event, all/grade 3-4	Tivozanib (n=259) %	Sorafenib (n=257) %
Dose reductions		
Related AEs leading to dose reduction	11/8	37/17
Related AEs occurring in >1.5% of patients		
Hand-foot syndrome	2/2	17/2
Diarrhea	1/1	5/4
Combined hypertension ¹	2/2	4/3
Lipase increase	<1/<1	3/3
Dose interruptions		
Related AEs	14/10	33/27
Related AEs leading to dose interruption in >1.5% of patients		
Diarrhea	2/1	3/3
Combined hypertension ¹	6/5	3/2
Hand-foot syndrome	2/<1	18/15
Rash erythematous	0/0	2/<1
Asthenia	1/<1	2/<1

¹Combined hypertension includes hypertension and hypertensive crisis.

Outcome of metastatic sarcomatoid renal cell carcinoma (sRCC): Results from the International mRCC Database Consortium.

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Background: Sarcomatoid differentiation in metastatic RCC (sRCC) is associated with poor prognosis. Robust data regarding outcome in the targeted therapy era is lacking. **Methods:** Clinical features, prognostic factors, and treatment outcomes in mRCC patients with and without sarcomatoid histology treated with targeted therapy were retrospectively analyzed and compared. **Results:** 2,286 patients were identified (non-sRCC(n=2,056); sRCC(n=230)). sRCC patients had significantly worse Heng prognostic group distribution compared to non-sRCC (11% vs 19% favorable risk, 49% vs 57% intermediate risk, and 40% vs 24% poor risk; $p<0.0001$). Time from original diagnosis to relapse (excluding synchronous metastatic disease) in the sRCC patients was 18.8 months compared to 42.9 months in non-sRCC group; $p<0.0001$. There was no significant difference in the incidence of CNS metastases (6-8%) or underlying clear cell histology (87-88%). Greater than 93% of patients received VEGF inhibitors as first line therapy; 21% achieved an objective response in the sRCC group as compared to 26% in the non-sRCC group with significantly more sRCC patients (43% vs. 21%) having primary refractory disease ($p<0.0001$, for both). sRCC patients had significantly less use of second-line ($p=0.018$) and third-line ($p=0.0004$) systemic therapy. The median PFS / OS was 4.5 months / 10.4 months in sRCC patients and 7.8 months / 22.5 months in non-sRCC patients ($p<0.0001$ for both). Sarcomatoid histology was associated with a significantly worse PFS and OS after adjusting for the individual Heng risk factors in multivariable analysis (HR 1.5, $p<0.0001$ for both). **Conclusions:** Patients with sRCC have worse baseline prognostic criteria, a shorter time to relapse and worse clinical outcome to targeted therapy compared to patients with non-sRCC. Additional insight into the biology of sRCC is needed to develop alternative therapeutics.

4566

General Poster Session (Board #31B), Mon, 8:00 AM-11:45 AM

Genome-wide methylation profiling to identify potential epigenetic biomarkers associated with response to sunitinib in metastatic renal cell cancer (mRCC) patients (pts).

Jenny J. Kim, Mariette Labots, Luigi Marchionni, Shahnaz Begum, Gerrit A. Meijer, Henk M.W. Verheul, Michael Anthony Carducci, Hans J. Hammers, Mohammad Allaf, George J. Netto, Mohammad Hoque; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Department of Medical Oncology, VU University Medical Center, Amsterdam, Netherlands; Johns Hopkins University, Baltimore, MD; Department of Pathology, VU University Medical Center, Amsterdam, Netherlands; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; The Johns Hopkins University, Baltimore, MD

Background: There exists a significant heterogeneity in the clinical response to sunitinib among pts treated for mRCC and, thus, a biomarker which would predict pts' response up front would be an invaluable tool in the clinical management of these pts. In this regard, whole genome methylation array was performed between 2 extreme groups: sunitinib responders (RES) and non-responders (NRES) to identify differentially methylated genes between these subsets of pts. **Methods:** mRCC pts who received sunitinib therapy with available frozen nephrectomy tissues (stored at -80°C) and clinical data were identified. RES were identified as pts with progression free survival (PFS) of $>$ or $=$ 11 months (mos) and NRES as those with PFS $<$ or $=$ 3 mos. After DNA extraction and quality assurance according to standard protocol, whole genome methylation array was performed using Infinium HumanMethylation450 BeadChip Kit - Illumina. Data normalization was achieved by subset-quantile within array normalization (PMID: 22703947). Differentially methylated regions were identified using logit transformed Beta values, using an F-test after shrinking variance via empirical Bayes (PMID: 21118553). **Results:** Total of 13 pts who received sunitinib therapy with available frozen nephrectomy tissues were identified. Of the 13, 5 pts qualified for each RES and NRES cohort as described in methods section. All pts in RES group had clear cell subtype. Two pts of the NRES group were of non-clear cell subtype. The QC plots showed that all arrays were successful. For RES vs. NRES, one genomic location, DENND2D, was significantly hypermethylated in the RES group with a false discovery rate (FDR) of $<10\%$. DENND2D has been identified as a tumor suppressor-like gene in non-small cell lung cancer and melanoma cell lines in the recent past. **Conclusions:** In this study, DENND2D was significantly hypermethylated in sunitinib RES compared to NRES among mRCC pts. Data analysis with a less stringent FDR is also being pursued. Technical validation as well as clinical validation of DENND2D utilizing a larger pt cohort are ongoing.

4567

General Poster Session (Board #31C), Mon, 8:00 AM-11:45 AM

Validation of an inverse association between programmed death ligand 1 (PDL1) and genes in the vascular endothelial growth factor (VEGF) pathway in primary clear cell renal cell (ccRCC).

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Background: Trials combining anti-PDL1 and anti-VEGF therapies for clear cell renal cell carcinoma (ccRCC) are underway; however the relationship between the expression of PDL1 and genes in the VEGF pathway is poorly understood. Using the Affymetrix platform, we observed an inverse association between the expression of PDL1 and key genes in the VEGF pathway. Herein, we validate this inverse association using an independent set of 100 primary ccRCC tumors. **Methods:** From our registry database we sampled 100 ccRCC tumors with varying PDL1 protein expression (0%-100%) determined by immunohistochemistry (IHC). We extracted RNA from FFPE slides and performed RT-PCR to quantify gene expression of PDL1, VEGF, VEGFR1, and VEGFR2. All genes were normalized to the POLR2a gene. We evaluated the association of PDL1 protein expression and VEGF gene expression using Spearman rank correlation. In addition, we employed a linear mixed effects model to compare the fold-change in expression of VEGF genes between PDL1 low (0-5%, n=68) and PDL1 high (>5%, n=32) tumors. **Results:** As expected, PDL1 protein expression positively correlates with PDL1 gene expression (corr=0.42, p<0.001). Validating our array data, PDL1 protein expression inversely correlates with expression of key VEGF genes: VEGF (corr=-0.23, p=0.01), VEGFR1 (corr=-0.34, p<0.001), and VEGFR2 (corr=-0.23, p=0.01). In our dichotomized analysis, we noted significantly higher expression of VEGF genes in the PDL1 low compared to the PDL1 high group: VEGF (fold change=1.82, p<0.001), VEGFR1 (FC=2.63, p<0.001), and VEGFR2 (FC=2.13, p=0.001). **Conclusions:** We independently validate an inverse association between the expression of PDL1 and key genes in the VEGF pathway in primary ccRCC. If validated further in larger studies, the existence of an immune evasive and an angiogenic phenotype within ccRCC could inform current clinical trials targeting these two pathways. Ultimately, whether VEGF signaling affects PDL1 expression, or whether angiogenic or immune evasive phenotypes predict response to anti-PDL1, anti-VEGF, or a combination of the two therapies remains unclear.

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General Poster Session (Board #31D), Mon, 8:00 AM-11:45 AM

VHL-mutant renal cell carcinomas contain cancer cells with mesenchymal phenotypes.

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Background: To study “cancer stem cells” it is imperative to account for all stromal cell populations within the tumour. The existence of “cancer stem cells” in clear cell renal cell carcinoma (ccRCC) has not been examined in *ex vivo* patient samples. **Methods:** We established a multiplex flow cytometry (FC) antibody panel in ccRCC, which reliably identified stromal lineages including CD45+ immune, CD31+/CD144+ endothelial and fibroblast-marker-positive subpopulations, thus allowing isolation of “lineage-negative” tumor cells. To verify the identity of tumour-derived populations as either cancer cells or normal stromal cells, we took advantage of the fact that mutations in *VHL* occur early during ccRCC tumorigenesis and are found in two-thirds of patients. **Results:** We sequenced 18 patient tumor samples, 12 of which had *VHL* exome mutations. Targeted re-sequencing of FC sorted subpopulations from these patients’ samples revealed that while CD45+ immune cells and CD31+/CD144+ endothelial cells were genetically normal, a population of *VHL*-mutant fibroblast-marker positive cells was consistently identified in every patient’s tumour. Immunohistochemistry showed that fibroblast marker-positive *VHL*-mutant cells do not have the large “clear cell” morphology typical of the majority of the cancer cells in these tumours. When purified and cultured, these fibroblast marker-positive *VHL*-mutant cells proliferate extensively under mesenchymal culture conditions, but displayed different morphologies to lineage-negative *VHL*-mutant tumor cells. Functional characterization of these FC sorted cell subpopulations is ongoing, including proliferation, migration, invasion, differentiation and treatment resistance. **Conclusions:** The phenotype and preliminary functional characterization of these *VHL*-mutant fibroblast-marker positive cells suggests a mesenchymal differentiation program in ccRCC, with implications for the ontogeny, biology and clinical management of *VHL*-mutant renal cancer.

