RANDOMIZED PHASE II STUDY OF FIRST-LINE EVEROLIMUS (EVE) + BEVACIZUMAB (BEV) VERSUS INTERFERON ALFA-2A (IFN) + BEV IN PATIENTS (PTS) WITH METASTATIC RENAL CELL CARCINOMA (MRC): RECORD-2

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Background: Study results demonstrated that IFN augments BEV activity and improves median PFS in pts with mRCC. Thus, combination BEV + IFN is a standard first-line treatment option for mRCC. Combining BEV with the mTOR inhibitor EVE may be an efficacious and well-tolerated treatment option. The open-label, phase II RECORD-2 trial compared first-line EVE + BEV and IFN + BEV in mRCC. Patients and methods: Therapy-naive pts with clear cell mRCC and prior nephrectomy were randomized 1:1 to BEV 10 mg/kg IV every 2 weeks with either EVE 1 mg/kg IV initially, followed by additional pts at 1 mg/kg. Pts received up to 12 cycles (4 doses/ cycle) of treatment or until unacceptable toxicity, confirmed progressive disease, or complete response (CR). Clinical activity was assessed by RECIST v1.0.

Results: In EVE + BEV (n = 182) and IFN + BEV (n = 183) arms, median age was 60/60 years, 76/72% of pts were men, MSKCC risk was favorable/intermediate/poor in 36/57/7% and 36/57/7% of pts, and 43/46% of pts had >2 organs involved, respectively. For EVE + BEV and IFN + BEV, median treatment duration was 8.5/8.3 months, respectively; 23/26% of pts discontinued due to AEs. In EVE + BEV and IFN + BEV arms, median PFS by central review was 9.3/10.0 months (HRIFN/EVE, 0.91; 95% CI, 0.69-1.19; P = 0.485), respectively; probability of subsequent phase III trial success (50% threshold for phase II success). In EVE + BEV (n = 182) and IFN + BEV (n = 183) arms, median age was 60/60 years, 76/72% of pts were men, MSKCC risk was favorable/intermediate/poor in 36/57/7% and 36/57/7% of pts, and 43/46% of pts had >2 organs involved, respectively. For EVE + BEV and IFN + BEV, median treatment duration was 8.5/8.3 months, respectively; 23/26% of pts discontinued due to AEs. In EVE + BEV and IFN + BEV arms, median PFS by central review was 9.3/10.0 months (HRIFN/EVE, 0.91; 95% CI, 0.69-1.19; P = 0.485), respectively; probability of subsequent phase III trial success was 5.1%. Results of central and local PFS analysis were consistent. Objective response rate was 27/28% in EVE + BEV and IFN + BEV arms, respectively. Median overall survival (OS) was not reached in the EVE + BEV arm and was 25.9 months (95% CI 21.1, 30.2) in the IFN + BEV arm. Most frequent AEs (%) were stomatitis (71), fatigue (41), proteinuria (37), and pyrexia (35) in IFN + BEV arm.

Conclusions: RECORD-2, PFS and tolerability were similar for first-line EVE + BEV and IFN + BEV. Final OS analysis will occur after 2-year follow-up.

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**COMPARATIVE ASSESSMENT OF SUNITINIB-ASSOCIATED ADVERSE EVENTS (AEs) AS POTENTIAL BIOMARKERS OF EFFICACY IN METASTATIC RENAL CELL CARCINOMA (mRCC)**

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**Background:** Previous retrospective analyses have separately identified treatment-associated hypertension (HTN), hand–foot syndrome (HFS), asthenia/fatigue (A/F), neutropenia (N), and thrombocytopenia (T) as potential biomarkers of sunitinib efficacy in mRCC patients using a pooled database of five clinical trials (NCT00054886, NCT00077974, NCT00383889, NCT00338884, NCT00137423; Pfizer). We assessed the relative strength and independence of each biomarker in a combined analysis of the same database.

**Methods:** Data from 770 mRCC patients who received sunitinib 50 mg on the approved 4-wk-on-2-wk-off schedule (Schedule 4/2; n = 544; 71%) or 37.5 mg/d combined (Schedule 2/2; n = 226; 29%) were included. Combined multivariate analyses, repeated using a 12-wk landmark to address potential bias from longer treatment, was performed (for Schedule 4/2 and both schedules combined). The following were included as covariates for prediction of PFS and OS: previously identified prognostic factors; HTN (SBP ≥140 mmHg); N and T (CTCAE grade ≥1); and any CTCAE grade HFS and A/F.

**Results:** HTN, HFS, and A/F remained significant independent biomarkers in sunitinib-treated mRCC patients on Schedule 4/2, with HTN and A/F (P < 0.05; Fisher’s exact test), but not with HFS. Dose reduction, adjusted for time on treatment, was not associated with clinical outcome. Results were similar with both schedules combined.

**Conclusions:** Combined multivariate analyses indicate that HTN and HFS, and to a lesser degree A/F, may serve as independent biomarkers of sunitinib efficacy in mRCC patients. Providers who observe these AEs therefore encouraged to continue sunitinib therapy, managing AEs with standard medical treatment with or without dose reduction as clinically indicated.

**Final multivariate models of associations between AEs and efficacy outcomes for mRCC patients on Schedule 4/2**

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>AE at any time point</th>
<th>AE by the 12-wk landmark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P*</td>
</tr>
<tr>
<td><strong>HTN during treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>0.291 (0.220–0.399)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>0.296 (0.237–0.427)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>HFS during treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>0.750 (0.595–0.945)</td>
<td>0.0148</td>
</tr>
<tr>
<td>OS</td>
<td>0.578 (0.437–0.766)</td>
<td>0.0011</td>
</tr>
<tr>
<td><strong>A/F during treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>0.491 (0.375–0.644)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>0.720 (0.541–0.959)</td>
<td>0.0245</td>
</tr>
</tbody>
</table>

NS = not significant.

**Wald chi-square test.**


**Background:** a/mUC are associated with poor prognosis and HER2 overexpression is observed in around 10%. T combined with chemotherapy led to improvement of overall survival (OS) in metastatic breast and gastric cancers patients (pts). We investigated efficacy and safety of T combined with gemcitabine (G) and cis- (C) or carbo-platinum (Ca) in this population.

**Methods:** a/mUC pts were screened for HER2(HER2 score ≥3+ or 2+ with positive FISH). Chemotherapy (CT)-naive pts were randomized: Arm A (GCi-Ca) = G (1000 mg/m2 on D1 & 8) and Ci (70 mg/m2) or Ca (AUC 5 on D1 every 3 weeks for 6 cycles with creatinine clearance cut-off >60 ml/min); Arm B (GCi-CaT)= Arm A + T (8 mg/kg charging dose then 6 mg/kg every cycle until progression). End-points: primary= PFS, secondary= OS, ORR and toxicity.

**Results:** Pts were screened from 2003 to 2008: 61 pts (59 HER2+ and 2 HER2+ / FISH+) were eligible, 32 (52%) and 29 (48%) were randomized in arms A and B, respectively. 52% and 48% received Gc and Ca respectively. Median age: 64 yr, sex-ratio = 54/47, local treatment: surgery = 59 (98%), radiotherapy = 13 (22%), neo- adjuvant CT = 18 (30%). Baseline: ECOG-PS 0–1 = 52 (82%), 2 = 18 (18%); primary disease site: bladder = 58 (92%); locally advanced: 11 (18%), metastatic: 50 (82%); visceral metastasis: 35 (57%). Median cycle number = 6 (range: 3-9). Grade 3/4 toxicities: neutropenia (72%; febrile = 3%), thrombocytopenia (43%), anemia (38%) were comparable between 2 arms. Dyspnea was mainly observed in GCi-CaT arm (16.2% vs 3.4%). No toxic death occurred. Median PFS (months = m) was 10.2 [95%CI: 5.2-13.4] and 9.3 [95%CI: 6.5-15.7] (p = 0.7) in the GCi-Ca and GCi-CaT arms, respectively. ORR was 66% and 53% in the GCi-Ca and GCi-CaT arms, respectively. Median OS (m) was 15.7 [95%CI: 10.2-23.7] and 16.8 [95%CI: 6.7-31.2] in the GCi-Ca and GCI-CaT arms, respectively. Longest OS was observed in GGT sub-group: 28 [95%CI: 12.4-50].

**Conclusion:** HER2 over-expression is rare in a/mUCs. No conclusion could be drawn on PFS due to lack of power. Dyspnea was more frequent in GCi-CaT arm. We hypothesize that trastuzumab could have a synergetic effect with cisplatinum leading to a longer OS.

**Disclosure:** S. Oudard: Advisory board or board of directors position to disclose: sanofi avents, Bayer, Novartis, Roche. Pfizer Compensated relationship to disclose: Roche, Novartis Honoraria to disclose: Sanofi, Amgen, Roche, Novartis, Roche, Pfizer. Goldwasser: Advisory board: Novartis Roche Pfizer Amgen Frénius Compensated consultant role: Novartis Roche Bayer Pfizer Amgen Honoria: Roche Bayer Pfizer Novartis Research funding: Roche Amgen Bayer Pfizer Nutricia Other: AACR 2012 meeting: Bayer J.P. Machiel: Uncompensated consultant role: Boehringer Ingelheim; Research funding to disclose: Sanofi; P. Beuzeboc: Compensated consultant role to disclose: Roche Honoraria to disclose: Roche. All other authors have declared no conflicts of interest.
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EXTERNAL VALIDATION OF THE ASSOCIATION OF PROGRESSION-FREE SURVIVAL AT 6 MONTHS (PFS6) WITH OVERALL SURVIVAL AT 12 MONTHS (OS12) IN SECOND-LINE THERAPY FOR ADVANCED UROTHELIAL CARCINOMA (UC)
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Background: We hypothesized that PFS at 6 months (PFS6) correlates with OS12 and may be a robust intermediate endpoint for phase II trials of second-line therapy for advanced UC.

Methods: Ten phase II trials of second-line chemotherapy and/or biologics were pooled. Progression was defined as tumor progression or death from any cause. Adjustment of PFS6 and OS12 were performed for variability between trials using random effects models. The relationship between PFS6 and OS12 was assessed at the trial level using Pearson correlation and weighted linear regression. The relationship between PFS6 and OS12 at the individual level was assessed using Pearson chi-square test with Yates continuity correction. Statistical analyses employed “R” statistical computing software, version 2.8.0. External validation was conducted in a phase III trial comparing best supportive care (BSC) with vinflunine plus BSC.

Results: Results from the pooled phase II dataset (n = 646) have been reported (ASCO 2012): the Pearson correlation between trial level PFS6 and OS12 was 0.66 (p = 0.037), and individual level agreement was seen in 82% of patients (kappa = 0.45). Pearson correlation between trial level response and OS12 was 0.37 (p = 0.30) and individual level agreement was seen in 78% (kappa = 0.36). Of the 357 patients in the external validation dataset, 17 had PFS censored before 6 months or OS censored before 12 months, leaving 340 evaluable patients. Of the progression events, 231 were objective progression, 104 were deaths and 5 were alive with PFS > 6 months and OS > 12 months. The PFS6 was 13.25% with BSC and 26.48% with vinflunine plus BSC. The individual level agreement of PFS6 and OS12 was 81% (κ= 0.44, p < 0.001) and of response and OS12 was 76% (κ= 0.17, p = 0.0002). Excluding the BSC arm showed an individual level agreement between response and OS12 of 82% (κ= 0.53, p < 0.0001).

Conclusion: PFS6 is robustly associated with OS12 at the trial and individual levels in the setting of second-line therapy for advanced UC. Given the suboptimal response of OS12 at the trial level, PFS6 may be a more optimal endpoint to capture the durable benefits of agents.

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THE TAXI-F II PROTOCOL FINAL RESULTS: A PHASE II TRIAL OF HIGH-DOSE CHEMOTHERAPY SUPPORTED BY HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH SEMINOMATOUS GERM-CELL TUMORS FAILING CHEMOTHERAPY AND WITH ADVANCED PROGNOSTIC FACTORS
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Background: High-dose chemotherapy (HDCT) has been shown to circumvent resistance in poor-prognosis germ cell tumors (GCT), mainly for patients whose relapses occur more than 4 weeks after cisplatin-based CT.

Patients and methods: This multicentric phase II trial was addressed to patients with poor-prognosis non-refractory GCTs. The main objectives were to determine the complete response rate and to monitor treatment-associated toxicities. Patients with adverse prognostic factors failing CT were to receive 2 cycles combining Epirubicin and Paclitaxel (EpiTax) followed by 3 consecutive HDCT [one using a Paclitaxel/Thiotepa association, 2 using the 5-day Ifosfamide-Carboplatin-Etoposide regimen]. Inclusion criteria included seminomatous GCT in relapse after 2 lines of CT, non-seminomatous GCT in relapse after 1 or 2 lines, partial remission after 1 line, primary mediastinal GCT in first relapse. Peripheral blood stem cells were collected after the EpiTax cycles.

Results: Between 09/2004 and 12/2007, 45 patients were included: 45 received 1 HDCT, 39 two HDCT, 29 patients received the complete protocol. Sixteen patients did not receive the entire protocol, 8 (53%) for toxic side effects. Two patients (4.4%) died of toxicities, 17 (37.7%) of disease progression. For a median follow-up time of 26 months (4–51 m), the final overall response rate was 66.7% (CR, 20.6%). The median PFS was 16 months (95%CI, 9-NA) and the median OS was 32 months (95%CI, 32–69). The 2-year PFS was a plateau set up at 50% (95%CI, 32–67%) and the 2-year OS was 71% (95%CI, 52–83%).

Conclusion: The TAXI-F II protocol was highly effective in non-refractory GCT patients failing CT.

Disclosure: F. Selle: consultancy for roche and Pharmaman. All other authors have declared no conflicts of interest.

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NEOADJUVANT (NACT) AND ADJUNCT CHEMOTHERAPY (ACT) FOR MUSCLE-INVASIVE BLADDER CANCER: A POPULATION-BASED OUTCOMES STUDY
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Background: Utilization of NACT and ACT for bladder cancer in the general population and the survival benefit associated with therapy is not well described. Here we report practice patterns and outcomes associated with NACT/ACT in the general population of Ontario, Canada.

Methods: Electronic records of treatment were linked to the population-based Ontario Cancer Registry to identify all patients who underwent cytorexy for bladder cancer in Ontario 1994–2008. Surgical pathology reports were obtained to identify cases with muscle-invasive disease. Utilization of NACT/ACT was compared across 3 study periods: 1994-98, 1999-03, 2004-08. Logistic regression was used to analyze factors associated with use of NACT/ACT. A Cox model and propensity score analysis was used to explore the association between ACT and survival.

Results: In 1994–2008 4876 patients underwent cystectomy. Surgical pathology reports were identified for 3429 cases; 2738 had muscle-invasive disease. While use of NACT did not change over the 3 study periods (5%, 3%, 6%; p = 0.004), utilization of ACT increased with time (16%, 19%, 23%; p = 0.001). In adjusted analyses younger age and less co-morbidity were associated with greater utilization of NACT/ACT. OS12 of T3/T4 tumors (OR 2.1, 95%CI 1.6–2.8), node positive disease (OR 7.2, 95%CI 5.5–9.5), and lymphovascular invasion (OR 1.7, 95%CI 1.2–2.3) were associated with greater utilization of ACT. While there was no substantial variation in utilization of NACT across geographic regions (range 3% to 5%), use of ACT varied considerably (range 12% to 31%). Five year overall (OS) and cancer-specific survival (CSS) for all muscle-invasive cases was 30% (95%CI 28–31%) and 34% (95%CI 32–36%). In Cox analysis T3/T4 tumors (HR 1.7, 95%CI 1.6–2.0), node positive disease (HR 1.9, 95%CI 1.7–2.1), and lymphovascular invasion (HR 1.8, 95%CI 1.6–2.1) were associated with inferior OS. Utilization of ACT was associated with improved OS (HR 0.70, 95%CI 0.6–0.8) and improved CSS (HR 0.70, 95%CI 0.6–0.8). This result was consistent in the Cox model and propensity score analysis.

Conclusions: Despite accumulating evidence and guidelines, NACT/ACT remains substantially underutilized in routine clinical practice. Our results suggest that ACT is associated with a substantial survival benefit in the general population.

Disclosure: All authors have declared no conflicts of interest.
GEMCITABINE, OXALIPLATIN, AND PANCYTALEX (GOT) ON A 2-WEEKLY SCHEDULE IN PATIENTS (PTS) WITH REFRACATORY UTERINE CARCINOMA: A PHASE II STUDY CONDUCTED AT THE UNIVERSITY OF SOUTHERN CALIFORNIA

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Background: Modern therapy for GCT has transformed the disease but challenges remain in managing primary poor risk and refractory cancer.

Methods: Phase II: 30 men with GCT progression ≤ 6 wks of a standard regimen (12) or after salvage (14) or stem cell regimen (3). Growing teratoma syndrome pts excluded. PS <2, Age >16. PD by RECIST/marker criteria. Regimen: Paclitaxel 170mg/m2/3h; Gemcitabine 800mg/m2/8mins; Oxaliplatin 100mg/m2/90min, increased to 170mg/m2 in cycle 2 if no major toxicity. Mg2+ & Ca2+ infused before oxaliplatin. G-CSF was not given prophylactically. The regimen was designed to maximize oxaliplatin density with full dosing of pts with recovering marrow & dose escalation for pts with limited toxicity in cycle 1. Retreatment criteria: ANC ≥ 1500 or 700 with neutrophils, platelets >75K. Pts with marker normalization had ≥ 3 further cycles. Primary endpoint: Response, 2nd os, PFS, toxicity. Patient characteristics: Med age 32y, Race: white 41%, Hispanic 48%, Asian 10%, KPS >90 66%. Primary site: testis 27, mediastinal 2, Histology: Seminoma: 7% Chorio 10%, YST 7%, Emb 3%. Seminoma 13%, Undifferentiated 5%, mixed NSGCT 55%. Prior surgery for primary: 20, met resection 13. Med prior chemotherapy lines: 2 (R 1–7). Med (range) pre-GOT LDEH 17E (109–450), AFP 22 (1–36002), bHCG 2.4 (2–247040) Endpoints: Median cycles 6 (1–14). Best RECIST response: CR2, PR7, SD11, PD 5; RR 31% (95%CI 17–50%), 5 pts (APR, ISD) who underwent definitive surgery after trial therapy were rendered NED. Med FU 28 mos (R 3–81).

Results: Med OS 16.7 mos (95%CI 11.9–21.5), 39.6 weeks (95%CI 32.1–48.1) for those treated with pazopanib and 13.4 weeks (95% CI 12.1–19.1) for placebo. IL-6, IL-8, and OPN were prognostic [Table]. Considering treatment groups, 2 clinical variables (hemoglobin<LLN [HR 1.82, p = 0.0044] and neutrophils>ULN [HR 1.95, p = 0.0151]) were predictors of short PFS in multivariate analysis. Adjusting for those 2, only OPN and IL-8 in the placebo arm (OPN high 7.9 v low 24 weeks, p = 0.034; IL-6 high 7.9 v low 24.1 weeks, p = 0.03), and OPN alone in the pazopanib arm (high 31.3 v low 14.4 weeks, p = 0.0072), remained prognostic. Although the 3 clinical classifications were associated with PFS, none was as strong a prognostic marker as the CAFs [Table].

Conclusion: In mRCC pts with good PS, circulating OPN and IL-6 are prognostic for PFS independent of established clinical criteria.

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QUALITY OF LIFE (QOL) AMONG RENAL CELL CARCINOMA (RCC) PATIENTS IN A RANDOMIZED DOUBLE BLIND CROSS-OVER PATIENT PREFERENCE STUDY OF PAZOPANIB (P) VERSUS SUNITINIB (S)

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Introduction: PISCES was a randomized, double blind, cross-over study of P versus S in 168 patients with metastatic RCC. P and S are oral tyrosine kinase inhibitors with demonstrated clinical efficacy in RCC, but different side effect profiles. After exposure to both treatments, P was preferred over S by a 3:1 margin (70% vs. 22%) among the 114 patients who completed the patient preference questionnaire.

Methods: Patients received either P for 10 weeks, followed by a 2-week washout period, and then 10 weeks of S, or 5 for 10 weeks, followed by a 2-week washout period, and then 5 weeks of P. The primary endpoint was patient treatment preference. Secondary endpoints included preference for P and QoL, as assessed by the Functional Assessment of Cancer Therapy-Fatigue (FACT-F), the EQ-5D, and a Supplementary Quality of Life Questionnaire (S-QLQ), which assessed worst symptoms in the mouth/throat, hands, and feet and limitations due to soreness. The S-QLQ and the FACT-F were administered at baseline and every two weeks thereafter. The EQ-5D was administered at baseline, the end of the washout period, and the end of period 2. Change from period baseline to period average score were compared across treatments. Crossover analyses compared patients' average scores on each treatment, adjusting for sequence.

Results: The FACT-F crossover analyses favored P over S in 2.5 points (p = 0.002). S-QLQ crossover analyses favored P over S on worst soreness in the hands, feet and mouth/throat (p < 0.05). Foot and mouth/throat soreness worsened more on S compared to P in each period. EQ-5D scores deteriorated more precipitously in S-treated patients in p2. Better general quality of life was the most common reason for preference cited among patients preferring P. Side effects most often identified as the primary reason for preference were fatigue for 26% of patients preferring P, and diarrhea for 24% of patients preferring S.

Conclusion: Patient-reported QoL crossover results favor P over S on fatigue, foot soreness, hand soreness and mouth/throat soreness. These results are consistent with previous studies. Additional analyses are pending.
patient preference for P over S, and should be considered in light of their comparative efficacy.

Disclosure: D. Cellai: Dr. Cellai has consulted to GSK and has received research grant support from GSK. K. Kaiser: Dr. Kaiser has received research grant support from GSK. J. Beaumont: Ms. Beaumont has received research grant support from GSK. J. Diaz: Dr. Jose Diaz is a GSK employee and stock owner. L. McCann: Dr. McCann is a GSK employee and stock owner. F. Mehmud: Dr. Mehmud is a GSK employee and stock owner. S. Lata: Dr. Lata is a GSK employee and stock owner. P. Bonc: Dr. Bonc has received honorarium from GSK and Pfizer. C. Porta: Dr. Porta has acted as consultant or speaker for GSK, Bayer-Schering, Pfizer, Novartis, Roche, Aveo, Astellas, Roche Holding, and Recordat and received research funding from Novartis and Bayer-Schering. B. Escudier: Dr. Escudier has received honorarium from GSK, Pfizer, Novartis, Bayer, Aveo, and BMS.

**AXITINIB VS SORAFENIB FOR ADVANCED RENAL CELL CARCINOMA: PHASE III OVERALL SURVIVAL RESULTS AND ANALYSIS OF PROGNOSTIC FACTORS**


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Purpose: In the phase III AXIS trial, axitinib prolonged progression-free survival (PFS) compared with sorafenib as 2nd-line therapy for metastatic renal cell carcinoma (mRCC) (Lancet 2011;378:1931). Nature overall survival (OS) data (as of Nov 1, 2011) are reported.

Methods: 723 patients (pts) with clear cell mRCC, progressive disease after 1 systemic therapy, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 were stratified by ECOG PS and prior therapy and randomized 1:1 to axitinib 5 mg twice daily (BID) or sorafenib 400 mg BID. OS was analysed as a secondary endpoint based on 425 events and compared using a 1-sided log rank test stratified by ECOG PS and prior therapy. Pretreatment prognostic factors were studied by multivariate analyses. Pts were grouped by diastolic blood pressure (dBP) ≥110 mmHg and by age. ECOG PS = 0, no bone metastases, elevated haemoglobin, and low corrected calcium. Pretreatment prognostic factors were studied by multivariate analyses. Pts were grouped by diastolic blood pressure (dBP) ≥110 mmHg and by age.

Results: Median OS (mOS) was 20.1 mo (95% confidence interval [CI] 16.7, 23.4) in the axitinib arm and 19.2 mo (95% CI 17.5, 22.3) in the sorafenib arm; hazard ratio (HR) 0.969 (95% CI 0.800, 1.174); P = 0.3744. In prior therapy subsets, mOS with axitinib vs sorafenib was: prior cytokine, 29.4 vs 27.8 mo (HR 0.815; 95% CI 0.555, 1.191); prior sunitinib, 15.2 vs 16.5 mo (HR 0.997; 95% CI 0.782, 1.270); prior bevacizumab plus interferon-α, 14.7 vs 19.8 mo (HR 1.825; 95% CI 0.942, 3.535); and prior temsirolimus, 14.0 vs 8.5 mo (HR 0.449; 95% CI 0.165, 1.278). Prognostic factors for longer OS with 2nd-line therapy (P < 0.01) included type of prior therapy, and prior temsirolimus, 14.0 vs 8.5 mo (HR 0.459; 95% CI 0.165, 1.278). Prognostic and own stock in Pfizer. S. Kim: Employee of and own stock in Pfizer. B.I. Rini: Pfizer. S. Hariharan: Employee of and own stock in Pfizer. B. Rosbrook: Employee of R.J. Motzer: Pfizer Consultant. Research funding from Pfizer. B. Escudier: Advisory role for Novartis, Bayer, Aveo, GSK. S. Negriev: Ad Board: Pfizer Honoraria; Novartis Research grants: GSK, Roche. M.E. Gore: Speaker bureau and advisory boards: Roche, GSK, Novartis, Bayer, Pfizer, Schering Plough, Bristol Myers Squibb, Aveo, AstraZeneca, Astellas. J. Taraz: Employee of and own stock in Pfizer. S. Harikan: Employee of and own stock in Pfizer. B. Rosbrook: Employee of and own stock in Pfizer. S. Kim: Employee of and own stock in Pfizer. B.J. Rin: Consulting and research funding from Pfizer. All other authors have declared no conflicts of interest.

Conclusions: Axitinib resulted in prolonged PFS and similar OS compared with sorafenib for 2nd-line mRCC. OS results and prognostic factors may be used in clinical trial design for novel agents in 2nd-line therapy.


**DETAILED COMPARISON OF THE SAFETY OF TIVOZANIB VERSUS SORAFENIB IN PATIENTS WITH ADVANCED/METASTATIC RENAL CELL CARCINOMA (mRCC) FROM A PHASE 3 TRIAL**

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Background: Tivozanib (TIVO), an oral tyrosine kinase inhibitor, potently and selectively inhibits vascular endothelial growth factor receptors 1, 2, and 3. A Phase 3
Hypertension was the most frequent TIVO-related AE but was easily managed with standard antihypertensives. Fewer pts in the TIVO arm had ≥ Grade 3 drug-related AEs than in the SOR arm (94 [36.3%] and 131 [51.0%], respectively). Pts in the TIVO arm required fewer overall dose reductions than did pts in the SOR arm (36 [11.3%] vs 114 [44.4%], respectively). Two deaths in the TIVO arm were due to myocardial infarction; cardiac failure was responsible for 2 deaths in each arm.

Conclusion: Pts on the TIVO arm experienced more hypertension and dysphonia, but less diarrhea, hand-foot syndrome, alopecia and discontinuations than pts on the SOR arm. Pts on the TIVO arm also had fewer overall dose reductions. These data demonstrate that TIVO is well-tolerated in pts with mRCC.


**796PD**

**TIVOZANIB PHARMACOKINETIC (PK)/PHARMACODYNAMIC (PD) ANALYSIS OF BLOOD PRESSURE (BP) AND SOLUBLE VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR 2 (sVEGFR2) IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA (RCC)**


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Background: Tivozanib is a potent, selective, long half-life tyrosine kinase inhibitor of VEGF receptors (VEGFRs) 1, 2, and 3, demonstrating activity against advanced RCC in Phase (II) II–III trials. This analysis explored the relationship between tivozanib PK and BP, as hypertension is a mechanism-based adverse event and a potential surrogate of response. The relationship between exposure and sVEGFR2 was also explored.

Methods: Pharmacokinetic, BP, and sVEGFR2 data from tivozanib-treated RCC patients (pts) from a Ph II (n = 21) and a Ph III (n = 259) study were pooled; pts were treated with 1.5 mg tivozanib daily for 21 days followed by a 2-day rest (24-day treatment cycle) in each study. A population PK model of tivozanib was constructed from PK data from Ph I–III studies, to obtain individualized predictions of steady-state values for Cavg. BP was measured at baseline and on Cycle 1 Day 15 (C1D15), C2D1 and C2D2 in the Ph II Ph II and Ph III studies, and was binned to the nearest 5 mm Hg. Analysis focused on BP shifts in 5 mm Hg increments. Serum samples for sVEGFR2 (Ph III only) were collected at baseline and on C1D15, C2D1, and C2D2–28. Models of drug exposure as predictors of longitudinal changes in BP and/or sVEGFR2 were constructed by non-linear mixed-effects modeling.

Results: Across pts, there was a statistically significant median 5 mm Hg increase in diastolic BP on C1D15, with similar upward increases noted on C2D1 and C2D2. The most common ≥10% drug related AEs and discontinuations are shown in the table.

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grades</th>
<th>All Grades</th>
<th>Grade ≥2</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>109 (42.1)</td>
<td>61 (23.6)</td>
<td>79 (30.7)</td>
<td>39 (15.2)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>47 (18.1)</td>
<td>11 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42 (16.1)</td>
<td>5 (1.9)</td>
<td>27 (10.4)</td>
<td>15 (5.8)</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>34 (13.1)</td>
<td>5 (1.9)</td>
<td>137 (53.3)</td>
<td>43 (16.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28 (10.8)</td>
<td>7 (2.7)</td>
<td>28 (10.9)</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>6 (2.3)</td>
<td></td>
<td>53 (20.6)</td>
<td></td>
</tr>
<tr>
<td>Discontinuations</td>
<td>14 (4.2)</td>
<td></td>
<td>14 (4.2)</td>
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</tbody>
</table>

Conclusion: PK/PD analysis of data from tivozanib Ph II–III studies showed that pts had a median increase in diastolic BP of 5 mm Hg on C1D15 and C2D1. Levels of serum sVEGFR2 were found to decrease significantly with time, and the effect size increased with tivozanib exposure. Relationships between exposure, BP, and sVEGFR2 and outcome are being explored.

Disclosure: R.J. Motzer: Only disclosure is research funding from AVEO Oncology, J. Loewy: Consulting fee or honoraria from qPharma LLC. L. Hodge: Consulting or honoraria from qPharma LLC. B. Esteves: AVEO Pharmaceuticals employees with stock options. A. Berkenblit: AVEO Pharmaceuticals employees with stock options. S. Oudard: Consulting- Pfizer. Bayer-Schering Roche. Sanofi Aventis. Pfizer: Concerted research collaboration with qPharma LLC. M. Cotreau: AVEO Pharmaceuticals employee with stock options. All other authors have declared no conflicts of interest.
OPEN-LABEL PHASE II TRIAL OF FIRST-LINE EVEROLIMUS MONOTHERAPY IN PATIENTS WITH ADVANCED PAPILLARY RENAL CELL CARCINOMA: RAPTOR INTERIM ANALYSIS

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Background: Treatment options for patients with papillary renal cell carcinoma (RCC) are limited. Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has demonstrated efficacy in clear cell metastatic RCC; mTOR signaling is also dysregulated in papillary RCC. The ongoing RAPTOR (RAD001) in Advanced Papillary Tumor Program in Europe; Clinical Trials.gov, NCT00688753) trial is evaluating everolimus monotherapy in treatment-naive patients with advanced papillary RCC. Here, we present the results of a preliminary analysis.

Results: At data cut-off (April 11, 2012), 71 of 92 (77%) enrolled patients were eligible for analysis according to central pathology review (confirmed papillary renal cancer); 16 of the 92 patients were still on treatment. Most patients were men (73%) and most were <65 years of age (73%). Median PFS by investigator’s assessment was 219 days (7.3 months; 95% CI, 5.6–15.2 months) and 55.2% of patients were progression free at 6 months. PFS assessment of patients still on treatment, independent radiology review, and safety assessment of all patients is ongoing.

Conclusions: Results of this interim analysis have demonstrated that everolimus provides clinical benefit to patients with advanced papillary RCC. These results support the further evaluation of everolimus as a first-line treatment option for patients with advanced papillary RCC.