4569

General Poster Session (Board #31E), Mon, 8:00 AM-11:45 AM

Association of hyperbilirubinemia in pazopanib- or sunitinib-treated patients in COMPARZ with UGT1A1 polymorphisms.

Toby Johnson, Chun-fang Xu, Toni K. Choueiri, Keith C. Deen, Zhengyu Xue, Arundathy N. Bartlett-Pandite, Christopher Carpenter, Robert John Motzer; GlaxoSmithKline, Uxbridge, United Kingdom; GlaxoSmithKline, Harlow, United Kingdom; Dana-Farber Cancer Institute, Boston, MA; GlaxoSmithKline, Collegeville, PA; GlaxoSmithKline, Research Triangle Park, NC; GlaxoSmithKline Research and Development, Collegeville, PA; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: A phase III randomized clinical trial (COMPARZ) comparing pazopanib vs sunitinib for treatment of advanced renal cell carcinoma demonstrated similar efficacies but different safety profiles for the two therapies. Elevations in serum total bilirubin have been observed in patients receiving either therapy. *UGT1A1* polymorphisms are associated with elevated bilirubin in the general population (Gilbert's syndrome). This study investigated the association between functional *UGT1A1* polymorphisms and on-therapy serum total bilirubin in the COMPARZ study. **Methods:** Patients homozygous or compound heterozygous for *UGT1A1* *28, *37, and *6 alleles were predicted to have reduced *UGT1A1* function. Logistic regression adjusted for ancestry principal components was used to compare patients with on-therapy hyperbilirubinemia ($\geq 1.5 \times$ upper limit of normal [ULN]; pazopanib, N = 62; sunitinib, N = 34) against patients exposed to treatment and with maximum on-therapy bilirubin $\leq 1 \times$ ULN (pazopanib, N = 213; sunitinib, N = 215), excluding patients with maximum on-therapy bilirubin between 1 and $1.5 \times$ ULN (pazopanib, N = 96; sunitinib, N = 104). **Results:** Patients with predicted reduced *UGT1A1* function had higher baseline bilirubin and also were more likely to experience hyperbilirubinemia when receiving either pazopanib ($P = 6.9 \times 10^{-8}$) or sunitinib ($P = 1.8 \times 10^{-3}$). After adjusting for baseline bilirubin, patients with predicted reduced *UGT1A1* function remained more likely to experience hyperbilirubinemia when receiving pazopanib ($P = 0.015$) or sunitinib ($P = 0.026$), with odds ratio (95% CI) 3.53 (1.28–9.76) and 4.41 (1.23–15.75), respectively. **Conclusions:** The data suggest that some instances of hyperbilirubinemia in patients treated with pazopanib or sunitinib may be benign manifestations of Gilbert's syndrome. Bilirubin fractionation or, if not available, *UGT1A1* genotyping, would enable further characterization of liver safety risk and help in making treatment decisions.

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General Poster Session (Board #31F), Mon, 8:00 AM-11:45 AM

Pharmacogenetics as predictor of sunitinib and mTOR inhibitors toxicity in patients with metastatic renal cell carcinoma (mRCC).

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Background: Single nucleotide polymorphisms (SNPs) in major pharmacokinetics (PK) and pharmacodynamics (PD) pathways of targeted agents may affect the incidence of drug toxicities. **Methods:** Germline DNA was extracted from whole blood or normal kidney parenchyma from mRCC pts of European ancestry in two cohorts: those treated with VEGF-targeted therapy (sunitinib) (n=159) or with an mTOR inhibitor (everolimus or temsirolimus) (n=62). Ten SNPs in 6 candidate genes: CYP3A4 (rs2242480, rs4646437, rs2246709), CYP3A5 (rs15524), ABCB1 (rs2032582, rs1045642), VEGFR2 (rs2305948), NR1H3 (rs2307424, rs2307418), FLT3 (rs1933437) were genotyped using Sequenom iPLEX Gold platform. Logistic regression model tested the association of genotype variants with adverse events of 1) grade 3/4 (G3/4) toxicity and G3/4 hypertension (for sunitinib cohort) and 2) grade 3/4 toxicity and all grade pneumonitis (for mTOR inhibitors cohort), adjusted for clinical factors associated with toxicity outcomes. **Results:** In the sunitinib cohort, median treatment duration was 7.7 months (IQR=3-15.5), 83 (52%) pts had grade 3/4 toxicities and 22 (14%) had grade 3/4 hypertension. Rare variant (AG) of CYP3A4 rs464637 was associated with the reduced risk of grade 3/4 toxicities (4 events/17 cases) vs. wild-type (GG, 73 events/134 cases), (Odds Ratio (OR) = 0.27, 95%CI: 0.08-0.88, p=0.03). No association between SNPs and hypertension was observed. In the mTOR inhibitor cohort, median treatment duration was 3.4 months (IQR=1.4-6), 21(34%) pts had G3/4 toxicities and 27 (43%) had all grade pneumonitis. No association between SNPs and G3/4 toxicities was observed. Rare homozygote (GG) of FLT3 SNP rs1933437 was associated with increased risk of all grade pneumonitis (7 events/ 9 cases) vs. wild-type (AA, 4 events/12 cases), however, given the very small variant group size, further investigation is required to verify the association. **Conclusions:** The minor allele of SNP rs464637 in the gene CYP3A4 may influence sunitinib toxicity. Further validation is needed to determine if the marker could be used for in targeted therapy dosing strategies and direct patient care. (IQR=Interquartile Range).

4571

General Poster Session (Board #31G), Mon, 8:00 AM-11:45 AM

A phase II trial assessing pazopanib (paz) as third-line therapy for metastatic renal cell carcinoma (mRCC): Clinical outcome and temporal analysis of molecular profile.

Sumanta Kumar Pal, Dewan Md Sakib Hossain, Qifang Zhang, Chan Gao, Paul Henry Frankel, Christopher Ruel, Jeremy Jones, Courtney Carmichael, Przemyslaw Twardowski, Robert A. Figlin, Marcin Kortylewski; City of Hope, Duarte, CA; City of Hope Comprehensive Cancer Center, Duarte, CA; City of Hope Beckman Research Institute, Duarte, CA; Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Paz, an oral vascular endothelial growth factor (VEGF) receptor inhibitor, was assessed in a phase III study conducted in patients (pts) with mRCC who were cytokine-refractory or treatment-naïve (Sternberg *et al* J Clin Oncol 2010). Clinical outcomes with paz have been associated with a molecular profile (Tran *et al* Lancet Oncol 2012). The activity of paz in the 3rd-line setting and temporal changes in molecular profile during paz therapy are poorly understood. **Methods:** Eligibility was limited to pts with 2 prior lines of therapy (including at least 1 VEGF-directed therapy), ECOG PS 0-2, and clear cell histology. Pts received paz 800 mg/daily on a 28d cycle, and were assessed for response by RECIST 1.1 every 2 cycles. A Simon MinMax 2-stage design was employed, with 80% power of declaring an encouraging overall response rate (ORR) of 23% (type I error=10%). Molecular profiles were assessed on a Luminex platform using the Human Cytokine 30-plex Cytokine Immunoassay (Invitrogen) at baseline, 6 mos and 12 mos. **Results:** 28 pts (20M, 8F) were enrolled, with a median age of 63 (range, 45-86). All patients received at least 2 lines of prior therapy, and 6 pts (21%) had received 2 prior lines of VEGF-directed therapy. In the pre-specified intent-to-treat analysis, 12/28 pts (43%) had a confirmed response (1 CR, 11 PR), with 1 additional unconfirmed PR. 8 pts (29%) had SD as a best response. Median PFS for the cohort was 17.4 mos (95% CI 14.7-NR). No grade 4 treatment-related toxicities were observed. The most common grade 3 toxicities were hypertension (46%) and proteinuria (14%). At baseline, IL-6 was marginally lower in patients who achieved PR/CR (responders) as compared to those who did not (non-responders; P=0.06). Amongst patients still on therapy at 6 months and 12 months, responders had lower levels of HGF, IL-2R, IL-6, IL-8, and VEGF (P<0.05 for each) at both time intervals. **Conclusions:** Paz demonstrated an ORR of 43%, representing the highest ORR observed to date in a 3rd-line trial in mRCC. At 6 and 12 months, differences in molecular profile emerged between responders and non-responders, potentially underscoring mechanisms of drug resistance. Clinical trial information: NCT01157091.

4572

General Poster Session (Board #31H), Mon, 8:00 AM-11:45 AM

Prognostic significance of bone metastases (BM) and bisphosphonate (BIS) therapy in patients with metastatic renal cell carcinoma (mRCC) treated with molecularly targeted agents (MTAs).