Disclosure: B. Escudier; Bernard Escudier has served as a consultant to and received honoraria from Bayer, Pfizer, Roche, Novartis, GlaxoSmithKline, and Aveo. S. Bracarda: Sergio Bracarda has served as an advisory board member to Pfizer, GlaxoSmithKline, Novartis, and Bayer, and has received honoraria from Pfizer and Novartis. K. Slama: Khemaies Slama is an employee of Novaris Pharma S.A.S. C. May: Christoph May is an employee of Novartis Pharma GmbH. C. Porta: Camillo Porta served as consultant/speaker for Novartis, Pfizer, GSK, Hoffman La Roche, Bayer-Schering, Aree Pharmaceuticals, Astellas, Boehringer Ingelheim, and Recordati and received research grants from Novartis and Bayer-Schering. V. Grunwald: Viktor Grunwald served as consultant to Roche, Bayer, Novartis, GlaxoSmithKline, and Aveo/Astellas, received honoraria from GlaxoSmithKline, Novartis, and Pfizer, and received research funding from Pfizer and GlaxoSmithKline.

All other authors have declared no conflicts of interest.

MVAC VS PLATINUM – GEMCITABINE (PG) IN A RISK-ADAPTED POLICY OF ADJUVANT CHEMOTHERAPY (ACT) AFTER RADICAL CYSTECTOMY (C) IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA (IBC)

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Background: ACT for IBC is controversial and supported by underpowered randomized trials. Additional information from metaanalysis or longitudinal studies can help to better define its role.

Patients and methods: From 1988 to 2011, patients (p) with IBC after C have been included in a risk-adapted institutional protocol. After being informed of their particular risk of relapse, status of the art and toxicity of ACT, p with extravesical or N+ disease were recommended ACT although some of them chose follow-up. The opposite occurred with pT2N0p c and ACT cohorts were prospectively followed according to the standard clinical practice. ACT was associated with a reduction in the risk of relapse and death versus C, in patients with extravesical extension or N+ (ICD 29: 2011 suppl abstr 4613). We present here the results of toxicity, progression-free survival (PFS) overall survival (OS) and cancer-specific survival (CSS) comparing MVAC vs PG in the cohort of p who received ACT.

Results: 527 have been included, 331 C and 196 ACT: 90 MVAC x3, 90 CDDP-Gem x4, 16 Carbo-Gem x4 (106 PG). All PG were included after year 2000. Median follow-up was 86 m. MVAC vs PG were well balanced in sex (males 92% vs 86%), G3 (97% vs 96%), surgical complications (28% vs 26%), and 9p who received full planned ACT (44% vs 52%). There were statistically significant differences in mean age (61 vs 67 y), non-papillary histology (71 vs 87%), and AJCC 2010 stage (T2N0/ T3-4N0/M+ : 23%/30%/47% vs 10%/37%/53%). There were no toxic deaths. Main differences in G3-4 toxicities were anemia (11 vs 18%) neutropenia (42 vs 30%), trombopenia (5 vs 15%), emesis (12 vs 7%) and mucositis (8 vs 4%). There were no significant differences between MVAC and PG in crude PFS, OS or CSS. Table shows the Hazard Ratio (HR) of relapse and death stratified by pathological stage and adjusted by most relevant covariates in a multivariate Cox model (* p < 0.05).

Conclusion: In our series of IBC, comparison of MVACx3 or PGx4 as ACT showed some differences in toxicity, but we could not find significant differences in efficacy between both schedules.

Disclosure: All authors have declared no conflict of interest.

MUSCLE INVASIVE URINARY BLADDER CANCER: RESPONSE TO NEoadjuVANT CHEMOTHERAPY is PREDICTOR OF IMPROVED PROGRESSION FREE SURVIVAL

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Purpose: To evaluate the prognostic factors and outcome of patients with muscle invasive carcinoma of urinary bladder.

Study design: Retrospective analysis.

Method: Between January 2005 to August 2011, 270 patients of carcinoma of urinary bladder were registered; 218 patients were evaluable for analysis. Results: Median age of study population was 58 years (range: 24 to 85 years) with male: female ratio of 8:5:1 and median duration of symptoms was 5 months (range: 1-40 months). Hematrua was most common presenting symptom (92%) followed by dysuria (25%). Transitional cell carcinoma was the most common histology (93%) followed by adenocarcinoma (4%) and squamous cell carcinoma (3%). Tumor was high grade in 79% of patients and muscle invasion was present in 91%. 28 patients (13%) had metastasis at presentation with bone being the commonest site. TNM (AJCC 7th) staging revealed stage IV: 50%, stage III: 46%, stage II: 12%, stage I: 2%, 42 patients (19%) received gemcitabine/platinum based neoadjuvant chemotherapy (NACT) with overall response rate of 57% (complete remission rate 33%). 110 patients underwent radical cystectomy and 54 out of 110 patients received adjuvant therapy. At a median follow up of 23 months median progression free survival (PFS) is 26.3 months (95% CI: 5.6–15.2 months) and 55.2% of patients were progression free at 6 months. PFS assessment of patients still on treatment, independent radiology review, and safety assessment of all patients is ongoing.

Conclusion: In our series of IBC, comparison of MVACx3 or PGx4 as ACT showed some differences in toxicity, but we could not find significant differences in efficacy between both schedules.

Disclosure: All authors have declared no conflicts of interest.

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<td>MVAC vs C</td>
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Invasive bladder cancer is the most common tumor in Egypt. Preservation protocol consists of transurethral resection followed by concomitant chemoradiotherapy. The induction part of Radiotherapy is usually delivered to the whole pelvis, The role of omitting pelvic radiation has not been addressed before.

Aim: To compare the toxicity, pelvic nodal relapse and overall survival of whole bladder irradiation only to standard technique of whole pelvis irradiation followed by bladder boost in patients with muscle invasive bladder carcinoma undergoing bladder preservation protocol.

Material and method: A total of 63 patients with transitional cell carcinoma, stage T3-4N0M0 bladder cancer were subjected to maximal TURB. Then, patients randomized into two groups: group I (32 patients) to receive whole pelvis radiotherapy 44Gy followed by 20 Gy bladder boost. While Group II (31 patients) were randomized to receive whole bladder radiotherapy alone for a total dose of 46 Gy. In both groups, concomitant cisplatin and paclitaxel were given weekly throughout the whole course of radiotherapy where conventional 2 Gy fraction was used. additionally, 4 cycles of Adjuvant cisplatin and paclitaxel were given after the end of chemo radiotherapy induction course.

Results: Three patients, two in group I and one in group II discontinued due to grade 3 toxicity. A median follow up of 56 months, regional relapse occurred in 7.1% of patients in group I and 10.3% in group II (p = 1). Distant metastases were detected in 17.9% of patient in group I and 13.8% in group II (p = 0.73). The 2-year disease free survival was 60% in group I and 63.3% in group II (p = 0.79). The whole 2-years survival rate was 75% in group I and 79.2% in group II (p = 0.689).

Radiation gastrointestinal (GI) Acute toxicity was higher in group I than in group II (p = 0.001), while late GI radiation toxicity was comparable in both groups.

Conclusion: treating the bladder only without elective pelvic nodal irradiation, did not compromise pelvic control rate, but significantly decreased the acute radiation toxicity.

Disclosure: All authors have declared no conflicts of interest.

EFFICACY AND PROGNOSTIC FACTORS OF NEOADJUVANT CHEMOTHERAPY IN RESECTABLE LOCAL-LY ADVANCED MUSCLE-INVASIVE BLADDER CANCER (MIBC) PATIENTS (P) IN AN OFF-PROTOCOL CLINICAL SETTING

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Introduction: Although neoadjuvant chemotherapy is a recommended treatment in MIBC, it has not gained widespread acceptance in clinical practice, due to the lack of predictive markers of efficacy and the absence of a standard chemotherapy regimen. Furthermore, since few studies have assessed the role of neoadjuvant chemotherapy in an off-protocol setting, there may be doubts about its feasibility.

Material and methods: We retrospectively analyzed 124 p with MIBC treated with neoadjuvant cisplatin-based chemotherapy at two centers from 1991 to 2010. Clinical and pathological variables were correlated with survival. All patients were classified as stage cT2-4N0M0 based on TUR (trans-urethral resection) and CT scan findings and were candidates for neoadjuvant chemotherapy followed by cystectomy.

Results: 10 p (8%) were cT2N0, 83 p (66%) cT3N0, and 31 p (26%) cT4aN0. Tumor response was assessed by a combination of clinical and radiological criteria. The median disease specific survival was 60 p (48%). Median survival (MS) and 5-year (5y) survival were 59 months (m) and 50%, respectively. Median OS was 5.2, 7.1, 8.3, 7.6 and 10.6 months respectively for patients having 5y survival that compares favorably with surgery alone.

Conclusion: Neoadjuvant chemotherapy followed by cystectomy is feasible in p with locally-advanced MIBC. Both CMY and CG are active regimens, with significant prognostic factors for overall survival (OS) in patients receiving second-line chemotherapy for advanced platinum-pretreated urothelial carcinoma (UC) include ECOG performance status (PS) ≤ 1, elevated T-stage (T3 or T4), local control (LC) > 90% and decreased Karnofsky performance status (KPS) ≤ 80.

Disclosure: All authors have declared no conflicts of interest.

PROGNOSTIC STRATIFICATION OF ADVANCED UROTHELIAL CARCINOMA (UC) RECEIVING SECOND-LINE SYSTEMIC THERAPY INCLUDING TIME FROM PRIOR CHEMOTHERAPY (TPFC) AS A PROGNOSTIC FACTOR

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Background: Prognostic factors for overall survival (OS) in patients receiving second-line chemotherapy for advanced UC (n = 748), 7 trials with available baseline TPFC, 15 trials with available baseline TFPC (TPFC) AS A PROGNOSTIC FACTOR

Purpose: To access safety, tolerance, local control and survival of transurethral resection of Bladder tumor (TURB) followed by concomitant cisplatin, paclitaxel and radiotherapy as selective organ preservation in patients with Muscle Invasive bladder. Additionally, Surviving and ERCC1 gene expression analysis and response to treatment chemotherapy also studied.

Methods and materials: A total of 63 patients with transional cell carcinoma (TCC), stage T2-T3, No, Mo bladder carcinoma were enrolled in a protocol of TURP followed by one daily radiotherapy (2Gy fraction for a total dose of 44 GY) with concomitant cis-platin 15mg/m2/ day,d1-3 weekly and paclitaxel 50mg/m2/day, weekly.Four weeks later, all patients were evaluated by cystoscopy and biopsy. Patients with complete response proceeded to consolidation Radiotherapy (2Gy/for a total 20Gy with concomitant cisplatin and paclitaxel, while those with recurrent tumor went on to salvage. Cystectomy. Following consolidation or salvage surgery, all patients went to complete 4 cycles of cisplatin and paclitaxel 175 mg/day every 21 days. RNA extraction from Biopsy before and after treatment was analysed for survivin and ERCC1 gene expression using real time PCR.

Results: Three patients could not tolerate the treatment and discontinued the protocol during the induction phase while the remaining sixty patients complete the induction phase. The complete response after the induction phase was 11.1%. Eleven percent of the complete responders developed superficial relapse with a median time of relapse of 16 months, while 8.9% developed invasive relapse with a median time of 18 months. 2-year disease for survival was 61.7%. Distant metastases we detected in 15% of patients. 2-year overall survival was 77.2%. RNA was analyzed from 65% of patient, real time PCR for ERCC1 and survivin was done, interpretation of data will be presented.

Conclusion: Maximal transurethral resection followed by concomitant cis-platin and paclitaxel, as a bladder preservation therapy, can be considered a valid alternative for treating selected patients with localized muscle invasive TCC of the bladder.

Disclosure: All authors have declared no conflicts of interest.
Background: Levels of bone turnover markers (BTM) might be correlated with outcome in terms of skeletal related events (SRE), disease progression and death. The aim of the study was to determine the possible correlation between BTM, disease progression, SREs and death in patients with genitourinary cancer and bone metastases (BM) treated with zoledronic acid (ZA).

Methods: Observational, prospective, multicenter study. Patients with genitourinary cancer (prostate, renal, bladder) and BM were included. BTM determined were: aminoterminal propeptide of type I collagen (P1NP) by automatised assays (Elecsys, Roche). All BTM were determined at baseline (V0) and every 3 months of treatment until Month 18 (V6). All patients started treatment with ZA 4 mg IV every 4–3 weeks at the beginning of the study.

Results: Data of 168 patients with genitourinary cancer were analyzed. In this work data of renal (RC) (n = 39) and bladder (BC) (n = 34) cancer patients are presented. Population basal characteristics: mean age (years): 65.1 (RC) / 64.4 (BC); median weeks at the beginning of the study.

Conclusions: Elevation of baseline BTM levels is frequently present in advanced genitourinary cancer with bone metastases. Addition of ZA to standard systemic therapy reduces BTM levels. A significant association was observed between elevated levels of β-CTX and disease progression and death (renal) and death (bladder) throughout follow-up.

Disclosure: All authors have declared no conflicts of interest.

References:
Annals of Oncology

SELECTING PATIENTS FOR HIGH-DOSE INTERLEUKIN-2 ON THE BASIS OF TUMOUR HISTOLOGY

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Background: High-Dose Interleukin-2 (HD IL2) remains an option for treatment of metastatic renal cancer. In carefully selected patients, it can produce high rates of response with many durable remissions (Shablab A et al., J Immunotherapy 2011, 34(11):107-122). There remain uncertainties about the optimal way to select patients for treatment and here we update our approach to selecting patients for HD IL2 and include the analysis of carbonic anhydrase IX (CAIX) expression which has been previously suggested to correlate with response.

Methods: We present the outcomes of 103 patients with “favourable histology” (less than 10% papillary features and at least one of ≥50% alveolar/solid (A/S) or ≥50% clear cell features) treated with first-line immunotherapy (including 19 who have failed prior targeted therapy) with HD-IL2. We examine the response rate in relation to histology and CAIX expression.

Results: Overall the response rate was 59/103 (57%) and the CR rate is 23/103 (22% - with 4 patients in PR and continuing treatment at the time of writing). Examination of the different features in relation to response suggested that the most important features were ≥50% A/S pattern as only 1/5 patients who had <50% A/S responded and that was not a CR. CAIX staining was only available for 47 patients but may provide further modest benefit in selecting patients for therapy. Certainly, no patient with <80% CAIX staining achieved a CR although 3/10 did respond. In the group with >50% A/S pattern and >80% CAIX staining the response rate was 22/37 (59%) and the CR rate was 9/37 (24% with 4 patients in PR and continuing treatment at the time of writing).

Conclusions: These results extend and confirm our previously reported series (of 57 patients) and the overall response rate remains around 50% and that, combined with many durable complete remissions, results in an overall median survival 55 months (64, 80) for 103 patients with an apparent plateau of 40% long term survivors. HD-IL2 remains an attractive option for carefully selected patients with metastatic clear cell renal cancer. The most tangible benefit of HD-IL2 is the ability to achieve durable complete remissions and our series suggests the optimal histological type in which to achieve this is patients whose tumour has <10% papillary features, ≥50% A/S pattern and expresses ≥80% CAIX.

Disclosure: All authors have declared no conflicts of interest.

BEVACIZUMAB (BEV) + LOW-DOSE INTERFERON-α2A (IFN) FOR FIRST-LINE TREATMENT OF METASTATIC RENAL CELL CARCINOMA (MRCC): FINAL SAFETY AND EFFICACY DATA FROM THE PROSPECTIVE BEVLIN STUDY

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Background: In the AVOREN trial, first-line BEV + IFN (9 MIU three times in a week [t/w]) was effective in patients (pts) with mRCC. A retrospective analysis found that efficacy was maintained and IFN-related toxicity was improved in pts with IFN dose reduced to 6 or 3 MIU. BEVLIN (MO21609) prospectively assesses the safety and efficacy of BEV with low-dose IFN (3 MIU) in mRCC.

Methods: BEVLIN is an open-label single arm, multinational phase 2 study. Nephrectomized, treatment-naive pts with clear cell mRCC and favourable/intermediate Motzer scores were treated with BEV 10mg/kg q2w + IFN 3 MIU t/w until disease progression. BEVLIN was designed to allow descriptive, cross-trial comparison with the BEV + IFN 9 MIU treated favourable/intermediate Motzer score subgroup. Primary end points are safety (specific grade [Gr] ≥ 3 IFN-associated adverse events [AEs]) and progression-free survival (PFS). Secondary end points are overall survival (OS); overall response rate (ORR); any Gr ≥ 3, overall, and serious AEs.