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Background: BM are frequently present in patients with mRCC. BM cause significant morbidity and are associated with high rates of skeletal related events (SREs). The purpose of this retrospective analysis was to assess the impact of BM and BIS use on outcomes including progression-free survival (PFS) and overall survival (OS) in patients with mRCC. **Methods:** We conducted a pooled analysis of patients with mRCC treated from 2003-2011 on phase III (NCT00083899, NCT00065468, NCT00678392) and phase II trials (NCT00054886, NCT00077974, NCT00083889, NCT00338884, NCT00137423). Statistical analyses were performed using Cox regression and the Kaplan-Meier method. **Results:** We identified 2,749 patients treated with sunitinib (n=1,059), sorafenib (n=335), axitinib (n=359), temsirolimus (TEM) (n=208), TEM + interferon-alfa (IFN) (n=208), or IFN (n=560). Most patients were male (71%), had baseline ECOG PS of 0 (47%) or 1 (51%), clear cell histology (91%), and prior nephrectomy (84%). 285 patients (10.4%) received treatment with BIS (zoledronic acid n=233, pamidronate n=57, unspecified n=1). No patients received denosumab. Of the 2,504 patients with data regarding site of metastasis at diagnosis, 31.9% (n=781) had BM. The rate of SREs in patients with BM compared to patients without BM was 6.4% versus 1.4% (p<0.0001). Presence of BM was associated with shorter PFS (5.1 vs. 6.7 months (mo), HR 1.195, 95% CI 1.076-1.328, p<0.0008) and OS (13.2 vs. 20.2 mo, HR 1.292, 95% CI 1.145-1.456, p<0.0001) when compared to those without BM. In patients with BM, the use of BIS was not associated with improved PFS (5.1 vs. 4.9 mo, HR 0.867, 95% CI 0.704-1.067, p=0.1785) or OS (13.3 vs. 13.1 mo, HR 0.904, 95% CI 0.722-1.132, p=0.3801) when compared to patients who did not receive BIS. In patients with BM stratified by type of first-line MTA (TKI, mTOR inhibitor, or IFN-based), use of BIS was not associated with improved PFS or OS. **Conclusions:** In this analysis, we confirm that the presence of BM is an adverse risk factor for shorter PFS and OS in patients with mRCC treated with MTAs. Treatment with BIS did not have a positive impact on survival in this cohort.

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General Poster Session (Board #32A), Mon, 8:00 AM-11:45 AM

Effective monotherapy despite intratumor heterogeneity: Clonal convergence within the PI3K pathway and sensitivity to mTOR inhibitors in patients with advanced renal cell carcinoma (RCC).

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Background: Rapalogs, inhibitors of mTOR, are approved for treatment of advanced RCC. Recent reports of clonal heterogeneity challenge the concept of targeted monotherapy and the development of genomic biomarkers. Still, a subset of patients (pts) derives extended benefit from single agent rapalogs. This study analyzed such outliers so as to explore the genomic background of rapalog sensitivity in the setting of clonal heterogeneity. **Methods:** Cases were chosen based on time to treatment failure > 20 mos and tissue availability. DNA was extracted from spatially separate areas in primary tumors, metastases and the germline. Custom target capture and ultra-deep sequencing identified small indels, single base pair substitutions and copy number changes across all exons of 230 target genes. **Results:** 4 pts contributed 13 specimens (11 primary tumor samples, 2 metastases); mean exon coverage was 443X. Genomic alterations with activating effect on PI3K pathway signaling were seen in 11 of 13 specimens (Table). Clonal heterogeneity was present in all pts. For 2 pts, different mechanisms activated the pathway in separate sites, in 1 pt through separate genes. **Conclusions:** Pathway-activating genomic events across all sites explain rapalog benefit in 3 of 4 pts. Different disease sites in the same pt can harbor separate mechanisms activating the targeted pathway. This suggests that clonal convergence within the PI3K pathway can create an oncogenomic landscape sensitive to rapalogs despite branching clonal evolution. It supports the notion of sampling >1 disease site during future biomarker development.

		Mutations	Copy no. alteration	Functional (Fct) effect
1	P1	TSC1 frameshift	Heterozygous deletion (Het del) TSC1	Fct loss TSC1
	P2	TSC1 frameshift		Fct loss TSC1
	P3	TSC1 nonsense		Fct loss TSC1
2	P1	TSC1 frameshift	Het del TSC1	Fct loss TSC1
	P2	TSC1 frameshift		Fct loss TSC1
	P3	TSC1 frameshift		Fct loss TSC1
3	M1	TSC1 frameshift	-	Fct loss TSC1
	P1	mTOR missense		Fct gain mTOR
	P2	mTOR missense		Fct gain mTOR
	P3	mTOR missense		Fct gain mTOR
4	P4	TSC1 nonsense	Het del TSC1	Fct loss TSC1
	P1	-		-
	M1	-		-

4574

General Poster Session (Board #32B), Mon, 8:00 AM-11:45 AM

Pazopanib (P) and bevacizumab (B) in patients with metastatic renal cell carcinoma (mRCC) or other advanced refractory tumors: Phase I combination study final analysis.

Sylvie Negrier, Diane Charlotte Imbs, David Pérol, Ratislav Bahleda, Antoine Hollebecque, Helen Jane Boyle, Celine Ferlay, Severine Metzger, Ellen Blanc, Jean-Charles Soria, Bernard J. Escudier, Etienne Chatelut; Léon-Bérard Cancer Centre, Lyon, France; Institut Claudius Regaud, Toulouse, France; Centre Léon Bérard, Lyon, France; Institut Gustave Roussy, Villejuif, France; Institut Gustave Roussy, INSERM U981, Villejuif, France

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 recent VEGFR inhibitor P with B in mRCC treatment-naïve patients (pts) or in pts with other advanced refractory solid tumors. **Methods:** This double center trial was conducted with 3+3+3 escalation doses of P + B. The maximum tolerated dose (MTD) was 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. After preliminary DLT results, an approved by IDSMB extension cohort was enrolled and treated at MTD level. The effect of B on steady-state pharmacokinetic (PK) of P was also investigated by comparing PK at day 1 (D1) and D15 (day of B infusion). **Results:** 25 pts were enrolled with mRCC (n=7) or other advanced refractory solid tumors (n=18). Median age is 62 (41-79), 14 pts are male. At DL2 (n=10) 3 nephrectomized and 2 non-nephrectomized pts experienced DLT, as presented in the Table. In the 6-non-nephrectomized-pt extension cohort at DL1, 3 additional DLT were observed. Mean P AUC at D1 was higher than previously described in phase I P monotherapy (Clin Cancer Res 2009;15:4220). Mean P AUC at steady-state (D15) at both P dose levels was also significantly higher, though without being influenced by B infusion. **Conclusions:** The MTD of the P + B combination is respectively 400 mg/d and 7.5mg/kg (DL1) in all patients. Final PK analysis showed that there is no influence of B on P PK and that P AUC is higher than previously reported. Clinical trial information: NCT01202032.

N	Dose level (DL)	B	P	DLT
9	DL1	7.5 mg/kg	400 mg	No DLT
6	(extension cohort at DL1)			3 DLT: 2 grade 3 MAHA*, 1 grade 3 AST/ALT
10	DL2	7.5 mg/kg	600 mg	5 DLT: 1 grade 3 AST/ALT*,# 1 grade 3 pulmonary embolism 2 (1+1*) grade 3 reversible MAHA, 1 grade 3 AST/ALT, grade 2 hyperbilirubinemia

* Microangiopathic hemolytic anemia. * Nephrectomized pt.

4575

General Poster Session (Board #32C), Mon, 8:00 AM-11:45 AM

Adoptive immunotherapy with autologous cytotoxic T lymphocytes (CTLs) pulsed ex vivo with patient-derived tumor cells in heavily pretreated, advanced renal cell carcinoma (aRCC) patients: A feasibility study.

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Background: Immunotherapy still remains the only treatment which proved able to induce long-lasting complete responses in aRCC. The aim of the present study was to evaluate the feasibility and safety of adoptive immunotherapy with *ex vivo*-generated autologous CTLs pulsed with patient-derived tumor cells in heavily pre-treated subjects with aRCC. **Methods:** This study was performed in accordance with local regulations on the production of cell derivatives; local Ethical Committee approval was obtained on a named patient basis, after obtaining each patient's informed consent. CTLs were generated stimulating CD8-enriched lymphocytes with dendritic cells (DCs) pulsed with fresh autologous tumor cells in the presence of IL-12 and IL-7; these specific anti-tumor CTLs were expanded and then reinfused after a lymphodepleting chemotherapy with CTX and fludarabine, followed by s.c. administration of low-dose IL-2. Disease status was assessed after every two re-infusions. Eight patients were enrolled, 6 with a clear cell RCC, 1 with a papillary RCC, and 1 with a mixed, papillary and collecting ducts, RCC. All patients have been previously treated with a median of 5 prior treatment lines; the median time between diagnosis of aRCC and tumor biopsy was 55 months (15-185). **Results:** Six of the 8 enrolled patients have produced suitable tumor cell lines, and 5 of them had been already re-infused with tumor-specific CTLs. All patients received at least 2 CTL infusions (range: 2-5+); mean of totally infused CTLs was 10.7×10^9 (range: 4-26.6). All CTLs infusions were well tolerated, with no evidence of autoimmune reactions. In terms of antitumor activity, one patient achieved a partial response, 3 had a slowly progressing disease, and one patient is still not evaluable; furthermore, in 3 patients disease-related symptoms improved. **Conclusions:** Our preliminary results suggest that immunotherapy with autologous CTLs pulsed *ex-vivo* with patient-derived tumor cells is feasible and safe in heavily pre-treated aRCC patients. Signs of activity were recorded, suggesting the need to further expand this cohort of patients.

Randomized phase II study of first-line everolimus plus bevacizumab (E+B) versus interferon α -2a plus bevacizumab (I+B) in patients (pts) with metastatic renal cell carcinoma (mRCC): Record-2 final overall survival (OS) and safety results.

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Background: RECORD-2 (NCT00719264) primary analysis demonstrated similar median progression-free survival (PFS) for pts with mRCC treated with E+B and I+B (Dec 2011 cut-off). The primary objective was not met; median PFS in E+B/I+B was 9.3/10.0 mo ($HR_{IFN/EVE}$, 0.91; 95% CI, 0.69-1.19; $P=0.485$) and probability of success (PoS) of a subsequent phase III trial was 5.1%. Here we present final OS and safety/exposure results (Aug 2012 cut-off). **Methods:** Untreated pts with clear cell mRCC and previous nephrectomy were randomized 1:1 to B 10 mg/kg every 2 weeks and either E 10 mg/day or I (9 MIU 3 times/week). The primary objective was treatment effect on PFS per central review based on an estimation of PoS ($\geq 50\%$) of a subsequent phase III study. Secondary objectives included OS and safety. **Results:** In E+B ($n=182$) and I+B ($n=183$) arms, median age was 60/60 years and 76/72% of pts were men, respectively. In both arms, most pts (93%) were of favorable/intermediate MSKCC risk. Median follow-up was 33 mo. In E+B and I+B arms, 51/52% of pts died, respectively. Median OS (95% CI) was 27.1 mo (19.9-35.3) in the E+B arm and 27.1 mo (20.4-30.8) in the I+B arm. After discontinuing study treatment, 64/60% of pts in E+B and I+B arms, respectively, received antineoplastic therapy. Median exposure duration in E+B and I+B arms was 8.5/8.3 mo, respectively; AEs resulted in treatment discontinuation for 23/25% of pts, respectively. The most frequent AEs (%) were stomatitis (63), proteinuria (50), diarrhea (40), hypertension (38), and epistaxis (35) in the E+B arm and decreased appetite (45), fatigue (42), proteinuria (38), asthenia (35), and pyrexia (35) in the I+B arm. The most frequent grade 3/4 AEs (%) were proteinuria (24), stomatitis (11), and anemia (11) for E+B and fatigue (17), asthenia (14), and proteinuria (10) for I+B. **Conclusions:** OS of E+B and I+B was similar. OS results are consistent with PFS primary analysis. First-line treatment with mTOR inhibitor-based therapy did not impair chance of survival relative to standard therapy. No new safety issues were identified and E+B remained generally well tolerated. Clinical trial information: NCT00719264.

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General Poster Session (Board #32E), Mon, 8:00 AM-11:45 AM

Multiplexed tissue protein assay as a predictor of response to targeted therapy in advanced renal cell carcinoma.

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Background: A number of prognostic biomarkers have been explored in advanced renal cancer, but to date none have been useful in therapeutic outcome prediction. **Methods:** Following regulatory approval, formalin-fixed paraffin embedded (FFPE) pre-therapy (sunitinib and/or mTOR inhibitors) tissue samples and clinical data on kidney cancer patients (pts) were obtained. The FFPE tissue was analyzed using layered immunohistochemistry which allows analysis of multiple biomarkers using a single tissue section. Multiplexed panels of protein biomarkers were used to probe tissue sections for proteins along the PI3K/AKT/mTOR and/or the VEGFR/PDGFR signaling pathways. Expression of biomarkers in tumor tissue was scored and predictive scores which correlated with the pt's clinical outcome status generated. **Results:** Tissue samples of 51 pts treated with sunitinib (S) were analyzed. A predictive score was generated by combining the scores assigned to VEGFR1 and VEGFR2 and multiplying the sum with the score of VEGFA. A predictive score equal to or above 24, was associated with response or stable disease (SD) at 12 weeks. Patients with a score <24 were predicted to have progression (PD) on S. Using this scoring method, 27 of the 33 responders tested and 15 of the 18 non responders were accurately identified. The accuracy of the test was noted to be 82.6% and sensitivity and specificity were 81.8% and 83.3% respectively. Tissue samples of 33 pts treated with mTOR inhibitor were analyzed using the same technique. Three biomarkers in the mTOR pathway (pmTOR (Ser 2448), p4EBP1 (Ser 65), p4EBP1 (Thr 37-46)) were used to create a predictive score. Eight of 12 OR/SD pts (sensitivity 67%) and 17 of 21 PD pts (specificity 76%) were accurately predicted using a score cut-off of 6 for an accuracy of 71.5%. Statistical modeling, results of ongoing validation testing, and score correlation with time to progression will be presented. **Conclusions:** These results indicate that an assay based on multiplexed protein analysis of tumor tissue is capable of providing clinically applicable information to help guide therapy. Funding source: Supported in part by NCI BRIDGE Grant 5R44CA123994-06 and by NCI SBIR Contract No. HHSN261201000135C.

Treatment response and survival outcome of patients with late relapse (LR) from renal cell carcinoma (RCC) in the era of targeted therapy.

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Background: A small subset of localized RCC patients will experience disease recurrence ≥ 5 years after nephrectomy. Clinical outcome of patients with LR has not been well characterized. **Methods:** Patients with mRCC treated with targeted therapy were retrospectively characterized according to time to relapse. Relapse was defined as diagnosis of recurrent metastatic disease >3 months after initial diagnosis. Patients with synchronous metastatic disease at presentation were excluded. Patients were classified as Early Relapsers (ER) if they recurred within 5 years while Late Relapsers (LR) recurred after 5 years. Demographics and outcomes were compared. **Results:** 1210 mRCC patients were identified; 903 (74.6%) with relapse within the first 5 years, 200 (16.5%) within >5 -10 years, and 107 (8.8%) after 10 years (range 10-35 years). Baseline characteristics are presented in the Table. Overall response rates to targeted therapy were better in LR vs. ER (35% vs. 24%; $p=0.009$). LR patients had significant longer progression free- (10.7 vs. 8.5 months; log rank $p=0.004$) and overall survival (34.0 vs. 27.3 months; log rank $p=0.003$). **Conclusions:** One quarter of patients that eventually developed metastatic disease treated with targeted therapy relapsed over 5 years from initial diagnosis. The proportion of patients that relapse after five years is substantial. mRCC patients presenting with LR have more favorable prognostic features, treatment response, and overall survival.

Baseline characteristics.

Characteristic	Early relapser (<=5yrs) N=903	Late relapser (>5yrs) N=307	P value
Age of metastatic disease (mean yrs)	59	62	0.0007
Heng prognostic score			<0.0001
Favorable	231 (31%)	119 (46%)	
Intermediate	422 (56%)	125 (49%)	
Poor	94 (13%)	12 (5%)	
>1 organ metastatic site			0.0001
Yes	634 (70%)	250 (81%)	
No	269 (30%)	57 (19%)	
Brain metastases			0.8152
Yes	68 (8%)	22 (7%)	
No	830 (92%)	285 (93%)	
Clear cell histology			0.0018
Yes	750 (86%)	261 (93%)	
No	120 (14%)	19 (7%)	
Sarcomatoid histology			0.0005
Yes	66 (8%)	4 (2%)	
No	741 (92%)	229 (98%)	
Furthman grade			<0.0001
1	22 (3%)	19 (12%)	
2	225 (32%)	77 (48%)	
3	317 (44%)	56 (35%)	
4	135 (19%)	7 (4%)	

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General Poster Session (Board #32G), Mon, 8:00 AM-11:45 AM

Impact of cytoreductive nephrectomy on disease-specific survival (DSS) in the cytokine and targeted therapy eras: Age- and TNM-stage matched analysis of SEER data.

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Background: The role of cytoreductive nephrectomy (CN) for patients with mRCC was well-defined in the cytokine era. However, its role is controversial in the era of targeted therapies. **Methods:** The Survival, Epidemiology, and End Results (SEER) Database was queried to compare the relative benefit of CN in the cytokine era (defined as 1992-2004) as compared to the targeted therapy era (defined as 2005-2009). Patients with mRCC and clear cell, papillary or chromophobe histology were identified, and divided into cohorts with and without CN. Within each category, patients diagnosed during the cytokine era were matched by age and TNM stage to patients diagnosed during the targeted therapy era. Associations between clinicopathologic characteristics and DSS were explored through univariate and multivariate analyses. **Results:** Amongst matched pts who had received CN (n=2,218), no significant differences in age, gender, race, histology (clear cell v non-clear cell), T-stage, or N-stage were observed. Median DSS was superior in those patients diagnosed during the targeted therapy era as compared to the cytokine era (22 mos v 17 mos, $P<0.0001$). On multivariate analysis including the aforementioned clinicopathologic variables and DSS, diagnosis during the targeted therapy era was an independent predictor of improved survival amongst patients who had received CN (HR 0.78, 95%CI 0.70-0.87; $P<0.0001$). Amongst matched pts who had not received CN (n=4,214), there were no differences in clinicopathologic characteristics. Median DSS was similar in patients diagnosed during the targeted therapy era as compared to the cytokine era within this group (4 mos for each; $P=NS$). **Conclusions:** Patients who received CN during the targeted therapy era had a superior DSS as compared to patients who received the procedure during the cytokine era. In contrast, patients who had not received CN had a similar DSS across both time periods. While prospective trials mature (i.e., CARMENA and EORTC 30073), these data support the continued use of CN in the context of targeted agents.

Association analysis of polymorphisms in genes related to sunitinib pharmacokinetics.