Results: 147 pts were enrolled in BEVLIN. Baseline pt characteristics were similar to the comparator AVOREN subgroup. The median follow-up was 29.4 months. Pts received a median of 22.5 cycles of BEV (18.0 in the AVOREN subgroup). Median PFS was 15.3 mos (95% CI: 11.7; 18.0) vs 10.5 mos (95% CI: 10.1; 12.9); median OS was 30.7 mos (95% CI: 25.7; not reached) vs 25.8 mos (95% CI: 22.7; 29.4); and ORR was 29% vs 36% in BEVLIN and the AVOREN subgroup, respectively. The rates of any Gr- and Gr ≥ 3 IFN-associated AEs were markedly lower in BEVLIN than in the AVOREN subgroup (Table). Overall rates of AEs of special interest were similar between studies, despite longer BEV duration in BEVLIN.

Conclusions: Use of low-dose IFN with BEV in BEVLIN resulted in a reduction in IFN-related AEs without compromising efficacy outcomes compared with a control AVOREN subgroup.

Disclosure: B. Melichar: Dr. Bohuslav Melichar has received honoraria for lectures from Roche and participated in an advisory board meeting. S. Bracarda: Dr. Sergio Bracarda is an Advisory Board member for Novartis, Pfizer, GSK, Bayer, Aves/ Astellas, Janssen &Janssen and Sanofi-Aventis. He has received honoraria for lectures from Novartis, Sanofi-Aventis and Pfizer. R. Janciauskiene: Dr. Janciauskiene has been principal investigator in a Hoffmann-La Roche sponsored trial and has been an invited speaker for Hoffmann-La Roche. B. Lutiger: Beatrice Lutiger is an employee of F. Hoffmann-La Roche AG. M.E. Gore: Dr. Martin Gore has participated advisory board meetings and is on the speaker’s bureau for Roche. G. Mickisch: Dr. Gerald Mickisch is a member of the BEVLIN Steering Committee. J. Bellmut: Dr. Joaquim Bellmut has participated in an advisory board meeting, and received a lectures fee from Roche. All other authors have declared no conflicts of interest.

TOLERABILITY OF TARGETED AGENTS IN FIRST-LINE TREATMENT OF METASTATIC RENAL CELL CARCINOMA (MRCC)

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Objectives: Between 2005 and 2009, six targeted agents were approved for the treatment of mRCC in the US. Clinical trials have reported median progression-free survival (PFS) of up to 11 months for treatment-naïve patients. None has demonstrated an improvement in median overall survival versus another targeted agent. This study aims to determine the tolerability of these agents in real-world practices.

Methods: Adult patients with mRCC diagnosed between Jan 1, 2006 and Dec 31, 2010 were identified from a large commercial insurance claims and Medicare supplemental database in the US. A minimum follow-up of 3 months and ≥1 pharmacy or medical claims on or after metastasis diagnosis date were required for one of the targeted agents: sunitinib (SUN), sorafenib (SOR), pazopanib (PAZ), everolimus (EVE), temsirolimus (TEM), or bevacizumab with or without interferon alpha (BEV). Tolerability was measured by rate of dose reduction and duration of treatment. Median duration of treatment was assessed using the Kaplan–Meier method. Adverse events (AE) were based on diagnosis or treatment indicative of AEs commonly associated with these agents.

Results: 1,622 patients were identified, of which 1,079 received first-line SUN, 284 SOR, 168 TEM, 40 PAZ, 26 EVE, and 25 BEV. With a median follow-up of 13 months, median duration of treatment was the longest for PAZ (6.9 mos), followed by SOR and EVE (both 4.9 mos), SUN (4.8 mos), TEM (3.5 mos) and BEV (1.0 mos). Dose reduction was observed in a higher percentage of patients receiving SUN (26%) compared to TEM (18.5%), BEV (12.5%), EVE (7.7%), PAZ (7.3%), and SOR (6%). Rates of AEs were 93%, 86%, 85%, 80%, and 56% for TEM, SUN, SOR, EVE, PAZ, and BEV, respectively.

Conclusions: Rates of AEs appear to be high among commonly used first-line agents, including the recently approved PAZ and EVE, and there was substantial need for dose reduction for the most prescribed SUN. Duration of treatment appeared to be substantially shorter than published PFS values, assuming treatment until progression for the majority of patients. It is important to determine if AEs...

Conclusions: These results suggest that PIK3CA rs6443624 genetic variation in PI3K/AKT/mTOR pathway in RCC patients who underwent palliative therapy with everolimus. Patients treated with everolimus 10 mg daily orally until disease progression. The genomic DNA was extracted from formalin-fixed, paraffin-embedded primary tumor RCC tissue. 12 potentially functional SNPs (4 in AKT1, 4 in PI3K3CA and 4 in PIK3CA) were determined using a real-time PCR genotyping assay and analyzed for association with response to therapy, progression free survival (PFS) and overall survival (OS).

Results: Median age of 45 enrolled patients was 62 years (range, 41–78). At a median follow-up duration of 8.6 months, the 6-month PFS rate was 53.3%. Partial response was observed in 4.4% (2/45) of the patients.Median PFS was significantly prolonged in the PIK3CA rs6443624 for the CC genotype in comparison to the AA/AC genotype (8.9 months versus 5.5 months, log rank, p = 0.0157). In the multivariate analysis elevated corrected serum calcium and PIK3CA rs6443624 for the AA/AC genotype were unfavorable predictors of PFS (HR 5.25; 95% CI, 1.75–15.75 and HR 3.48; 95%CI, 1.47–8.25, respectively, p < 0.05). 1-year OS rate for patients with PIK3CA rs6443624 CC and AA/AC genotype was 86% and 51%, respectively (p = 0.0018). In multivariate analysis PIK3CA rs6443624 and elevated LDH serum level remained significant for OS (HR 18.7; 95% CL2.70–129.38 and HR 9.7; 95% CL 12.43 – 43.07, respectively; p < 0.05).

Conclusion: These results suggest that PIK3CA rs6443624 genetic variation in PI3K/AKT/mTOR pathway may modulate clinical outcomes in patients with RCC who undergo chemotherapy with everolimus. Further clinical studies are needed to confirm these findings.

Disclosure: All authors have declared no conflicts of interest.

The phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway is involved in growth regulation, proliferation control and metabolism in renal cell carcinoma (RCC). In our prospective pilot study, we determined whether common genetic variants in the AKT/P3K, FRAPI (encoding mTOR) are associated with clinical outcomes in RCC patients who underwent palliative therapy with everolimus.

Results: Median age of 45 enrolled patients was 62 years (range, 41–78). At a median follow-up duration of 8.6 months, the 6-month PFS rate was 53.3%. Partial response was observed in 4.4% (2/45) of the patients. Median PFS was significantly prolonged in the PIK3CA rs6443624 for the CC genotype in comparison to the AA/AC genotype (8.9 months versus 5.5 months, log rank, p = 0.0157). In the multivariate analysis elevated corrected serum calcium and PIK3CA rs6443624 for the AA/AC genotype were unfavorable predictors of PFS (HR 5.25; 95% CI, 1.75–15.75 and HR 3.48; 95%CI, 1.47–8.25, respectively, p < 0.05). 1-year OS rate for patients with PIK3CA rs6443624 CC and AA/AC genotype was 86% and 51%, respectively (p = 0.0018). In multivariate analysis PIK3CA rs6443624 and elevated LDH serum level remained significant for OS (HR 18.7; 95% CL2.70–129.38 and HR 9.7; 95% CL 12.43 – 43.07, respectively; p < 0.05).

Conclusion: These results suggest that PIK3CA rs6443624 genetic variation in PI3K/AKT/mTOR pathway may modulate clinical outcomes in patients with RCC who undergo chemotherapy with everolimus. Further clinical studies are needed to confirm these findings.

Disclosure: All authors have declared no conflicts of interest.

The allogeneic tumor cell-based cancer vaccine MGN1601 shows promising efficacy and a favourable safety profile in the late stage mRCC patients. A phase 2 clinical study in mRCC patients with MGN1601 as third-line therapy is under development.

Disclosure: M. Schroff; Board member of Mologen. M. Schmidt: Mologen employee. E. Weith: Mologen employee. M. Tschakal: Mologen employee. B. Wittig; Member of Scientific Advisory Board of Mologen. All other authors have declared no conflicts of interest.
A PHASE Ib CLINICAL TRIAL OF THE MULTITARGETED KINASE INHIBITOR LENVATINIB (E7080) IN COMBINATION WITH EVEROLIMUS FOR TREATMENT OF METASTATIC RENAL CELL CARCINOMA (RCC)

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Background: Lenvatinib (L) is an oral tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT, and PDGFR. Everolimus (E) is an oral mTOR inhibitor approved for RCC. This Phase (Ph) Ib/2 study investigates the combination of L plus E in RCC patients (pts) (NCT01136733). The Ph 1b component reported here assessed safety, tolerability, and maximum tolerated dose (MTD). The 3-arm randomised Ph 2 comparing PFS of L plus E and L alone versus E alone is ongoing.

Methods: Pts with advanced metastatic or resectable RCC, ECOG PS 0-1, age ≥ 18 y were eligible for Ph 1b. Pts received L plus E daily, in 28-day cycles. A standard 3 + 3 dose-escalation design with expansion cohort was used to identify the MTD. The optimal dosing regimen was reviewed and employed in the MTD cohort. Pts were randomized 1:1 to receive L plus E or L alone. Pts with progressive disease (PD) were removed from treatment, and pts with stable disease (SD) were continued on L at the previously assigned dose for at least 2 cycles or until progression, unacceptable toxicity, or withdrawal of consent. For pts who experienced PD, the investigator may select to continue treatment with L alone.

Results: 20 pts (M/F: 14/6; median age: 59 y [range 46-72]; median of 2 prior therapeutic regimens [range 0-5]; 1720 pts [85%]) had received prior anti-VEGF treatment (tx); 7/20 pts [35%] had also received prior mTor-targeted tx). 3 pts died from complications (SU vs. IFN, n = 12). The model indicated that QoL results based on Day 28 collection were different in model means of endpoints across all available post-baseline observations (CTA) by assessment day. The model indicated that QoL results based on Day 28 collection were different in model means of endpoints across all available post-baseline observations (CTA) by assessment day.

Conclusion: Pts with advanced metastatic RCC who are candidates for Ph 2b are randomized to receive L plus E (if MTD cohort) or L alone (if lower dosing cohort). Pts may continue L alone. A Ph 2a trial is underway to test this regimen in the adjuvant setting.

SUNITINIB (SU) DOSING SCHEDULE AND DATA COLLECTION TIMEPOINTS: IMPACT ON QUALITY OF LIFE (QOL) OUTCOMES IN METASTATIC RENAL CELL CARCINOMA (mRCC)

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Background: In a randomized phase III trial, SU was associated with superior QoL compared with interferon alfa (IFN). Here, we report implications related to the timing of collection of QoL data as it relates to SU-approved dosing in mRCC (4 weeks on treatment, 2 weeks off treatment; Schedule 4/2) and the extent to which such timing affects reported outcomes.

Methods: 750 treatment-naive patients with mRCC were randomized 1:1 to receive SU 50 mg orally once daily on Schedule 4/2 or IFN 9 MU subcutaneously thrice weekly. QoL measures included FACT-G, FKSI-15, FKSI-DRS, EQ-5D, and EQ-VAS. Higher scores indicated better outcomes (better QoL or fewer symptoms). Patients completed QoL questionnaires on Days 1 and 28 of each cycle, up to a maximum of 30 cycles. SU data were analyzed to describe how the timing of QoL collection may affect results. Random coefficients mixed-effects models were used.

Results: Data were used from all assessments collected (Days 1 and 28 at every cycle). The model indicated that QoL results based on Day 28 collection were consistently and statistically worse (lower QoL scores) than results based on Day 1 (Table). Based on a comparison with previously reported between-arm differences with SU vs. IFN, each variation could potentially diminish or increase the observed treatment effect by 38% to 62%.

Conclusions: To account for overall patient QoL experience on therapy, in this case, SU on Schedule 4/2, careful consideration must be given to the timing of QoL data collection. For SU in mRCC, QoL data should be collected both on and off treatment within a cycle. If QoL data are collected only at the last or first dose, scores will be overly negative or positive, respectively. Hence, if QoL data are collected at only a single timepoint within a cycle, it may not represent the full extent of QoL as experienced by patients on SU and may lead to misinterpretation of the true QoL outcomes.

Model means of QoL endpoints with SU by assessment day

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Day 1 (i.e., after 2 weeks off drug)</th>
<th>Day 28 (i.e., after 4 weeks on drug)</th>
<th>Difference between Day 1 and Day 28</th>
<th>P value</th>
<th>Difference between Day 1 and Day 28 as percentage of treatment effect* (SU vs. IFN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FKSI-15</td>
<td>46.3</td>
<td>44.3</td>
<td>2.0</td>
<td>&lt;0.0001</td>
<td>50%</td>
</tr>
<tr>
<td>FKSI-DRS</td>
<td>29.9</td>
<td>28.9</td>
<td>1.0</td>
<td>&lt;0.0001</td>
<td>43%</td>
</tr>
<tr>
<td>FACT-G</td>
<td>82.9</td>
<td>80.2</td>
<td>2.7</td>
<td>&lt;0.0001</td>
<td>40%</td>
</tr>
<tr>
<td>EQ-SD</td>
<td>0.76</td>
<td>0.73</td>
<td>0.03</td>
<td>&lt;0.0001</td>
<td>62%</td>
</tr>
<tr>
<td>EQ-VAS</td>
<td>76.1</td>
<td>73.2</td>
<td>2.9</td>
<td>&lt;0.0001</td>
<td>38%</td>
</tr>
</tbody>
</table>

Disclosure: A. Bushmakin: Employed by Pfizer as an Associate Director of Biosciences and holds Pfizer stock. J.C. Cappelleri: Employed with Pfizer as a Senior Director of Biosciences and holds Pfizer stock. R. Sandin: Employed by Pfizer as a Senior Director of Health Economics Outcomes Research and holds Pfizer stock. B. Korytowsky: Employed by Pfizer as an Associate Director of Biosciences and holds Pfizer stock. E. Matczak: Employed by Pfizer as a Medical Director, holds Pfizer stock, and receives honoraria from Pfizer. D. Cell: Advisory relationship with Pfizer. Research funding from Pfizer.

FIRST LINE TARGETED AGENTS AND COST OF CARE FOR PATIENTS WITH METASTATIC RENAL CELL CANCER (mRCC)

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Objectives: Between 2005 and 2009, six targeted agents were approved for the treatment of mRCC in the US. Selection of agents for first and subsequent lines of therapy is important in optimizing outcomes. We aim to determine the impact of first-line agents on total costs of care in mRCC patients.

Methods: Adult patients with mRCC diagnosed from Jan 1, 2006 to Dec 31, 2010 were identified from a large commercial insurance claims and Medicare supplemental database in the US. Follow-up >3 months and ≥1 pharmacy or medical claims on or after metastasis diagnosis date were required for one of the targeted agents: sunitinib (SUN), sorafenib (SOR), pazopanib (PAZ), everolimus (EVE), temsirolimus (TEM), or bevacizumab (BEV). Δ interferon α. Costs were measured in 2010 US dollars per patient per month (PPPM) over the entire follow-up period, and included patient out of pocket (OOP) costs, insurance-paid costs for mRCC drugs, other outpatient prescriptions (Rx), inpatient services, emergency room visits (ER), office visits, and other outpatient services including lab, radiology, outpatient surgery, and office-administered medications.
Results: 1,626 patients were identified. 1,079 received first-line SUN, 284 SOR, 168 TEM, 40 PAZ, 26 EVE, and 25 BEV. With a median follow-up of 13 months, the mean healthcare cost PPPM was:

<table>
<thead>
<tr>
<th>1st-line Agent</th>
<th>Cost PPPM</th>
<th>Total</th>
<th>Inpatient</th>
<th>Other outpatient</th>
<th>mRCC drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEM</td>
<td>$15,900</td>
<td>$6,480</td>
<td>$4,959</td>
<td>$3,532</td>
<td></td>
</tr>
<tr>
<td>BEV</td>
<td>$15,429</td>
<td>$5,629</td>
<td>$3,795</td>
<td>$4,021</td>
<td></td>
</tr>
<tr>
<td>EVE</td>
<td>$14,519</td>
<td>$3,585</td>
<td>$6,007</td>
<td>$4,063</td>
<td></td>
</tr>
<tr>
<td>SUN</td>
<td>$14,084</td>
<td>$6,208</td>
<td>$3,834</td>
<td>$2,965</td>
<td></td>
</tr>
<tr>
<td>PAZ</td>
<td>$12,461</td>
<td>$5,039</td>
<td>$3,895</td>
<td>$2,766</td>
<td></td>
</tr>
<tr>
<td>SOR</td>
<td>$12,266</td>
<td>$4,759</td>
<td>$3,662</td>
<td>$3,938</td>
<td></td>
</tr>
</tbody>
</table>

Inpatient costs accounted for the largest share of total cost. Other outpatient services and mRCC drug costs were the next lowest cost drivers. ER and office visits and other Rx each averaged less than $500 PPPM. OOP cost averaged $453 PPPM, but ranged from $380 for EVE to $2,045 for BEV.

Conclusions: Different first-line targeted agents appear to be associated with different total costs of care in mRCC. Patient characteristics, incidence and severity of adverse events, rates and duration of response, and choice of subsequent therapies may all play a role. Further characterization of such underlying factors may help optimize patient care and reduce cost.


Sorafenib in patients with Renal Cell Carcinoma and Brain, Bone or Lung Metastases: Subanalysis of the Non-interventional Predict Study

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Background: Clinical trials in advanced renal cell carcinoma (RCC) tend to exclude patients (pts) with brain metastases (mets). We report safety and efficacy outcomes from a subanalysis of Predict (NCT 00895674), a large, non-interventional study of sorafenib in pts with advanced RCC, according to sites of mets.

Methods: Pts were eligible based on a diagnosis of advanced RCC and a decision by the investigator to prescribe sorafenib under compliance of the local product label. Physician assessments of efficacy and tolerability were collected for up to 12 months.

Results: Of the efficacy population (n = 2,311), 1,079 pts (47%) had mets in >1 organ. Physician assessments of efficacy and tolerability were collected for up to 12 months.

Table: 817P

<table>
<thead>
<tr>
<th>Event</th>
<th>Metastases subsets</th>
<th>Brain (n = 121)</th>
<th>Bone (n = 673)</th>
<th>Lung, all (n = 1723)</th>
<th>Lung, only (n = 779)</th>
<th>Overall (n = 2,599)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>77 (63.6)</td>
<td>401 (59.6)</td>
<td>1011 (58.7)</td>
<td>406 (52.1)</td>
<td>1479 (56.9)</td>
<td></td>
</tr>
<tr>
<td>Any drug-related AE</td>
<td>58 (47.9)</td>
<td>316 (47.0)</td>
<td>861 (50.0)</td>
<td>366 (47.0)</td>
<td>1240 (47.7)</td>
<td></td>
</tr>
<tr>
<td>Any SAE</td>
<td>39 (32.2)</td>
<td>156 (23.2)</td>
<td>297 (17.2)</td>
<td>90 (11.6)</td>
<td>477 (18.4)</td>
<td></td>
</tr>
<tr>
<td>Any drug-related SAE</td>
<td>12 (9.9)</td>
<td>42 (6.2)</td>
<td>89 (5.2)</td>
<td>30 (3.9)</td>
<td>140 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Most frequent any grade drug-related AE*</td>
<td>20 (16.5)</td>
<td>106 (15.8)</td>
<td>366 (21.2)</td>
<td>188 (24.1)</td>
<td>520 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>19 (15.7)</td>
<td>111 (16.5)</td>
<td>306 (17.8)</td>
<td>114 (14.6)</td>
<td>443 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (6.6)</td>
<td>58 (8.6)</td>
<td>155 (9.0)</td>
<td>65 (8.3)</td>
<td>220 (8.5)</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (4.1)</td>
<td>36 (5.4)</td>
<td>96 (5.6)</td>
<td>44 (5.7)</td>
<td>145 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (5.8)</td>
<td>24 (3.6)</td>
<td>44 (2.6)</td>
<td>12 (1.5)</td>
<td>76 (2.9)</td>
<td></td>
</tr>
</tbody>
</table>

Background: Sunitinib had a manageable safety profile and encouraging efficacy in a global expanded-access mRCC study (ClinicalTrials.gov, NCT00130897; Pfizer) initiated prior to regulatory approval, in patients (pts) ineligible for other trials (Gore et al, 2009). Here we report final results.

Methods: Pts aged ≥18 yrs with treatment-naïve or previously treated mRCC received oral sunitinib on the approved 50 mg/day 4-wk-on/2-wk-off schedule. Safety was assessed regularly and tumor measurements were done as per local standard practice using RECIST-defined response. Analyses included all pts who received ≥1 dose of sunitinib.

Results: 4,577 pts were enrolled. From July 2005 to November 2011, 4,543 pts received treatment, including poor prognostic pts with brain metastases (7%), Eastern Cooperative Oncology Group performance status ≥2 (14%), non-clear cell RCC (12%) and age ≥65 yrs (13%). Median treatment duration was 2.5 mos (95% CI: 1.9, 3.1) and median follow-up was 13.6 mos. 4,298 pts (95%) discontinued; reasons included lack of efficacy (37%), death (20%) and adverse events (AEs; 15%).

The most common treatment-related AEs of any grade were diarrhea (47%), fatigue (40%), nausea (36%), decreased appetite (31%), mucosal inflammation (28%), stomatitis and vomiting (both 28%), hand-foot syndrome (HFS; 27%), dysgeusia (25%), hypertension (24%), thrombocytopenia (23%) and asthenia (22%). The most common treatment-related AEs of grade 3/4 were fatigue (9%), thrombocytopenia (8%), HFS (6%), asthenia (both 5%), hypertension and neutropenia (both 6%) and diabetes (5%). In 4,219 evaluable pts, the objective response rate (ORR) was 16% (n = 660) with subgroup ORR as follows: baseline brain metastases (30/324 [9%]), ECOG PS ≥2 (11/464 [2%]), and age ≥65 yrs (42/858 [5%]). Median progression-free survival was 9.4 mos (95% CI: 8.8, 10.0) and overall survival was 18.7 mos (95% CI: 17.5, 19.5).

Results from this global expanded-access mRCC trial confirm the efficacy and safety of sunitinib in >4,500 pts with wide-ranging disease states in a real-world setting. The sunitinib AE profile in this broad population was manageable and consistent with prior trial results.


**Disclosure:** All authors have declared no conflicts of interest.

820P  IMPLEMENTATION OF TARGETED THERAPY IN DENMARK FOR PATIENTS WITH METASTATIC RENAL CELL CARCINOMA: RESULTS FROM THE DANISH RENAL CANCER GROUP (DARENCA) STUDY-2

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Background: Treatment options for metastatic renal cell carcinoma (mRCC) have expanded since the introduction of targeted therapies. The impact of these new treatment options on overall survival in a complete national cohort of patients is unclear.

Objective: To analyze Overall Survival (OS), Progression Free Survival (PFS) and Time to Treatment Failure (TTF) in a complete national cohort of patients.

Design, setting and participants: All Danish patients with mRCC starting first line treatment with immunotherapy, TKIs or mTOR-inhibitors between 2006 and 2010 were included. Baseline and outcome data were collected retrospectively. Untreated patients referred for treatment were also assessed.

Outcome measurements and statistical analysis: OS, PFS and TTF was calculated using the Kaplan-Meier method. Differences between OS and treatment year were assessed using the log rank test. Differences in distributions were tested with the Chi-square test.

Results and limitations: Between 2006 and 2010, a total of 1,073 patients were referred. Of these, 759 patients received first line treatment and 314 received no systemic treatment. The proportion of treated patients increased from 64% in 2006 to 75% in 2010 (p = 0.02). In 2006 22% received targeted therapy and this increased to 75% in 2010 (p = 0.00001). In 2006 31% of first line patients received second line treatment compared to 41% in 2010 (p = 0.001). From 2006 to 2010 we observed an improved median OS from 11.5 to 15.7 months (p = 0.03), improved median PFS from 4.1 to 5.5 months (p = 0.001) and an improved median TTF from 3.1 to 4.9 months (p = 0.006) for first line treatment. The untreated population of 314 patients had a median OS of 3.1 months from date of metastatic disease with no significant change from 2006 to 2010.

Conclusions: In a complete national cohort of patients, implementation of targeted therapy has resulted in improved treatment options and outcome for patients with mRCC.

Disclosure: A.V. Soerensen: has received a research grant/funding from Pfizer. F. Donskov: has received a research grant from Novartis. E.Q. Bergan: Employee of Pfizer Denmark Aps. All other authors have declared no conflicts of interest.

**Disclosure:** All authors have declared no conflicts of interest.

820P  SUNITINIB GLOBAL EXPANDED-ACCESS TRIAL IN METASTATIC RENAL CELL CARCINOMA (mRCC) – FINAL RESULTS

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Background: Sunitinib is an oral multikinase inhibitor with promising activity in patients with metastatic renal cell carcinoma (mRCC) who failed initial VEGFR-TKI therapy. REACT (RAD001 Expanded Access Clinical Trial in
The REACT trial provided everolimus in advance of regulatory approval with the overall population. No complete responses were documented in this trial. Disease in 67 (55.8%) patients and a partial response in 1 patient (0.8%), comparable to that reported for global REACT. No grade 4 events. Investigator-assessed best overall responses were stable disease in 67 (55.8%) patients and a partial response in 1 patient (0.8%), comparable to that reported for global REACT. No complete responses were documented in this trial. Conclusions: The REACT trial provided everolimus in advance of regulatory approval and commercial availability to mRCC patients in the UK who failed initial VEGF-TKI therapy. Everolimus was well tolerated, and safety findings were consistent with those reported for global REACT.

Disclosure: S. Chowdhury: Consultant or Advisory: Novartis, Pfizer, GSK, Sanofi-Aventis, Janssen-Cilag, Dendreon. All other authors have declared no conflicts of interest.
Methods: Baseline characteristics and outcomes of 336 patients affected by mRCC receiving TTs were collected from the database of IRCCS Istituto Nazionale Tumori of Milan. The main characteristics of patients were: ECOG PS 0/1/2 186 (55%)/131 (39%)/19 (6%); clear-cell histology 291 (87%); previous nephrectomy 293 (87%). According to Motzer criteria 32% of patients showed low risk, 48% intermediate and 20% high risk. Overall, 167 (50%) patients received one TTs, while 116 (34%), 42 (13%) and 11 (3.3%) received 2, 3 and 4 TTs, respectively. Altogether, 245 (73%) patients received sorafenib (So), 212 (63%) sunitinib (Su), 33 (10%) bevacizumab regimen and 73 (22%) other TTs, including everolimus, temsirolimus and axitinib. Kaplan Meier curves were used to describe the survival of these patients according to the identified prognostic factors. The uni- and multi-variate analyses for OS were carried out by means of Cox proportional hazard regression analysis.

Results: At a median follow-up of 43 months, 199 patients (57%) had died. The median OS was 24 months (95% CI: 20.0-27.0) and the 5-year OS was 24.6% (95% CI: 18.7-30.8). In the univariate analyses, there were no significant differences in the hazard ratios (HR) for sorafenib followed by sunitinib compared to sunitinib followed by sorafenib (HR 1.1/So/Su = 1.16; 95% CI: 0.57-2.33) or compared with other therapies (HRother sequential th. / So-Su = 1.21; 95% CI: 0.78-1.88; p = 0.674). In the multivariate analysis, in terms of OS no statistical difference was reported as regards the sequence used (Su/So vs So/Su; p > 0.05) or bevacizumab regimen as compared to Su and/or So used sequentially (p > 0.05). In the uni and multivariate analysis ECOG PS, nephrectomy status, Fuhrman grade and previous cytokines treatments are independent predictive factors of outcome (p < 0.01).

Conclusions: These efficacy data suggest that TTs improve OS in mRCC, without any statistical difference among different sequences of TTs. No cross-resistance between different TTs were documented.

Disclosure: All authors have declared no conflicts of interest.
Patients and methods: This is a single arm, open label phase 2 study. Treatment naive patients with ECOG 0/1 and a histological/cytological diagnosis of RCC, who were considered suitable for treatment with sunitinib were enrolled into this study. The study is being conducted in 2 parts. The objective of Stage A is to establish the MTD of Sun-Cyclo and evaluate the efficacy and toxicity of Sun-Cyclo in a small cohort (n = 19) of patients. The objective of Stage B is to further evaluate efficacy and toxicity in an expanded population (n = 35). Sun-Cyclo was given as per following schedule: Sunitinib 50mg OD (4on/2off) and cyclophosphamide 50mg OD continuously. We report here the interim results of Stage A.

Results: A total of 19 patients have been enrolled into this study out of which 17 were evaluable for analysis. The MTD of Sun-Cyclo was 50mg Sunitinib (4on/2off) and 50mg Cyclophosphamide. The RR was: partial response 4 (21%), stable disease 10 (62.5%) and progressive disease 2 (12.5%). The median PFS was 11.00m (95% CI 7.9-14.1m) and the 1year PFS rate was 46.8%. The commonest grade 3 toxicities were fatigue (12.5%), neutropenia (37.5%) and thrombocytopenia (18.8%). 10 patients had dose reductions (4 (40%) had 1 dose reduction to 37.5mg and 6 (60%) had 2 dose reductions to 25mg). 12 patients had treatment delays with a median of 7 days (range: 2–28).

Conclusion: The combination of Sun-Cyclo was relatively well tolerated. The RR and PFS with Sun-Cyclo are similar to phase III results with sunitinib alone in RCC.

Disclosure: K. Edmonds: Nil related to this research. K. Khubra: Nil related to this research. L. Pickering: Pfizer: Research funding, honoraria, consultant role. M.E. Goes: Pfizer, Speaker bureau, advisory board. J. Larkin: Pfizer: Research funding, honoraria, consultant role. All other authors have declared no conflicts of interest.

829P EVALUATION OF SAFETY, TOLERABILITY AND ACTIVITY OF TEMSIROLIMUS IN PATIENTS WITH ADVANCED OR METASTATIC RENAL CELL CARCINOMA (a/mRCC) IN THE USUAL HEALTH CARE SETTING

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Introduction: Temsirolimus (TEMs), an i.v. mTOR inhibitor, is approved in the EU for the first-line treatment of patients with a/mRCC who have at least 6 of 9 prognostic risk factors. A pivotal study had demonstrated significantly increased overall survival with TEMs in poor risk patients compared to the former standard Interferon (10.9 vs 7.3 mo; p = 0.0078). To better identify the safety profile and efficacy of TEMs during clinical routine, collection of data in a postapproval non-interventional trial seems to be adequate.

Methods: A registry for a/mRCC patients treated with TEMs was started in Germany in January 2008 (NCT00700258). Primary objective: evaluation of the safety profile of TEMs. Secondary objectives: tolerability and anti-tumor activity of TEMs; profile of patients; sequence of systemic therapies. Inclusion criteria: histologically confirmed a/mRCC treated with TEMs and written informed consent by the patient.

Results: 118 active study centers recruited 455 patients from Feb. 2008 to April 2012. Preliminary data are available for 430 patients: 68.7% male, median age 68 years, median Karnofsky index 80%. Histological subtype: 75.3% clear cell, 10.9% papillary and 2.6% chromophobe RCC. According to modified MSKCC criteria 96.0% of patients (n = 323) were classified as poor risk and 4.0% as intermediate risk patients. Adverse events (AE) and serious adverse events (SAE) defined as drug related were observed in 41.2% and 10.2%, respectively. Skin disorders, fatigue, nausea, diarrhea, peripheral edema, anemia and dyspepsia of any grade were the most frequent AEs. Median progression-free survival for the total patient population was 151 days (d), for the subgroup of 1st line patients 162 d, for patients ≥ 65 yrs 155 d. Median overall survival for all patients was 381 d.

Conclusions: Patient population in the registry represents the expected pattern in a/mRCC regarding distribution of age, sex, and histology. Safety profile and clinical efficacy of TEMs in the usual health care setting confirm the phase III data. In addition, for patients ≥ 65 years safety and clinical efficacy of TEMs are comparable to results of the overall study population.