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Background: Sunitinib is approved as systemic therapy for mRCC, GIST and pNET. Interpatient variability in the pharmacokinetics (PK) of sunitinib is high, which may have serious consequences for efficacy and toxicity of the drug. The objective of this study was to evaluate whether polymorphisms in candidate genes involved in sunitinib metabolism are related to the PK of sunitinib and its active metabolite SU12662. **Methods:** In this multicenter study, steady state sunitinib plasma concentrations and genotypes were prospectively obtained from 115 patients. Single nucleotide polymorphisms (SNPs) and haplotypes in 8 genes encoding *CYP1A1*, *CYP3A4*, *CYP3A5*, *ABCB1*, *ABCG2*, *NR1I2*, *NR1I3*, and *POR* were evaluated as covariates in a population pharmacokinetic model describing both sunitinib and SU12662 PK using NONMEM. First, candidate genotypes/haplotypes were individually tested for a potential association with sunitinib or SU12662 clearance. Next, potential significant SNPs ($p < 0.05$) were simultaneously included in a multivariate model and tested by backward elimination with a significance threshold of $p < 0.0005$. **Results:** Four out of 37 screened genotypes (from 14 different SNPs) were related to sunitinib clearance (*CYP3A4**22 CC and CT, *CYP3A5**3 GG, and *ABCB1* (2677 TT)). *CYP3A5**3 AG genotype was associated with clearance of SU12662. In the multivariate analysis, none of the SNPs reached the predefined significance threshold of $p < 0.0005$. Nevertheless, *CYP3A4**22T allele carriers showed a 22.5% decreased clearance of sunitinib ($p < 0.01$). **Conclusions:** Our data suggest that individual SNPs or haplotypes in *CYP1A1*, *CYP3A4*, *CYP3A5*, *ABCB1*, *ABCG2*, *NR1I2*, *NR1I3* and *POR* are not clearly associated with sunitinib or SU12662 clearance. Several (environmental) factors may also influence the PK of sunitinib. Interestingly, the recently identified *CYP3A4**22 SNP potentially has an impact on drug exposure. Replication studies in larger groups of patients are needed to verify the role of *CYP3A4**22 for sunitinib clearance.

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General Poster Session (Board #33A), Mon, 8:00 AM-11:45 AM

Novel stratification of the recurrence risk following surgical extirpation of clear cell renal cell carcinoma using tissue biomarkers in the mammalian target of rapamycin pathway.

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Background: Aberrant activation of the mammalian target of rapamycin (mTOR) pathway promotes invasiveness and metastatic potential in a variety of malignancies. The aim of the present study was to evaluate the association of altered expression of mTOR pathway components with recurrence outcome in non-metastatic clear cell renal cell carcinoma (ccRCC) patients. **Methods:** Immunohistochemistry for phos-S6, phos-mTOR, mTOR, phos-AKT, HIF-1 α , RAPTOR, PTEN, PI3K, and phos-4EBP1 was performed on tissue microarrays of patients treated for non-metastatic kidney cancer between 1997-2010. Patients were defined as having a low (<) or high risk (\geq) of nomogram predicted recurrence (2001 MSKCC RCC post-op) using an 8% cutoff. The relationship between individual marker expression, as well as combined marker score (low, intermediate and high defined as ≤ 3 , 4-5, >5 altered biomarkers; respectively) with the actual and predicted relapse rates was assessed. **Results:** The study included 419 non-metastatic ccRCC patients (pT1-T2 79.5%, pT3-T4 20.5%, Fuhrman nuclear grade 1-2 in 69%, 3-4 in 31%). 219 and 200 patients had low (<8%) and high (\geq 8%) nomogram-predicted 5-year risk of recurrence respectively. With a median follow-up of 2.2 years, recurrences were detected in 5 (2.3%) of the predicted low risk and 30 (15%) of the predicted high risk patients. mTOR pathway biomarker profiles were not predictive for patients at low predicted risk of recurrences. For patients at high predicted risk of recurrence, low, intermediate and high combined marker scores were found in 84 (42%), 79 (39.5%), and 37 (18.5%), respectively. The actual rates of recurrence were noted for 8.3% of low, 13.9% of intermediate and 32.4% of high combined marker score in a statistically significant distribution ($p=0.027$). **Conclusions:** The cumulative number of aberrantly expressed mTOR biomarkers correlates with a higher rate of recurrence. The combined marker score may help further stratify patients with high nomogram predicted risk of recurrence. Our data supports prospective evaluation of these biomarkers to augment current clinico-pathologic predictors of outcomes in ccRCC.

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General Poster Session (Board #33B), Mon, 8:00 AM-11:45 AM

Overcoming sunitinib-induced resistance by dose escalation in renal cell carcinoma: Evidence in animal models and patients.

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Background: Sunitinib is considered a first-line therapeutic option for patients with advanced clear cell renal cell carcinoma (ccRCC). However, despite the clinical efficacy, eventually tumors develop resistance and progress. Thus, we have tested the hypothesis whether sunitinib dose-escalation could overcome initial drug resistance. **Methods:** Human patient-derived ccRCC xenografts were implanted in SCID mice and were randomly assigned into two groups (sunitinib and vehicle). Mice were treated with sunitinib 5 days/week with a dose-escalation schema starting from 40 mg/kg to 60 mg/kg and 80 mg/kg. Tumor volumes and body weights were assessed weekly. Tumor tissues and blood were collected prior to dose increments. In selected patients treated with 50 mg sunitinib and presenting minimal toxicities, dose was escalated to 62.5 and 75 mg at the time of tumor progression. **Results:** Our preclinical results show that patient-derived tumors (RP-01 and RP-02), although initially responsive to sunitinib 40 mg/kg, eventually became resistant to treatment. Following dose increase to 60 mg/kg, we observed again tumor response but eventually the tumors became resistant. A similar effect was noticed when we further escalated sunitinib to 80 mg/kg. Immunohistochemistry analysis shows decreased tumor vascularization during response to sunitinib, but then hypervascularization at the time of resistance. Associated increase in expression of the methyltransferase EZH2, the histone marks H3K27me3, H3k4me2 and H3K9me2 in tumors resistant to sunitinib was observed. Analysis of sunitinib and VEGF/VEGFR2 blood and tumor levels will be reported. In parallel, our clinical experience shows that intra-patient sunitinib dose-escalation was safe and clinical benefit was observed. Details on tumor responses and toxicities will be reported. **Conclusions:** Overall, our results suggest that sunitinib-induced resistance may be overcome in part by increasing the dose of the VEGF receptor tyrosine kinase inhibitor in mouse models and ccRCC patients, and highlights the potential role of epigenetic changes associated with sunitinib resistance.

4583

General Poster Session (Board #33C), Mon, 8:00 AM-11:45 AM

Contrasting vascular response to sunitinib as measured by DCE-CT, DCE-MRI, and DCE-US in renal cell carcinoma (RCC) patients (pts).

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Background: Imaging (DCE-MRI, DCE-CT, DCE-US) provides information about the integrity and hemodynamics of the tumor microvasculature. **Methods:** 34 treatment (Rx) naive pts with RCC and abdominal tumor suitable for imaging received sunitinib 50 mg on a standard 4/2 schedule. DCE-US, DCE-CT, and DCE-MRI were done at baseline, during the first course and after 2wks off Rx. Imaging parameters included vessel permeability (Ktrans), extracellular volume fraction (v_e) and $K_{trans}/v_e = K_{ep}$ (by DCE-MRI), permeability surface product (PS) by DCE-CT, blood volume (BV), by DCE-CT and DCE-US and blood perfusion (by DCE-US). A morphology parameter (MP) was developed that relates flow kinetics of the microbubble contrast agent to tumor vascular morphology by DCE-US. **Results:** Several imaging parameters predicted for progression free survival (PFS) in responding pts (N=26). Baseline imaging parameters correlated with PFS: Ktrans by DCE-MR (Spearman $r = 0.53$, $p = 0.01$, N=24), BV by DCE-CT ($r = 0.48$, $p = 0.02$, N=25) and disorganized vessel morphology (large MP) by DCE-US ($r = -0.45$, $p = 0.02$, N=24). Changes from baseline imaging parameters correlated with PFS: BV by DCE-US at 2 wks ($r = -0.46$, $p = 0.02$, N=24), K_{ep} by DCE-MR at 2 wks ($r = -0.45$, $p = 0.03$, N=24) and MP at 1wk ($r = 0.67$, $p = 0.02$, N=12). There was a correlation between imaging methods: BV measured by DCE-CT correlated with BV by DCE-US ($r = 0.46$, $p = 0.03$, N=23) and K_{ep} by DCE-MR ($r = 0.59$, $p = 0.003$, N=22); Permeability measured by DCE-MR (Ktrans) and DCE-CT (PS) correlated at 2wks ($r = 0.56$, $p = 0.01$, N=21). A combination of baseline US and MR parameters identified responders and non-responders with a sensitivity of 83% and specificity of 90%. **Conclusions:** This is the first study to contrast DCE-US, DCE-CT and DCE-MRI imaging in pts receiving antiangiogenic therapy. Baseline parameters for all three methods can predict for PFS. Changes from baseline in DCE-US and DCE-MRI parameters also predict for PFS. There is a correlation between imaging methods in parameters that measure BV and permeability. A novel DCE-US parameter was developed (MP) that quantifies the degree of tumor vascular disorganization. Baseline values in MP and changes during Rx correlate with PFS. Clinical trial information: OCT1205.

4584

General Poster Session (Board #33D), Mon, 8:00 AM-11:45 AM

Phase II trial of vandetanib in Von Hippel-Lindau-associated renal cell carcinoma.

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Background: Germline mutations in the von Hippel Lindau (VHL) gene are associated with the development of bilateral multifocal clear-cell renal cell carcinoma (RCC). VHL patients with localized disease are surgically managed, with nephron sparing resection recommended once tumors reach 3 cm. Patients typically undergo multiple surgeries with significant cumulative morbidity. In this phase 2 trial of vandetanib, a dual VEGFR2/EGFR inhibitor, a systemic approach to these tumors was explored. **Methods:** Patients with VHL-associated RCC were treated with 300 mg vandetanib daily until disease progression or unacceptable toxicity. Cross sectional imaging was performed at baseline and every 12 weeks. The primary endpoint was overall renal tumor response assessed by RECIST. **Results:** A total of 34 subjects were enrolled, with a mean age of 47 years (range 28 – 72). The median number of targeted lesions per subject was 2 (range 1 – 6) and the mean tumor diameter was 2.3 cm (range 1.2 – 4.0). Twenty-seven (80%) subjects had baseline imaging and at least one follow-up study to allow response evaluation. Median time on study was 6.1 months (range 1.0 – 23.3). Thirteen (38%) subjects demonstrated overall reduction in tumor burden with a median reduction of 6% (range 4-54%). One (3%) subject had a PR by RECIST and 26 (77%) had stable disease as their best response. Eleven (32%) subjects were taken off study due to growth of at least one lesion that met criteria for surgical resection or disease progression. Nine (27%) subjects required dose reductions due to toxicity. Although the majority of adverse events encountered on trial were grade 2 or less, 9 (27%) subjects were taken off trial due to drug-related toxicities and 9 (27%) withdrew due to intolerable side effects. Rash (71%), and QTc prolongation (41%) were the most common adverse events noted. **Conclusions:** In the largest phase II study of a systemic agent for VHL-related RCC, vandetanib demonstrated anti-tumor activity. Despite a reasonable safety profile, poor tolerability necessitated drug withdrawal in a significant proportion of patients. Newer agents that selectively target the VEGF receptors may offer a more tolerable alternative and might optimize clinical benefits in this population. Clinical trial information: NCT0056695.

4585

General Poster Session (Board #33E), Mon, 8:00 AM-11:45 AM

Continuation of sunitinib following RECIST progression on first-line sunitinib.

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Background: In the last seven years the FDA and the EMA have approved seven agents for treatment of RCC. Five of these target the VEGF pathway. **Methods:** We conducted a detailed analysis of data from the sunitinib registration trial examining the growth and regression rate constants and the stability of the growth rate as measures of effectiveness and to understand development of resistance. **Results:** Sufficient data was available for the analysis of 350/374 patients enrolled. Statistically valid data was obtained in 321(91.7%). The median regression rate constant was 0.0048 days^{-1} , and in 59 patients no evidence of growth was recorded while on study, only regression. The median growth rate was $0.00082 \text{ days}^{-1}$ and this rate was stable a median of 267 days, remaining stable beyond 300 days in 172 patients, beyond 600 days in 95 patients, and beyond 900 days in 49 pts. A suggestion of a possible increase of the growth rate while sunitinib was administered could be discerned in only 15/321 pts. With a median growth rate $0.00082 \text{ days}^{-1}$ the estimated time to progression were sunitinib discontinued and then re-started would have been a minimum of 7.3 months. Thus a meaningful outcome could be achieved provided continued sunitinib is tolerable. Finally with an estimated 47%, 27% and 13% of tumor still sensitive to sunitinib 100, 200 and 300 days after starting therapy, shrinkage with a new TKI in patients who discontinue sunitinib before day 300 for toxicity may not be a sign of non-cross resistance, but of residual sensitive tumor. **Conclusions:** Prolonged stability of the growth rate of RCC on sunitinib is consistent with intrinsic and not acquired resistance. Baring toxicity, continued sunitinib beyond RECIST criteria for progression may provide a beneficial outcome and can be considered a treatment alternative in selected patients. Randomized trials to assess the value of VEGF TKI's in patients whose disease has "progressed" on sunitinib should consider including an arm that continues sunitinib to test this hypothesis.

4586

General Poster Session (Board #33F), Mon, 8:00 AM-11:45 AM

First-, second-, third-line therapy for metastatic renal cell carcinoma (mRCC): Benchmarks for trials design from the International mRCC Database Consortium (IMDC).

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Background: Limited data exists on outcomes for mRCC patients treated with multiple lines of therapy. Benchmarks for survival are required for patient counseling and clinical trial design. **Methods:** Outcomes of mRCC patients from the IMDC treated with 1, 2, or 3+ lines of targeted therapy (TT) were compared and adjusted by proportional hazards regression. Overall survival (OS) and progression-free survival (PFS) benchmarks were calculated using different population inclusion criteria. OS and PFS are calculated from the line of therapy under consideration unless otherwise specified. **Results:** 2,705 patients were treated with TT of which 1,533 (57%) received only 1st-line TT, 734 (27%) received 2 lines of TT, and 438 (16%) received 3+ lines of TT. The median OS of patients that received 1, 2 or 3+ lines of TT *starting from initial TT* was 14.9, 21.0, and 39.2 months, respectively ($p < 0.0001$). On multivariable analysis adjusting for baseline Heng prognostic factors, the use of 2nd-line and 3rd-line therapy were each independently associated with better OS (HR=0.738 and 0.626, respectively, both $p < 0.0001$). Survival benchmarks derived from patients in the IMDC using selected inclusion criteria as seen in contemporary mRCC clinical trials are shown below. **Conclusions:** Patients that are able to receive more lines of TT live longer. Survival benchmarks provide context and perspective when interpreting and designing new clinical trials.

Population (data from IMDC)	PFS (mon) (95% CI)	OS (mon) (95%CI)
All patients	7.2 (6.7-7.7) n=2,659	20.9 (19.6-22.5) n=2,705
1st line therapy in intermediate/poor risk patients with diagnosis to treatment interval < 1 year (ADAPT (AGS003) trial design)	5.6 (5.3-6.1) n=1,174	14.7 (13.3-16.5) n=1,189
1st line therapy in patients with prior nephrectomy (TIVO-1 (Tivozanib) trial design)	8.2 (7.8-8.6) n=2,080	24.8 (23.1-27.3) n=2,117
2nd line therapy (INTORSECT trial design)	3.9 (3.6-4.3) n=1,151	13.0 (12.2-14.7) n=1,157
3rd line therapy (all patients)	4.0 (3.4-4.5) n=425	12.1 (10.7-13.9) n=455
3rd line therapy in patients with 1 prior VEGF and 1 prior mTOR inhibitor (GOLD (dovitinib) study)	4.4 (3.3-5.2) n=140	18.0 (11.8-24.0) n=147

Phase II study of dovitinib in first line metastatic or (nonresectable primary) adrenocortical carcinoma (ACC): SOGUG study 2011-03.

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Background: Dovitinib is a novel targeted therapy that inhibits the fibroblast growth factor receptor (FGFR). Preclinical studies have pointed to a major role of this pathway in adrenocortical carcinoma (ACC) thus we aimed to test its clinical efficacy in this tumor. **Methods:** A phase II proof of concept trial was designed. Since this is an extremely infrequent disease sample size calculation was done taking as a basis the first stage of a two-stage Gehan model. Thus 15 patients needed to be included to show a treatment efficacy of at least 15% (probability of Type I error $\alpha = 0.05$, power $[1 - \beta] = 0.8$). Main inclusion criteria was advanced non-resectable ACC, histologically confirmed, with no prior therapy other than mitotane. Primary endpoint was response rate (RR) by RECIST 1.1 assessed by an independent radiologist. Secondary endpoints included clinical benefit (RR plus stable disease), progression free (PFS) and overall survival (OS). Dovitinib was administered at 500mg daily dose 5 days on 2 days off for 6 months. Continuation of therapy was permitted at physician criteria. **Results:** From January 2012 to August 2012, 17 patients (5 male and 12 female) have been included in 7 institutions. Median age was 53 years (range 26-72); ECOG was 0-1 in 15 patients, 2 in one patient and N/A in one patient. 77 cycles, defined as one month on treatment, have been administered with dose reductions in 6 (7.8%). Grade 3-4 adverse events deemed as related to the drug were: rash (6%), asthenia (12%), diarrhea (6%), GGT elevation (18%), nausea (6%), hypertriglyceridemia (6%), hypertension (6%), hyperkalemia (6%). 13 patients withdrew treatment because of disease progression and 4 remain on dovitinib. No toxic death was reported. After a median follow-up of 5, 2 months (range 2,27 - 9,7) no objective response has been observed. Median PFS was 1,8 months (CI 95% [1,35 -2,25]), median OS has not been reached and clinical benefit has been achieved in 35% of patients with long lasting stable disease (>6 months) in 23%. **Conclusions:** Though no objective response was observed, a significant number of long lasting stabilizations have been achieved with an acceptable toxicity. These encouraging results merit further study. Clinical trial information: NCT01514526.

TPS4588[^]

General Poster Session (Board #33H), Mon, 8:00 AM-11:45 AM

The Borealis-2 clinical trial: A randomized phase II study of OGX-427 plus docetaxel versus docetaxel alone in relapsed/refractory metastatic urothelial cancer.