830P THE PREDICTIVE AND PROGNOSTIC ROLE OF 6-METHYLGLUANINE-DNA METHYLTRANSFERASE (MGMT) AND TISSUE TRANSLUMINASE-2 (TGASE-2) IN METASTATIC RENAL CELL CARCINOMA (mRCC) PATIENTS TREATED WITH SUNITINIB

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Background: Although anti-angiogenic drugs are widely used in mRCC, the predictive markers for these agents cannot be well defined yet. MGMT is recently shown to be anti-angiogenic and responsible for the anti-proliferative effect of sunitinib in glioblastoma cell lines. In preclinical studies, MGMT positive cells demonstrate high sVEGFR-1/VEGFA ratio, increased VEGFR-2 and TGase-2 protein level. mRCC is known to be responsible for drug resistance, cell proliferation, migration and angiogenesis. In vitro studies showed that TGase-2 inhibits VHL and this leads to increase of HIF-1α and KGF-1R.

Objective: To investigate the predictive and prognostic role of MGMT and TGase-2 in mRCC patients who were treated with sunitinib.

Methods: We analyzed 82 RCC patients retrospectively. 43 of 82 survive without recurrence (non-metastatic group), 39 of 82 were already metastatic at the diagnosis or at metastasis during follow up (metastatic group). Expression of MGMT and TGase-2 proteins were assessed by immunohistochemical (IHC) staining in tissue samples. In the metastatic group, all patients received sunitinib as anti-angiogenic therapy and the overall survival (OS) analysis of these patients were performed.
according to time of sunitinib initiation. OS analysis of the entire group (metastatic and non-metastatic) were performed according to the time of diagnosis.

Results: In the metastatic group (n = 39), the ones with low MGMT had median OS of 8 months while ones with high MGMT had median OS of 47 months (P = 0.498). The ones with low TGase-2 had mean OS of 35.2 months while ones with high TGase-2 had mean OS of 27.9 months (P = 0.366).In the entire group, the ones with low MGMT had mean OS of 115 months while ones with high MGMT had median OS of 189 months (p = 0.498). The ones with low TGase-2 had mean OS of 212 months while ones with high TGase-2 had mean OS of 133 months (p = 0.281).

Conclusions: Higher MGMT and lower TGase-2 may be predictors of good response to sunitinib. Independent of the treatment, in the entire group the ones with higher MGMT and lower TGase-2 have better survival. All these results are not statistically significant.

Disclosure: All authors have declared no conflicts of interest.

A RETROSPECTIVE STUDY OF METASTASECTOMY IN METASTATIC RENAL CELL CARCINOMA

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Introduction: Despite significant advances in the systemic therapy for metastatic renal cell carcinoma (mRCC) long term survival is rare. Systemic VEGF directed therapy can be toxic and is expensive. Metastatectomy can delay or even completely avoid systemic therapy. 5-year cancer specific survival rates of up to 73% have been reported in select patients.

Methods: Patients who underwent metastasectomy for RCC recurrence in our institution between 2001–2011 were identified through a clinical database that was cross-referenced with a pathology database and multi-disciplinary team records.

Patient characteristics N= 36 

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>25/11</td>
<td>70/30</td>
</tr>
<tr>
<td>Median Age (range 44-85)</td>
<td>65</td>
<td>NA</td>
</tr>
<tr>
<td>Primary tumour pt2 or less</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Radical nephrectomy</td>
<td>31</td>
<td>97%</td>
</tr>
<tr>
<td>Clear cell histology</td>
<td>20</td>
<td>100%</td>
</tr>
<tr>
<td>Median time to metastasectomy months (range)</td>
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<td>3–120</td>
</tr>
<tr>
<td>Number of metastases</td>
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<td>27</td>
</tr>
<tr>
<td>Site of metastases</td>
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</tr>
<tr>
<td></td>
<td>Adrenal</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Bone</td>
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</tr>
<tr>
<td></td>
<td>Other***</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Upper GI</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
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</tr>
<tr>
<td>Minimum Heng risk score at time of metastasectomy</td>
<td>Favourable</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>1</td>
</tr>
</tbody>
</table>

Results: evaluable patients n = 32; **n = 20 *** includes chest wall, ovary, thyroid, contralateral kidney Median time to first progression from surgery was 21 months (range 0-50). On progression 17/18 patients had repeat metastasectomy with 10/17 relapsing at a site different to the original surgery. To date 11/36 have received additional therapy including tyrosine kinase inhibitors (n = 7), radiotherapy (n = 3) and interferon (n = 1). Median overall survival from first metastasectomy has not been reached at mean follow up of 27 months. 27 patients are alive at last follow up with 14 disease free. Of the 13 evaluable patients, none are free from recurrence at 5 years.

Discussion: Despite limitations of retrospective design, selection bias and size, this data shows that metastasectomy is feasible in selected patients with mRCC. Our patients included a group with characteristics that have previously been described as less favourable for resection. Despite this preliminary overall survival data is encouraging.

Conclusion: Metastasectomy is an important treatment option for selected patients with metastatic renal cell carcinoma. All patients should be managed in a multi-disciplinary manner to ensure that patients are considered for metastasectomy when appropriate.

Disclosure: All authors have declared no conflicts of interest.

C-MYC AS A NEW PREDICTIVE BIOMARKER FOR SUNITINIB IN METASTATIC RENAL CLEAR CELL CARCINOMA

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Background: Sunitinib is a tyrosin kinase inhibitor with proven efficacy in renal cell carcinoma (RCC). However we still lack properly validated molecular predictors of response. Two subtypes of sporadic VHL-deficient RCC were proposed based on HIF1α and HIF2α expression and c-Myc activation. This molecular subclassification could provide a framework for current targeted therapies. This study aims to explore the predictive value of this molecular signature.

Methods: An observational prospective study involving 10 Spanish Hospitals was designed to collect formalin-fixed paraffin-embedded primary tumor tissue samples. We enrolled consecutively attending adults who had a centralized pathologically confirmed diagnosis of RCC with a clear-cell histology and advanced disease. Eligible patients were treatment naive and scheduled for sunitinib following routine clinical practice. The protocol was approved by the medical ethics committees of all participating institutions, and signed informed consent was obtained for all patients. Selected biomarkers were analyzed by immunohistochemistry following established protocols.

Results: From March 2009 to February 2011, 80 patients were included. At the time of the analysis, tumor samples were available for 64 patients and 58 were evaluable for c-Myc expression. Only 33% (19/58) showed c-Myc immunostaining (any score: 1–3) and 67% (39/58) were negative for c-Myc expression (scored as 0). Both groups were well balanced and non significant differences in risk prognostic factors were found. Regarding Sunitinib efficacy, significant differences in PFS were found between both molecular subgroups. A median PFS of 5.4 months was found in patients with c-Myc positive primary tumors vs. 11.4 months in patients with c-Myc negative primary tumors (HR = 2.54, 95%CI (1.28, 5.07), p = 0.0062). Correlation of c-Myc expression with other related biomarkers is underway.

Conclusions: Although, this is a small sample and validation is still needed, these results suggest a promising value for c-Myc immunostaining as a novel tool to identify those patients with RCC with more probabilities of obtaining benefit with Sunitinib through an accessible and reproducible technique. This study was supported by an Independent Investigator Research grant from Pfizer Inc.

Disclosure: P. Maroto: Compensation of consultant/Advisory role at Pfizer. E. Esteban: Compensation of consultant/Advisory role at Pfizer. All other authors have declared no conflicts of interest.

DYNAMIC CHANGES IN PLASMA OSTEOPONTIN AS A MARKERS OF TUMOR RESPONSE IN METASTATIC RENAL CELL CARCINOMA (RCC) PATIENTS TREATED WITH PAZOPANIB


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Background: In a Phase II RCC study of pazopanib (VEG102616) a response rate of 34.7% and disease control rate (CR + PR + SD) of 80% were observed (Hutson, JCO 2009). Previously, we reported that elevated levels of E-Selectin, lower levels of IL-6 and HGF were correlated with lower PFS and decrease in tumor shrinkage. Higher levels of IL-6 and IL-8 correlated with greater tumor burden (Tran ASCO 2010). IL-8, OPN, HGF and TIMP1 correlated with PFS and IL-6, IL-8 and OPN were prognostic markers (Yuan GU ASCO 2011, Tran ESMO 2011). In this study, we measured CAF levels at baseline, week 4 and week 12 after initiation of pazopanib therapy and evaluated for dynamic changes in CAF as potential marker for tumor response and clinical benefits

Methods: Six candidate CAFs (TIMP1, IL-6, IL-8, HGF, E-Selectin, and OPN) were measured in 173 patients (pts) whose plasma samples were collected during the
target lesions at baseline on 17 August 2018
by guest
Downloaded from https://academic.oup.com/annonc/article-abstract/23/suppl_9/ix258/218485

Results: Decreases in OPN levels from baseline at week 4 (p = 0.030) and week 12 (p = 0.006) show significant correlations with MTS. At week 4, changes in E-Selectin from baseline was trending (p = 0.053) in correlation with MTS. With PFS, changes in IL-6 level from baseline at week 12 has near significant correlation with PFS (p = 0.05). E-Selectin has an inverse baseline to week 4 significant correlation with best response status week 4 (p = 0.0245) but not at week 12.

Conclusion: Decreasing levels of osteopontin from baseline at week 4 and 12 correlated with improved tumor shrinkage; while increase in IL-6 portends shorter PFS and E-Selectin was inversely correlated with best response status. Additional investigation is needed to evaluate the dynamic changes of CAIX as an approach to monitor patients while on pazopanib therapy as marker of tumor response.

Disclosure: Y. Liu: Stock ownership; Yes; GSK Membership on an advisory board or board of directors: No; Corporate-sponsored research: No; Other substantive relationships: No. Martin: Stock ownership; Yes; GSK Membership on an advisory board or board of directors: No; Corporate-sponsored research: No; Other substantive relationships: No. L. Baker-Neblert: Stock ownership; Yes; GSK Membership on an advisory board or board of directors: Yes; GSK Membership on an advisory board or board of directors: No; Corporate-sponsored research: No; Other substantive relationships: No. J. Neyman: Stock ownership; No; Membership on an advisory board or board of directors: No; Corporate-sponsored research: No; Other substantive relationships: No.

All authors have declared no conflicts of interest.

Background: There is no consensus on including the primary lesion as the target lesion when evaluating the response of non-nephrectomized metastatic renal cell carcinoma (mRCC) patients. We evaluated whether best overall response changes by designating primary renal lesions as either target or non-target lesions and assessing response per RECIST in mRCC pts treated with sunitinib. In addition, we evaluated whether discordance, if any, leads to a difference in predictive value of response in terms of progression-free survival (PFS) and overall survival (OS).

Patients and methods: Among pts with histologically confirmed mRCC treated with sunitinib at Asian Medical Center, pts with an intact primary tumor and at least one extra-renal measurable lesion were included. To measure the influence of including the primary lesion as the target lesion, when evaluating the response of non-nephrectomized metastatic renal cell carcinoma (mRCC) patients (pts), we evaluated whether best overall response changes by designating primary renal lesions as either target or non-target lesions and assessing response per RECIST in mRCC pts treated with sunitinib. In addition, we evaluated whether discordance, if any, leads to a difference in predictive value of response in terms of progression-free survival (PFS) and overall survival (OS).

Results: Forty-one pts were included in this study. Median ΔSOD of the primary lesion was –18.0% (range, –100.0–120.0%), respectively. For metastasis-only target lesions, the best overall response of two pts (4.9%) changed from SD to PR. When we categorized pts into responders and non-responders, response determination using metastasis-only target lesions, was documented separately. For examining differences of target lesions and best overall response, assessed from all target lesions and from metastasis-only target lesions, a TMA was constructed and analyzed. For examining differences of target lesions and best overall response, assessed from all target lesions and from metastasis-only target lesions, a TMA was constructed and analyzed.

Conclusion: Decreasing levels of osteopontin from baseline at week 4 and 12 correlated with improved tumor shrinkage; while increase in IL-6 portends shorter PFS and E-Selectin was inversely correlated with best response status. Additional investigation is needed to evaluate the dynamic changes of CAIX as an approach to monitor patients while on pazopanib therapy as marker of tumor response.

Disclosure: Y. Liu: Stock ownership; Yes; GSK Membership on an advisory board or board of directors: No; Corporate-sponsored research: No; Other substantive relationships: No. Martin: Stock ownership; Yes; GSK Membership on an advisory board or board of directors: No; Corporate-sponsored research: No; Other substantive relationships: No.

All authors have declared no conflicts of interest.

Background: Among pts with histologically confirmed mRCC treated with targeted therapies (TTS) for metastatic renal cell carcinoma (mRCC), the primary lesion might be more representative of tumor response determined using metastasis-only target lesions, than overall response of two pts (4.9%) changed from SD to PR. When we categorized pts into responders and non-responders, response determination using metastasis-only target lesions, was documented separately. For examining differences of target lesions and best overall response, assessed from all target lesions and from metastasis-only target lesions, a TMA was constructed and analyzed.
Methods: Pts with clear-cell mRCC who received 3 TTs were included. A questionnaire was sent to main Italian centers involved in the treatment of mRCC. Demographic data, history of RCC, type and length of first, second and third lines were collected. Values of serum HB, PLT, neutrophils, LDH and Ca, ECOG-Ps, previous and number of metastatic sites <2 before the start of third line were evaluated. Cleveland Clinic, French, Heng, and MSKCC scores and relative survival were calculated.

Results: Following the screening of 1905 pts, 252 (13%) with 3 TTs were identified. The median age was 60 yrs (range 52-68), 73% were male, 96% had nephrectomy and 38% were metastatic at diagnosis. At 1st line, the M0 class was good, intermediate, and poor in 48%, 47% and 5% of pts, respectively. The median OS from the start of 3rd line was 14.3 mos (95%CI, 10.1 – 18.6). Rate and survival by prognostic group according to each classification are reported in table below. When prognostic factors were considered separately, at the univariate level, ECOG-PS ≤ 2, Hb < LLN, LDH > 1.5ULN, Ca > ULN, PLT > ULN, Neu > ULN, and sites of disease > 2 had negative prognostic role. Multivariate analysis shows an independent prognostic role only for ECOG-PS ≥ 2 (HR: 1.8; 95%CI: 1.1-2.8), Hb < LLN (HR: 1.9; 95%CI: 1.2-2.6) and neu ≥ ULN (HR: 2.1; 95%CI: 1.2-3.8). Pts were stratified in 3 groups according to the presence of none, 1 or ≥ 2 prognostic factors. The median OS was 20.3, 16.6 and 7.8 months, respectively (p < 0.0001)

Conclusions: Current nomograms are able to predict survival in patients with mRCC in first and second line treatment

Disclosure: All authors have declared no conflicts of interest.

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Table: 836P

<table>
<thead>
<tr>
<th>P Group</th>
<th>Cleveland Clinic</th>
<th>French</th>
<th>Heng</th>
<th>MSKCC</th>
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<tbody>
<tr>
<td></td>
<td>Pts (%)</td>
<td>PFS (mos)</td>
<td>p</td>
<td>Pts (%)</td>
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<td>NR</td>
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<td>43</td>
<td>10.2</td>
<td>13</td>
<td>9.1</td>
</tr>
</tbody>
</table>

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838P

**EXPRESSION AND CLINICAL IMPORTANCE OF E-CADHERIN, DYSADHERIN AND CHEMOKINE LIGAND 2 (CCL2) IN RENAL CELL CARCINOMA (RCC)**


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**Aim:** Dysadherin is a cell adhesion molecule that related with aggressiveness and progression in many cancers. Dysadherin acts role either with E-cadherin dependent or CCL-2 mediated that E-cadherin independent. We studied expression and clinical importance of dysadherin and e-cadherin as adhesion molecules and CCL-2 in RCC.

**Method:** Between 2006 and 2010, 38 patients with RCC were evaluated retrospectively. Median age of the patients (27 male, 11 female) was 60 (range, 33–84). While median tumor size was 5.75 cm (range, 2–30 cm), 13 patients were stage 4, one patient was stage 3, 5 patients were stage 2, 19 patients were stage 1. 15 patients were Fuhrman grade 3, 21 patients (55.3%) had capsule invasion, 10 patients (26.3%) had perirenal fat tissue involvement and 4 patients had (10.5%) renal vein thrombosis. Dysadherin did not express in 10 patients. Low expression (less than 93%) was detected in 25 patients (65.8%), enhanced expression (more than 30%) was detected in 3 patients (96.9%). E-cadherin did not express in 11 patients (28.9%), low expression was detected in 23 patients (60.5%), moderate-high expression was detected 4 patients (10.6%), CCL2 did not express in 14 patients, low expression was detected in 7 patients (18.4%), moderate-high expression was detected in 17 patients (44.3%). Although moderate positive correlation between dysadherin and CCL2 (r = +0.25, p = 0.49) e-cadherin and CCL2 (r = +0.32, p = 0.01) were detected, moderate negative correlation between dysadherin and e-cadherin was detected (r = -0.22, p = 0.33). Moderate negative correlation was detected between grade of tumor and e-cadherin (r = -0.32, p = 0.49). Median overall survival (OS) was 46.6 months (range, 38.9-54.3), in univariate analysis, stage, grade of tumor, capsule invasion, tumor thrombosis, perirenal fat tissue involvement were significant on OS (p < 0.05), however dysadherin, E-cadherin and CCL2 were not associated with OS (p>0.05). Stage and vascular thrombosis were significant on overall survival in multivariate analysis.

**Conclusion:** This is the first study that evaluated adhesion molecules in RCC and there is no association these parameters and clinical outcome.

Disclosure: All authors have declared no conflicts of interest.

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839P

**EFFICACY AND SAFETY OF TEMSIRILOMUS IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA: RESULTS FROM THE SPANISH EXPERIENCE**

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Temsirolimus (TEM) is an mTOR inhibitor approved for first-line treatment of patients with poor-prognosis metastatic renal cell carcinoma (RCC). In a phase III trial TEM showed a statistically significant benefit in overall survival when compared to interferon-α. Recently, several authors have described that TEM also appears to be

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Effectiveness was assessed by RECIST (v1.1). Clinical benefit (CB; partial response + stable disease) was observed in 91% of patients treated with S1, 89% of patients treated with PZ, and 83% of patients treated with EV. Median PFS was 11.9 months (95% CI: 9.2-19.0 months) for the S1 group, 10.7 months (95% CI: 8.8-14.0 months) for the PZ group, and 5.2 months (95% CI: 4.4-6.8 months) for the EV group. The HR for PFS was 0.59 (95% CI: 0.40-0.86; log-rank test, P = 0.002) in favor of S1 compared with EV. The median time to treatment discontinuation due to AEs was 11.9 months for S1, 9.2 months for PZ, and 5.2 months for EV. Grade 3-4 AEs occurred in 18% of patients who received S1, 15% of patients who received PZ, and 29% of patients who received EV. No deaths due to AEs were reported.

Conclusions: This prospective, randomized, double-blind, placebo-controlled trial showed that S1 is superior to EV in previously treated patients with mRCC in terms of PFS and tolerability. The findings of this study support the use of S1 in routine clinical practice.

Disclosure: All authors have declared no conflicts of interest.
investigated angiogenesis pathway molecules, sVEGFR-2, VEGF-A, and bFGF, in plasma as potential biomarkers of everolimus efficacy in RECORD-1.

Material and methods: Patients received everolimus 10 mg daily (n = 277) or placebo (n = 139), both with ECOG in plasma samples were collected on day 1 of the first four 28-day treatment cycles; plasma levels of sVEGFR-2, VEGF-A, and bFGF were assessed using ELISA. A mixed effects model was used to assess treatment effect over time on each biomarker. Hazard ratios (HR) for prognostic effects were obtained using log baseline biomarker values as continuous variables in a stratified Cox proportional hazards model.

Results: Plasma values for sVEGFR-2, VEGF-A, and bFGF were available for 45/45/39% of everolimus patients and 50/50/45% of placebo patients. Baseline characteristics of patients with biomarker data were similar to the overall population. Mean log baseline values for sVEGFR-2, VEGF-A, and bFGF were similar for both arms; 91.5/1.6 for everolimus and 91.5/1.8 for placebo, respectively. Median PFS was significantly improved with everolimus vs placebo, regardless of baseline levels of any of the biomarkers analyzed (P < .001), suggesting that none of them is predictive of everolimus efficacy. Lower VEGF-A baseline level (HR, 1.27; 95% CI, 1.03-1.57; P = .028) was significantly associated with longer PFS in the trial population, suggesting that this biomarker may be prognostic for mRCC. Over the time course of the study, a significant everolimus treatment effect over placebo on reducing bFGF and sVEGFR-2 levels was observed (P = .0095 and P < .001, respectively), but not on VEGF-A level.

Conclusions: Everolimus provided significant clinical benefit over placebo, regardless of baseline biomarker levels. However, lower VEGF-A level was seen as a potential prognostic factor for longer PFS. Plasma levels of bFGF and sVEGFR-2 were significantly down-regulated from baseline by everolimus treatment.

Disclosure: S. Ouaddar: Stephane Ouaddar received honoraria from Bayer, Novartis, Pfizer, Roche, and Sanofi-Aventis. B. Escudier: Bernard Escudier has received honorarium from Novartis, Pfizer, GSK, Aveo, and Bayer. J. Thompson: John Thompson received clinical study support from Novartis. V. Grunwald: Viktor Grunwald served as consultant to Roche, Bayer, Novartis, Pfizer, GlaxoSmithKline, and Aveo/Astellas, received honoraria from GlaxoSmithKline, Novartis, and Pfizer, and received research funding from Pfizer and GlaxoSmithKline. S. Bracarda: Sergio Bracarda has served as advisor for Pfizer, Bayer-Scherling, GlaxoSmithKline, Novartis, Aveo/Astellas, Boehringer-Ingehelm, Johnson & Johnson, and Sanofi-Aventis and has received speaker fees from Pfizer, Novartis, and Sanofi-Aventis. A. Pannecroix: Ashok Pannecroix is an employee of Novartis Pharmaceuticals Corporation. S. Gogov: Sven Gogov is an employee of Novartis Pharma AG. D. Chen: David Chen is an employee of Novartis Pharmaceuticals Corporation. R.J. Motzer: Robert Motzer has received research funding from Novartis. All other authors have declared no conflicts of interest.

Results: 194 axi and 124 eve pts who were su-r were analyzed. While AXIS trial included only pts that progressed on 1 line of tx, 65% of su-r eve pts had 3 plus lines of therapy. Some pts were included in the eve trial without having progressed on 1st line tx. Available pt characteristics were comparable across two groups, except for difference in MSKCC risk categories (36% vs 17% poor risk pts in axi and eve) and duration of prior sunitinib. MSKCC risk category and duration of prior sunitinib were significant predictors of OS. The final PFS equation included MSKCC risk group and age. Estimated median OS and PFS was 15.2 and 5.1 months for axi compared to 10.6 and 3.6 months for eve group respectively. Estimated difference in mean OS and PFS between axi and eve was 7.6 and 2.6 months. Conclusion: This analysis suggest that su-r RCC pts treated with axi may have an improved OS and PFS compared to pts treated with eve. Our analysis could not account for all differences between trials, such as number of prior therapies, however, a STC can provide additional comparative context.

Disclosure: I. Proskorovsky: I am an employee of United BioSource Corporation. As a research consulting organization, it received funding from Pfizer for the research undertaken in this abstract. A. Benedict: I am an employee of United BioSource Corporation. As a research consulting organization, it received funding from Pfizer for the research undertaken in this abstract. S. Negrier: Dr. Negrier has received honorariums from Pfizer and Novartis as well as research grants from GlaxoSmithKline and Roche. J. Larkin: research funding from Pfizer and Novartis, advisory role to Pfizer, Novartis, COX, IMS, Astra, R. Sandin: Employee of Pfizer AB, Stock or other ownership interests in Pfizer Inc. C. Chen: Employee and stockholder of Pfizer only.

AXITINIB (AXI) AND EVEROLISOM (EVE) IN THE TREATMENT (TX) OF SUNITINIB-REFRACTORY (SU-R) PATIENTS (PTS) WITH METASTATIC RENAL CELL CARCINOMA (mRCC): RESULTS OF A SIMULATED TX COMPARISON (STC) ANALYSES

I. Proskorovsky1, A. Benedict2, S. Negrier3, J. Larkin4, R. Sandin5, C. Chen6

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Background: Axitinib is a novel VEGF targeted agent for mRCC pts who failed 1 prior systemic therapy. The AXIS trial compared axi to sorafenib and showed a significantly longer PFS in pts treated with axi, including the su-r subgroup. No direct comparison is available between axi and eve but is an important clinical question. The goal of this analysis was to compare OS and PFS in su-r pts treated with axi and eve.

Methods: Pts who were su-r and received axi in the AXIS trial and eve in RECORD-1 trial were considered for this analysis. A STC method (Caro et al 2010) was used to derive OS and PFS curves for a hypothetical cohort of “axi like” pts had they received eve in the AXIS trial. Pt level AXIS data was used to derive predictive equations for OS and PFS. Parametric survival analysis identified the best fitting distribution and significant predictors of OS and PFS. These equations were calibrated using pt characteristics and median OS and PFS reported in the literature.
Conclusions: In pts with RCC treated in clinical practice settings, some AE rates were numerically higher in pts with comorbidities. There were no notable differences in duration of Sor therapy. Number (%) pts with AEs (safety population)

<table>
<thead>
<tr>
<th>Comorbidity subset</th>
<th>Hypertension (n = 760)</th>
<th>Diabetes (n = 267)</th>
<th>Total population (n = 2599)</th>
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<tr>
<td>Any AE</td>
<td>524 (69.0)</td>
<td>177 (66.5)</td>
<td>1479 (56.9)</td>
</tr>
<tr>
<td>Any drug-related AE</td>
<td>436 (57.4)</td>
<td>146 (54.7)</td>
<td>1240 (47.7)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>191 (25.1)</td>
<td>71 (26.6)</td>
<td>477 (18.4)</td>
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<tr>
<td>Any drug-related SAE</td>
<td>59 (7.8)</td>
<td>20 (7.5)</td>
<td>140 (5.4)</td>
</tr>
</tbody>
</table>

Most frequently reported any grade drug-related AEs (preferred term)*

- Hand-foot skin reaction: 173 (22.8)
- Nausea: 177 (23.3)
- Diarrhea: 62 (8.2)
- Rash: 49 (6.5)
- Hypertension: 52 (6.8)
- Alopecia: 51 (6.5)
- Nausea: 33 (4.3)

Other AEs in relevant system organs classes

**Cardiac disorders**

- Nausea: 7 (0.9)

**Renal and urinary disorders**

- Rash: 7 (0.9)
- Nausea: 3 (0.1)

**Vascular disorders (excluding hypertension)**

- Rash: 7 (0.9)
- Nausea: 2 (0.7)

*Occurring in ≥5% of patients in any subset. Including rash, rash generalized, rash erythematous, rash maculo-papular, rash pustular, rash macular, rash pruritic, exfoliative rash, rash papular.

**Purpose:** The mammalian target of rapamycin (mTOR) kinase is a well-established therapeutic target in renal cell carcinoma (RCC). We explored the activity and safety of Temsirolimus as II-line treatment for advanced RCC pts in a multicenter phase II trial.

**Methodology:** in this open-label trial, Temsirolimus (25 mg/wk i.v.) was administered to advanced RCC pts with documented progression after any II-line treatment. Primary endpoint was PFS rate at 6 mos. Tumor response was assessed every 8 wks. Considering a 6-mo PFS rate of 20% unacceptable (p ≤ 0.20) and a 6-mo PFS rate of 40% (p ≤ 0.40) of interest, a minimum targeted accrual of 47 pts in the sunitinib-pretreated group was to be pursued in order to reach 90% power at a significance level of 5%.

**Results:** From May 2009 to January 2012, 76 pts were enrolled (median age: 67 yrs, range: 36-86; M/F: 58/18; ECOG PS 0/1/2: 51/19/6); I-line therapy included sunitinib (60 pts), bevacizumab (8), sorafenib (3), cytokines (2), or other (3). With 18/57 evaluable patients free from progression at 6 mos in the sunitinib-pretreated group the primary endpoint was met and trial accrual was stopped. Median PFS was 4.0 mos (95% CI: 2.7–5.3) and 4.6 mos (95% CI: 2.8–6.5) in the overall (n = 71) and sunitinib-pretreated (n = 57) populations, respectively; OS in the same groups was 13.7 mos (95% CI: 9.1–18.3) and 14.6 mos (95% CI: 8.9–20.3), respectively. Six out of 71 pts (8%) had PR and 33/71 (46%) had SD as their best response. Toxicity (n = 68) was mild with G3 anemia, neutropenia and thrombocytopenia in 2, 1, and 1 pts, respectively; G3 hyperglycemia and G3 hypertriglyceridemia in 2 and 7 pts, respectively; G4 hypercholesterolemia in 2 pts; G3 stomatitis in 5 pts; G3 asthenia in 3 pts; G3–4 pulmonary toxicity in 2 pts; G3 diarrhea in 2 pts; G3 cutaneous rash in 1 pt. Only 1 hypersensitivity reaction occurred during Temsirolimus infusion. Treatment compliance was good, with <10% of weekly administrations omitted and 15/67 (22%) pts requiring dose reductions (to 20 mg/wk and 15 mg/wk in 11 and 4 pts, respectively). Mean number of weekly administrations received was 15. Final analysis will be presented at the meeting.

**Conclusions:** Temsirolimus is an active and well-tolerated II-line treatment for advanced RCC; results of currently ongoing phase III trials are awaited to further define its role in this setting.

**Disclosure:** All authors have declared no conflicts of interest.
**Annals of Oncology**

**CLINICAL EFFICACY OF SUNITINIB AS POST-OPERATIVE ADJUVANT THERAPY IN PATIENTS WITH HIGH-RISK RENAL CELL CARCINOMA**

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**Objective:** To evaluate the efficacy and safety of Sunitinib as post-operative adjuvant therapy in patients with high-risk renal cell carcinoma (RCC).

**Methods:** A total of 60 patients with resected, histologically confirmed clear cell RCC were enrolled in this study. Patients received orally Sunitinib either at a dose of 50mg on treatment schedule 4/2 (once daily for 4 weeks followed by 2 weeks off) or at a dose of 37.5mg once daily for three 6-week cycles from 1 month after surgery.

**Results:** All 60 patients tolerated Sunitinib treatment well and no patient discontinued treatment due to adverse events. Most adverse events were grade I or II. The most frequently reported adverse events were neutropenia (56.7%), thrombopenia (53.3%), leucopenia (48.3%), hand-foot syndrome (46.7%) and hypertension (36.7%). The most frequently reported grade 3 or 4 toxicities were thrombopenia (25%), neutropenia (15%), hand-foot syndrome (11.7%) and leucopenia (8.3%). The majority of adverse events occurred within the first 6 weeks of Sunitinib treatment, and was ameliorated 1 month after 3 cycles finished. No irreversible adverse event was observed. As of April 5, 2012, no recurrence occurred in patients except one death due to cerebrovascular accident unrelated to treatment, with both 6-month and 9-month disease-free survival (DFS) rate of 100%.

**Conclusion:** Myelosuppression occurred less frequently in high-risk RCC patients treated with Sunitinib as operative adjuvant therapy than in advanced RCC patients, with a better benefit trend. However, long-term follow-up data are needed to further confirm the efficacy of Sunitinib in the adjuvant setting.

**Disclosure:** All authors have declared no conflicts of interest.

**OVERALL SURVIVAL (OS) IN METASTATIC RENAL CELL CARCINOMA (mRCC): A COMPARISON BETWEEN SORAFENIB (SO) AND BEST SUPPORTIVE CARE (BSC) AFTER FIRST LINE TREATMENT WITH SUNITINIB (SU) IN SWEDEN**

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**Background:** There is a paucity of efficacy data after first line treatment with SU in mRCC. This retrospective register study compared OS in patients treated with SO and BSC after first line treatment with SU in Sweden.

**Methods:** Three Swedish national health registers were used: the Swedish Cancer register (diagnosis and death), the National Patient Register (in-/out-patient data), and the Swedish Prescribed Drug Register. 135 patients identified with mRCC, diagnosed no later than 2009, were recorded as having received 1st-line treatment with SU: 59 patients received SO and 76 patients received BSC. Multivariate analyses was performed using the Cox proportional hazards model including estimation of adjusted OS. The regression model included the covariates: age, gender, nephrectomy, time since diagnosis and metastatic disease, time since mRCC diagnoses and stage, systemic therapy, geographical region, institutional size, and duration of first line SU treatment. Sensitivity analysis with combinations of explanatory variables, was performed to test the robustness of the results.