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Background: Heat shock protein 27 (Hsp27) is over-expressed in many cancers including bladder, lung, prostate, and breast. Increased Hsp27 has been associated with inhibition of chemotherapy-induced apoptosis, increased tumor cytoprotection, and development of treatment resistance. OGX-427 is an antisense oligonucleotide designed to bind Hsp27 mRNA, inhibiting production of the Hsp27 protein. Inhibition of Hsp27 has been shown to increase apoptosis, inhibit tumor growth, and sensitize tumor cells to chemotherapy in a variety of malignancies, including urothelial cancer. Results of preclinical and phase 1 studies suggest that addition of OGX-427 to chemotherapy is well tolerated and may improve treatment efficacy. BOREALIS-2 is a randomized, multicenter, phase 2 study of OGX-427 in combination with docetaxel (DOC) vs. DOC alone in locally advanced/metastatic bladder cancer patients who received at least one line of prior platinum-based therapy. The primary objective is to evaluate overall survival. Secondary objectives include comparisons of safety and tolerability, disease response, and serum levels of Hsp27 and other pathway-related proteins. Associations between clinical outcomes, levels of Hsp27 and other proteins, and circulating tumor cells will be evaluated. **Methods:** Patients (N=200) are randomized in a 1:1 ratio following stratification (time from prior systemic chemotherapy; Bellmunt criteria). Up to 2 prior systemic therapies are allowed. Treatment-arm patients receive three loading doses of OGX-427 (600 mg) followed by up to ten 21-day treatment cycles (OGX-427 1000 mg on Days 1, 8, and 15 and DOC 75 mg/M² IV on Day 1). Control-arm patients receive DOC 75 mg/M² IV on Day 1 of each cycle. Treatment may continue until disease progression, unacceptable toxicity, completion of 10 cycles, or patient withdrawal. Patients who discontinue DOC due to toxicity after ≥ 2 cycles and do not have disease progression may receive maintenance therapy with OGX-427. One interim futility analysis will be performed. The trial will not be stopped early based on efficacy. Clinical trial information: NCT01780545.

TPS4589

General Poster Session (Board #34A), Mon, 8:00 AM-11:45 AM

A phase II study of cabozantinib (XL184) in patients with advanced/metastatic urothelial carcinoma.

Andrea Borghese Apolo, Howard L. Parnes, Ravi Amrit Madan, James L. Gulley, John Joseph Wright, Kattie Khadar, Jane B. Trepel, Jeffrey Schlom, Philip M. Arlen, Maria Merino, Seth M. Steinberg, Peter L. Choyke, Maria Liza Lindenberg, Karen A. Kurdziel, Les Folio, William Douglas Figg, Piyush K. Agarwal, Donald P. Bottaro, William L. Dahut; National Cancer Institute, Bethesda, MD; Division of Cancer Prevention, National Cancer Institute, Bethesda, MD; Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; National Cancer Institute, Rockville, MD; Medical Oncology Branch, National Cancer Institute, Bethesda, MD; Laboratory of Tumor Immunology and Biology, Medical Oncology Branch, National Cancer Institute, Bethesda, MD; National Cancer Institute, National Institutes of Health, Bethesda, MD; Biostatistics and Data Management Section, CCR, National Cancer Institute, Bethesda, MD; Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; Molecular Imaging Program, CCR, NCI, NIH, Bethesda, MD; Radiology and Imaging Sciences, National Institutes of Health, Bethesda, MD; Molecular Pharmacology Section, National Cancer Institute, National Institutes of Health, Bethesda, MD; Urologic Oncology Branch, National Cancer Institute at the National Institutes of Health, Bethesda, MD

Background: Accumulating evidence supports MET as a therapeutic target in urothelial carcinoma. Activated MET can promote angiogenesis and tumor growth by upregulating VEGF and may play a role in urothelial carcinoma pathogenesis. Cabozantinib inhibits primarily VEGFR2 and MET pathways. Cabozantinib has been approved by the FDA for the treatment of progressive metastatic medullary thyroid cancer, is in Phase 3 trials for metastatic castration-resistant prostate cancer and has demonstrated clinical activity in multiple solid tumors. We previously reported that shed MET levels in serum and urine of patients with urothelial carcinoma correlate with stage, presence of visceral metastases and urinary source and that cabozantinib is effective in reversing HGF-driven urothelial carcinoma cell growth and invasion. These data support the evaluation of cabozantinib in patients with metastatic urothelial carcinoma. **Methods:** This is a phase II study of oral cabozantinib 60mg daily given continuously in 28-day cycles. There are three study cohorts: [1] metastatic urothelial carcinoma [2] bone only metastatic urothelial carcinoma [3] metastatic non-urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis. A maximum of 55 subjects will be enrolled. Up to 45 patients will be accrued to cohort 1. The remainder will be enrolled on exploratory cohorts 2 & 3. A two-stage single-arm phase II design will be employed. The primary objective is to determine the objective response rate in patients with metastatic urothelial carcinoma who have progressed on prior chemotherapy. Secondary objectives include progression free survival, safety and toxicity, and overall survival. Exploratory objectives include tumor tissue Met expression, shed MET levels in serum and urine, immune subsets, genetic biomarkers, molecular markers of angiogenesis and circulating tumor cells, correlation with clinical response parameters. Finally we will explore treatment evaluation with FDG and NaF PET/CT compared to standard imaging. This study is supported by the Cancer Therapy Evaluation Program (CTEP). NCT01688999 Clinical trial information: NCT01688999.

TPS4590

General Poster Session (Board #34B), Mon, 8:00 AM-11:45 AM

ASPEN: A randomized phase II trial of everolimus versus sunitinib in patients with metastatic non-clear cell renal cell carcinoma.

Andrew J. Armstrong, Susan Halabi, Tim Eisen, Walter Michael Stadler, Robert R Jones, Ulka N. Vaishampayan, Jorge A. Garcia, Robert E. Hawkins, Christian K. Kollmannsberger, Christine Lusk, Samuel Broderick, Daniel J. George; Duke Cancer Institute, Durham, NC; Duke University Medical Center, Durham, NC; Cambridge University Hospitals NHS Foundation Trust, Department of Oncology, Cambridge, United Kingdom; The University of Chicago, Chicago, IL; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Cleveland Clinic, Cleveland, OH; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; BC Cancer Agency, Vancouver, BC, Canada; Pharmanet i3, The Woodlands, TX; Duke Clinical Research Institute, Durham, NC

Background: Currently no level 1 evidence exists to guide therapeutic decisions in patients with metastatic non-clear cell renal cell carcinoma. Case series and retrospective analyses suggest that strategies targeting either the VEGF or mTOR/TORC1 pathways have clinical activity in papillary, chromophobe, or poorly differentiated histologic subtypes. **Methods:** We are conducting an international, randomized phase 2 trial of patients with metastatic non-clear cell RCC; either papillary, chromophobe, or undifferentiated histology; any Motzer risk group; and who have had no prior systemic therapy. All patients contribute tissue to an international biorepository for correlative genomic, genetic, and protein biomarker studies, along with companion longitudinal plasma and urine angiome studies. Patients are randomized to either everolimus or sunitinib (1:1) at FDA approved dosing until progression. The primary endpoint is progression free survival. Trial status: Seventy-three out of a planned 108 subjects have been enrolled at the time of abstract submission: median age 64, 59 white, 10 black, 4 unknown race, and includes 42 papillary and 31 chromophobe/undifferentiated histologies, 49 men and 22 women. Accrual is anticipated to be completed by December 2013. Accrual distribution by country is currently 43 (USA), 27 (UK), and 3 (Canada). The first DSMB meeting was conducted after 40 subjects completed at least 6 months of therapy and concluded that there were no unexpected safety signals and that the study should proceed. Tissue (primary, some metastatic, urine, plasma, whole blood) has been collected on all patients to date through the Duke Center for Human Genetics Biorepository. Clinical trial information: NCT01108445.

TPS4591

General Poster Session (Board #34C), Mon, 8:00 AM-11:45 AM

Phase III randomized sequential open-label study to evaluate the efficacy and safety of sorafenib followed by pazopanib versus pazopanib followed by sorafenib in the treatment of advanced/metastatic renal cell carcinoma (SWITCH-2 study).

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Background: Sorafenib (SO) and pazopanib (PA) are both effective treatments for metastatic RCC (mRCC). For optimal treatment of mRCC patients (pts) it is essential to compare efficacy and safety of different sequential 1st and 2nd line treatments. The primary endpoint of this study is to evaluate if total PFS of SO followed by PA is non-inferior to PA followed by SO. Secondary objectives include time to progression during second-line treatment; time to first-line treatment failure in each arm, and PFS in first- and second-line treatment; overall survival; disease control rate in first- and second-line, safety and tolerability, and health-related quality of life. Also, a comprehensive translational research programme is integrated. **Methods:** Major inclusion criteria: pts with metastatic/advanced RCC not suitable for cytokines and for whom study medication constitutes first-line therapy; 18-85 years, ECOG PS 0 or 1, MSKCC score low or intermediate; at least one measurable lesion (RECIST 1.1). 544 pts will be randomized to the sequence SO→PA or PA→SO. Treatment under each drug continues until progression or intolerable toxicity. Between 1st and 2nd line therapy will be a treatment-free period of 1-4 wks. SO and PA are given in their registered doses. Pts undergo CT/MRI after every second cycle, i.e. after every 8 wks. The experimental arm will be considered to be non-inferior as long as the lower limit of the HR 95 % confidence interval (one-sided) excludes a median total PFS lower than 13.1 mos (=non inferiority margin). 383 events need to be observed to have 80% power to reject the null hypothesis of inferiority ($HR \geq 1.225$) when the true $HR=0.95$. Recruitment started in June 2012. Study centers are in Germany, The Netherlands, and Austria. Clinical trial information: NCT01613846.

TPS4592

General Poster Session (Board #34D), Mon, 8:00 AM-11:45 AM

A phase III comparative study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus everolimus in patients (pts) with advanced or metastatic renal cell carcinoma (mRCC) previously treated with antiangiogenic therapy.

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Background: Standard approved treatments for pts with mRCC include interleukin-2 as well as therapies that target the vascular endothelial growth factor (eg, sunitinib, pazopanib) or mammalian target of rapamycin (eg, temsirolimus, everolimus) pathways. However, most pts may develop resistance, and overall survival (OS) improvement has only been shown in one phase 3 trial in poor-risk pts. Everolimus demonstrated a 3-month improvement in median progression-free survival (PFS) vs placebo, with no OS improvement (Motzer RJ, et al. Lancet. 2008;372:449-56). A phase 1 study of the fully human programmed death-1 (PD-1) receptor blocking monoclonal antibody nivolumab showed encouraging antitumor activity with previously treated mRCC (objective response rate [ORR], 29% (10/34); stable disease at ≥ 24 weeks [wks], 27% [9/34]). PD-1 is an immune checkpoint receptor that negatively regulates T-cell activation and PD-1 overexpression by tumor infiltrating lymphocytes has been associated with poor prognosis in multiple tumor types. Therefore, an ongoing, randomized, open-label, global phase 3 trial was developed to evaluate the clinical benefit of nivolumab in mRCC pts previously treated with anti-angiogenic therapy. **Methods:** Approximately 822 pts with advanced or metastatic clear-cell mRCC who have received ≤ 2 prior anti-angiogenic therapies and ≤ 3 total prior systemic regimens will be randomized 1:1 to receive nivolumab 3 mg/kg IV every 2 wks (Arm A) or everolimus 10 mg PO daily (Arm B). Pts will be stratified by region, MSKCC risk group, and number of prior anti-angiogenic therapy regimens. Tumor response will be assessed using RECIST 1.1 every 8 wks following randomization for the first year and then every 12 wks until disease progression or treatment discontinuation, whichever occurs later. The primary endpoint is OS. Secondary endpoints include PFS, ORR, OR duration, adverse events, OS in PD ligand 1 (PD-L1) positive or negative subgroups, and patient-reported outcomes. The trial is open and enrolling pts. Clinical trial information: NCT01668784.

TPS4593

General Poster Session (Board #34E), Mon, 8:00 AM-11:45 AM

A phase I study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) in combination with sunitinib, pazopanib, or ipilimumab in patients (pts) with metastatic renal cell carcinoma (mRCC).

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Background: Vascular endothelial growth factor receptor-tyrosine kinase inhibitors are established therapies for mRCC. However, sunitinib and pazopanib rarely elicit durable responses. Programmed death-1 receptor (PD-1) is an immune checkpoint modulator that suppresses T-cell activation by interacting with its ligands (PD-L1/2) on antigen presenting cells and some tumor cells. Nivolumab, a PD-1 receptor blocking antibody, has shown durable responses in previously treated pts with mRCC in Phase 1 and 2 trials. Ipilimumab is an immune checkpoint inhibitor (anti-CTLA-4 antibody) already approved for the treatment of advanced melanoma. We describe an ongoing Phase 1 dose-escalation and expansion study evaluating combination of nivolumab with sunitinib, pazopanib or ipilimumab in pts with mRCC. **Methods:** Patients with histologically confirmed mRCC are treated on 4 parallel arms: nivolumab 2.0 or 5.0 mg/kg + sunitinib standard dosing (Arm S), nivolumab 2.0 or 5.0 mg/kg + pazopanib standard dosing (Arm P), nivolumab 3 mg/kg + ipilimumab 1 mg/kg as induction (Arm I-1), and nivolumab 1 mg/kg + ipilimumab 3 mg/kg as induction (Arm I-3) with nivolumab 3 mg/kg maintenance for both arms. Arms S and P are being conducted in 2 phases: nivolumab dose-escalation phase for previously treated pts (≤ 18 pts/arm) and then dose-expansion phase for treatment-naïve pts (20 pts/arm) if the maximum tolerated dose is ≥ 5 mg/kg. Arms I-1 and I-3 are fixed-dose cohorts (20 pts/arm) including both treatment-naïve and previously treated pts. Most of the study population consists of pts with clear-cell histology; non-clear cell mRCC pts are allowed in the dose-escalation cohorts of Arms S and P. The primary objectives are to assess safety and tolerability, and to determine the recommended Phase 2 dose in pts with mRCC. The secondary objective is to assess preliminary antitumor activity (objective response rate and response duration per RECIST 1.1). Exploratory objectives are to evaluate overall survival, pharmacodynamics, and predictive biomarkers for the combinations, and pharmacokinetics and immunogenicity of nivolumab. Clinical trial information: NCT01472081.

TPS4594

General Poster Session (Board #34F), Mon, 8:00 AM-11:45 AM

A phase II multicenter study of the efficacy and safety of sunitinib given on an individualized schedule as first-line therapy for metastatic renal cell cancer.

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Background: Retrospective reviews have shown poorer than expected response rate (RR), progression free survival (PFS) and overall survival (OS) in Sunitinib treated (Rx) Renal Cell Cancer (RCC) patients (pts) who experience minimal toxicity. This study is based on an individualized (indiv) Rx strategy where dose/schedule modifications (DSM) were done to maximize dose and minimize time off Rx in 172 pts (Bjarnason ASCO-GU 2011). Pts started on 50mg 28 days (d) on/14d off. DSM were done to keep toxicity (fatigue, skin, GI, hematology) at \leq grade-2. DSM-1 was 50mg 14d/7d with indiv increases in d on Rx based on toxicity. DSM-2 was 50mg 7d/7d with indiv increases in d on Rx. DSM-3 was 37.5mg continuously with indiv 7d breaks. DSM-4 was 25mg continuously with indiv 7d breaks. In pts with clear cell histology PFS was inferior (5.8 mo) on the standard 50mg 28d/14d schedule vs. DSM schedules (>14 months, $p=0.0002$) These data, confirmed in 185 pts at MD Anderson (Jonasch KCA 2012), suggest that pts with minimal toxicity after 28d on Rx may benefit from dose escalation. **Methods:** A prospective phase II study has opened in 11 centers in Canada. DSM are done as described above. Pts with minimal toxicity after 28d are escalated to 62.5 mg and then 75 mg on a 14d /7d schedule. We expect to dose escalate 25% of pts and maintain another 40% of pts on a 50 mg dose that would otherwise have been dose reduced. The primary objective is the PFS associated with this strategy. Secondary objectives include dose intensity, RR, OS, toxicity, and quality of life. Samples for Sunitinib pharmacokinetics are obtained during the first course and again when the ideal sunitinib schedule has been established. Samples for biomarker and DNA correlative studies are collected. Based on the standard arm of the EFFECT trial (identical eligibility criteria), we assume a median PFS of 8.5 months in pts Rx using standard dosing. We expect pts treated with the indiv dosing will have a median PFS of 14 months. With $\alpha=0.05$, a two-sided, single-arm non-parametric survival test would have over 90% power to detect this difference with a total of 110 pts on study. Study enrollment began in July 2012 with 25 pts currently on study. Clinical trial information: NCT01499121.

TPS4595

General Poster Session (Board #34G), Mon, 8:00 AM-11:45 AM

Phase II randomized study of dalantercept in combination with axitinib compared to axitinib alone as second-line treatment in patients with metastatic renal cell carcinoma.

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Background: The treatment of metastatic renal cell cancer (mRCC) with therapies targeting the vascular endothelial growth factor (VEGF) pathway delays disease progression; however, overcoming tumor resistance to these agents remains a therapeutic challenge. Activin receptor-like kinase 1 (ALK1) is a type 1 receptor in the TGF- β superfamily and is selectively expressed on activated endothelial cells. While VEGF drives the proliferative stage of angiogenesis, ALK1 is primarily involved in the maturation phase. Dalantercept is a human ALK1-Fc receptor fusion protein that binds to bone morphogenetic proteins (BMP) 9 and 10 (ligands for ALK1) and acts as a ligand trap. Preclinically, dalantercept showed delayed tumor growth in solid tumor models, including RCC models alone and in combination with sunitinib. In RCC models, the addition of dalantercept to sunitinib enhanced the reduction in tumor blood flow compared to sunitinib alone. Dalantercept showed anti-tumor activity in a completed phase 1 study in 37 pts. with advanced solid tumors. Based on this promising data, we hypothesize that ALK1 inhibition may be synergistic with axitinib, a VEGFR tyrosine kinase inhibitor (TKI), in pts. with mRCC. **Methods:** A two-part, multi-center, open label phase 2 study to evaluate safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of dalantercept plus axitinib as second line therapy is ongoing. In Part 1, dose escalation using a 3+3 design will assess the safety and PK of dalantercept SC every 3 weeks plus axitinib 5 mg PO BID until disease progression or unacceptable toxicity. Once the maximum tolerated dose (MTD) has been determined, up to 20 pts. may be enrolled in an expansion cohort to establish safety for the recommended dose for Part 2. Part 2 will include 112 pts. randomized 1:1 to dalantercept plus axitinib vs. axitinib alone. Key eligibility criteria are one prior TKI in the first-line setting, ECOG \leq 1, and measurable disease. The primary efficacy endpoint is PFS. Secondary endpoints are OS, TTP, ORR, DOR, DCR, and PD biomarkers on archived tumor and serum specimens including BMP9/10 and ALK1 expression. Clinical trial information: NCT01727336.