**Results:** Patients characteristics differed between the SO and BSC patients, but available information did not indicate a clear advantage in favor of any treatment arm. OS for patients prescribed with SO was improved compared with OS for BSC patients. Including all covariates, median adjusted OS was 9.9 vs. 6.6 months, respectively for patients treated with SO and BSC (HR = 0.652, 95% CI: 0.412, 1.030; P = 0.067). Sensitivity analysis showed a robust and significant reduction in risk of death for patients treated with SO, range of 29-42% (HR: 0.58-0.71). In all models, nephrectomy was independently associated with significantly improved OS. Other individual covariates were generally not statistically significant, likely due to a low number of observations.

**Conclusion:** An improved OS for mRCC patients was seen in patients receiving SO compared to BSC after first line treatment with SU. Some caution should be taken with interpreting the results as confounding due to unmeasured covariates may exist.

**Disclosure:** P. Sandström: Has had an advisory role for Pfizer, Roche, GSK, Novartis, and Bayer, has received honoraria from Pfizer, Roche, bayer, GSK and Novartis and has received research funding from Pfizer and Bayer. R. Sandin: Rickard Sandin is an employee of Pfizer AB and owns Pfizer stock. J. Kowalski: Jan Kowalski is consultant and received compensation from Pfizer for the statistical work for the abstract. T. Wahlgren: Thomas Wahlgren is an employee of Pfizer AB and owns Pfizer stock. M. Jakobson: Maria Jakobsson is an employee of Pfizer AB and owns Pfizer stock. S. Lundstam: Has had an advisory board role for GSK and Bayer, has received honoraria from Pfizer and GSK, and has received research funding from Pfizer. B. Ljungberg: Has had an advisory role for Pfizer, GSK, Novartis, Asellas and Bayer, and has received honoraria from Pfizer, Novartis, GSK, and Bayer and U. Harmenberg: Has had an advisory role for Pfizer, Roche, GSK, Novartis, and Bayer, has received honoraria from Pfizer, Roche, and Novartis and has received research funding from Pfizer, GSK, and Novartis.

**SUNITINIB RECHALLENGE IN METASTATIC RENAL CELL CARCINOMA PATIENTS**

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**Background:** Sunitinib is an active agent in the first line treatment of metastatic clear cell kidney cancer, based on the result of a global phase III study. However, complete remission is rarely seen and multiple sequential therapies are used in this patient population. Since options in third line setting are limited, we assessed the clinical activity of sunitinib rechallenge after failure on other therapies.

**Methods:** 323 kidney cancer patients were treated with sunitinib from November 2005 to January 2012 in our department. Retrospective data were collected for those 9 patients who we rechallenged with sunitinib failing to at least two previous therapies, including sunitinib. Patient characteristics, objective response based on RECIST criteria and progression-free survival (PFS) were analysed. Tumor assessment was performed every 2nd cycle of sunitinib or every 3 months.

**Results:** Data of 8 men and 1 woman of median age (at sunitinib challenge 59 years, at sunitinib rechallenge 63 years) with metastatic clear cell cancer of the kidney were analysed. All patients had nephrectomy prior treatment. Initial treatment with sunitinib was associated with a median progression free survival (PFS) of 13.7 months. Objective response was partial remissions (PR) as best response. At the time of re-exposure patients again showed clinical benefit which was associated with a median PFS of 6.8 months and consisted of 1 (11%) PR and 5 (55%) disease stabilizations. PD was seen in 3 (33%) patients.

**Conclusions:** In sunitinib-responsive patients, re-challenge with sunitinib has been successful and was well tolerated either after an other TKI or mTOR inhibitor and it seems to be a valid option as a third line treatment.

**Disclosure:** All authors have declared no conflicts of interest.

**GENETIC POLYMORPHISMS AND SUNITINIB TOXICITY IN METASTATIC RENAL-CELL CARCINOMA**

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**Background:** Sunitinib (SU) is a multi-targeted receptor tyrosine kinase inhibitor that is approved for the treatment of renal cell carcinoma (RCC). However, several patients either do not respond to treatment or they experience significant toxicity. Our study aims to find genetic markers of toxicity and efficacy using a commercially available DNA microarray genotyping system.

**Methods:** 30 patients with newly diagnosed metastatic RCC, from January 2010 to May 2011, were evaluated prospectively at Hospital 12 de Octubre (Madrid, Spain). Pts received SU in repeated 6-wk cycles of 50 mg/day (4 wks on followed by 2 wks off treatment). A total of 92 of single nucleotide polymorphisms (SNPs) in 34 genes in the pharmacokinetic and pharmacodynamic pathways of drugs were analyzed.

**Disclosure:** All authors have declared no conflicts of interest.

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SAFETY OF SUNITINIB AS FIRST-LINE THERAPY IN CHINESE PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (mRCC)

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Background: Based on the effectiveness and safety profile established in two single-arm phase II trials and a pivotal phase III trial versus interferon-alfa, sunitinib is approved worldwide for advanced RCC. Here we report a single-arm, open-label phase IV study to assess use of sunitinib as first-line therapy in Chinese patients with mRCC.

Methods: Treatment-naïve patients aged 18–80 yr with ECOG performance status 0/1 and histologically confirmed mRCC received oral sunitinib 50 mg/od on the approved 4-wk-on-2-wk-off schedule. Treatment continued until disease progression, unacceptable toxicity, or consent withdrawal. The primary endpoint was progression-free survival (PFS). Tumor measurements were performed at screening, regular intervals, suspected disease progression, to confirm response, and end of treatment/withdrawal. Safety was assessed regularly using NCI CTCAE version 3.0.

Results: 105 patients received treatment. Mean age was 54.6 yr, 75% were male, and mean BMI was 23.9 kg/m². The most common site of baseline metastases was the lungs (76%). Median (range) number of treatment cycles completed was 8 (0–27). All patients discontinued treatment; reasons included disease progression/relapse (63%) and treatment-related AEs (8%). In 105 treated patients, median PFS was 61.7 wk (54.2 mo; 95% CI: 53.1–69.7 wk) and median overall survival (OS) was 133.4 wk (30.7 mo; lower bound of 95% CI: 94.1 wk). In 103 evaluable patients, objective response rate (ORR) was 31.1% (95% CI: 22.3–40.9%). Most treatment-emergent AEs were grade 1/2 severity and the most common were hand-foot syndrome (64%), decreased white blood cell count (53%), fatigue (51%), decreased platelet count (51%), diarrhea (49%), and decreased appetite (43%). There were no occurrences of treatment-emergent congestive heart failure, left ventricular dysfunction, or cardiomyopathy.

Conclusions: With median PFS of 61.7 wk (14.2 mo) and OS of 133.4 wk (30.7 mo), sunitinib is comparable. The AE profile is acceptable and generally similar to that in other single-agent sunitinib studies and/or in patients with advanced RCC.

Disclosure: S. Oudard: Advisory board to disclose: Sanofi Aventis, Bayer, Novartis, Roche. Pfizer: Consultant relationship to disclose: Novartis, Roche. Honoraria to disclose: Sanofi Aventis, Bayer, Novartis, Roche. Pfizer: All other authors have declared no conflicts of interest.

PRELIMINARY RESULTS OF EARLY ASSESSMENT OF RESPONSE WITH PERFUSION-CT IN PATIENT WITH METASTATIC RENAL CELL CARCINOMA TREATED WITH SUNITINIB

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Introduction: The fact that renal cell carcinoma (RCC) is highly dependent of angiogenesis has allowed the development of antiangiogenic drugs (e.g. sunitinib). The assessment of response was based on Response Evaluation Criteria in Solid Tumors (RECIST) but in RCC there is no good correlation between response rate and survival data. So, it is necessary to adopt new image methods that allow a more accurate assessment of response.

Objectives: To evaluate the pattern of response with perfusion-CT one month after the beginning of the antiangiogenic treatment and correlate with the radiologic evolution.

Material and methods: Patients (pts) with metastatic RCC and candidates for sunitinib treatment were selected. A volumetric study (21 cm) with perfusion-CT (Flash Definition, Siemens, Erlangen, Germany) was done in these patients starting the treatment, 1 and 4 months after the antiangiogenic initiation. We defined 6 types of response patterns based on changes in density (D), perfusion (P) and size (S) of the metastases.
Patients and methods: Asian patients. Therefore, this study was undertaken to evaluate RECORD-1, the actual incidence of everolimus-associated NIP was unknown in advanced RCC patients who failed to show clinical benefit in wider population and routine use, as certain patient subtypes are under-represented, notably those with poorer prognostic factors and pretreated. The data were collected through national registry Onco-AIFA as per the mandatory reporting. Pitfalls of using the Cockcroft-Gault formula when calculating carboplatin dose for the adjuvant treatment of patients with stage I seminoma.

Disclosure: All authors have declared no conflicts of interest. Disclosure: All authors have declared no conflicts of interest.

RESULTS: From March 2011 to May 2012, 16 pts were included. The median age was 62 years (43-79), the majority of pts had clear cell carcinoma (n = 13, 81.25%) and good prognosis (n = 14, 87.5%) based on Motzer criteria. We present the results of 1-month evaluation: In 12 pts (75%) a decrease of D and P was observed. This pattern was correlated with a partial response in 8 pts (66.6%). Two pts (16.6%) had a stable disease and two more pts were lost before 4 months CT. This pattern was correlated with a partial response in 8 pts (66.6%). Two pts (16.6%) had a stable disease and two more pts were lost before 4 months CT. The case of S, associated with a decrease of P and D, was related to haemorrhagic necrosis and it should not be confused with disease progression. This pattern was found in only 2 pts (12.5%). In both cases, the changes in D and P preceded the changes in S. Stability of D, P and S was found in only one patient (6.25%) who had a papillary variant of MRC. An increase of D and P was related with disease progression in one patient (6.25%) and with stability in another case (6.25%).

Conclusion: The changes in D and P precede the changes in S, and could be predictive of response to antiangiogenic treatment. Long-term follow-up data and a larger series will be presented at the meeting.

Disclosure: All authors have declared no conflicts of interest.

Disclosure: All authors have declared no conflicts of interest.
Background: High-dose VIP chemotherapy (HD-VIP) plus ABST given as first line treatment might be a strategy in patients with advanced germ cell tumors (GCT) with poor prognosis. The objective of the trial was to investigate the addition of darbepoetin alfa to HD-VIP in order to reduce anemia/red blood cell (RBC) transfusions.

Methods: This was a randomized, open-label multicenter phase 2 study conducted in 20 hospitals. Darbepoetin 2.25 mcg/kg weekly or 500 mcg Q3W s.c., started with HD-VIP (dose level 6), was applied in arm B (arm A: HD-VIP alone). The primary objective was freedom from blood transfusions (FFT). Secondary objectives included objective remission rate (ORR) after chemotherapy, 24-mos PFS and OS, median course of hemoglobin (Hb) levels during 3 HD-VIP cycles as well as drug safety.

Results: 202 patients were included in the correlation analysis and 181 patients in the comparison of different subgroups, respectively. Lower BMI and higher age were significantly associated with lower ECD. Pearson correlation coefficients 0.59 (p < 0.001) and −0.36 (p < 0.001), respectively. Tables show potential under- and overdosing of C when using CG (ECD expressed as percentage of ACD) in different age groups (Exact test p = 0.001) and groups with different BMI (Exact test p = 0.026).

Discussion: CG significantly underestimates GFR in leaner and older patients. According to our data over a third of patients with BMI 20–25 or aged 41–50 would be at risk for undertreatment if CG were used routinely. Physicians need to be aware of these limitations when using CG to calculate C dose in patients with stage I seminoma.

Disclosure: All authors have declared no conflicts of interest.

Disclosure: All authors have declared no conflicts of interest.

Table 857P

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;90% ACD</th>
<th>90-110% ACD</th>
<th>&gt;110% ACD</th>
<th>BMI (kg/m²)</th>
<th>&lt;90% ACD</th>
<th>90-110% ACD</th>
<th>&gt;110% ACD</th>
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<tr>
<td>21-30 n = 29</td>
<td>14% 4</td>
<td>72% 21</td>
<td>14% 4</td>
<td>20-25 n = 60</td>
<td>35% 21</td>
<td>57% 34</td>
<td>8% 5</td>
</tr>
<tr>
<td>31-40 n = 84</td>
<td>14% 12</td>
<td>68% 57</td>
<td>18% 15</td>
<td>25-30 n = 81</td>
<td>21% 17</td>
<td>69% 56</td>
<td>10% 8</td>
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<tr>
<td>41-50 n = 68</td>
<td>40% 27</td>
<td>56% 38</td>
<td>4% 3</td>
<td>30-40 n = 33</td>
<td>15% 5</td>
<td>58% 19</td>
<td>27% 9</td>
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</table>

Conclusion: This review’s outcome broadly correspond with published data although with increased incidence of relapse following standard adjuvant chemotherapy- presumably an artifact of small numbers. Adjuvant treatment increases 5yr RFS compared to active surveillance but excellent CSS is achieved after either. The vast majority of radiotherapy (85%)was offered in the first two thirds of the study period and reflects older practice. The absence of risk factors appears to reduce the rate of relapse and should guide treatment decisions. The increasing awareness of the importance of assessing risk factors when deciding on treatment is reflected in their improved identification in later patients and the increasing use of a surveillance strategy in those at lower risk of relapse.

Disclosure: All authors have declared no conflicts of interest.

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Disclosure: All authors have declared no conflicts of interest.
Our results on selected relapsed pts suggest that EC samples retained 95% (CI) of 1.93 (0.85–4.37) target for treatment. This may be representative of a significantly larger patient series. A trend towards a poorer prognosis and shorter survival characterized CD30+ cases.

Disclosure: All authors have declared no conflicts of interest.

INTRODUCTION: Despite cisplatin-etoposide based induction chemotherapy, 20-30% of germ cell tumor (GCT) patients will require salvage treatment. Cisplatin-ifosfamide based salvage regimen produces durable remission at the cost of severe toxicity. In this study, we report our experience with first salvage chemotherapy.

MATERIAL AND METHODS: Medical records of patients receiving first salvage chemotherapy with vinblastine 0.11mg/kg iv d1-d2, ifosfamide 1200mg/m2 iv d1-d5 and cisplatin 20mg/m2 iv d1-d5 (VeIP) for GCT were reviewed. Those who continued to respond were given more than 4 cycles of chemotherapy. Overall response rate (ORR) was assessed by CT and/or MRI scans using WHO response criteria at the completion of chemotherapy.

RESULTS: From April 2006 to April 2011, 350 patients of GCT were treated at Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore (Pakistan). Out of those 350 patients, 34 were treated with VeIP chemotherapy as first salvage for primary progressive (n = 2) or relapsed (n= 32) GCT (non-seminoma = 30; seminoma = 2). Thirty-five patients were male and only 1 was female. Median age at the time of diagnosis was 26 years (range from 17 to 58) and most (54.3%) had poor prognostic features according to IGCCCG. Median time of relapse after primary induction chemotherapy was 8067 months (95% CI 6.49 to 9.642). Median of 4 cycles salvage VeIP were administered (range 1-6 cycles). One patient died during salvage chemotherapy due to sepsis. Response assessment was possible in 29 patients. ORR was 31.4% (CR = 6.7% and PR = 25%), SD in 26.7% and PD in 36.7% patients. Surgical resection of residual mass was not possible in any of our patients. Three patients were further treated with radiation therapy. Twenty patients continued follow up (median 1.93 years; from 0.51 to 4.9) after completion of VeIP. At the time of analysis, 6 patients died and 21 were alive. Median PFS after VeIP was 6033 months (36.68 to 8.459) while median OS had not yet reached.

CONCLUSIONS: VeIP showed radiologic shrinkage of tumor in one-third of our patients and resulted in reasonably long survival of our high risk relapsed patients. Our results were comparable with International data.

Disclosure: All authors have declared no conflicts of interest.

PERSISTANCE OF CD30 EXPRESSION IN EMBRYONAL CARCINOMA (EC) CELLS: A RETROSPECTIVE STUDY IN MULTI-RELAPSED OR CHEMOTHERAPY (CT) REFRACTORY GERM CELL TUMOR (GCT)


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INTRODUCTION: Germ-cell tumors (GCTs) are highly curable with cisplatin-based chemotherapy. The BEMP chemotherapy (Indianapolis) has become a standard in the management of GCT. The aim of this study was to evaluate the long-term side effects of a modified BEMP regimen, with of bleomycin as a continuous infusion.

Patients and methods: The military hospital of Val de Grace has developed a modified BEMP regimen with the aim of reducing bleomycin-induced toxicity in patients with GCTs: bleomycin 15mg/dl-5 as an IV continuous injection, etoposide 100mg/m2 (dl-5) and cisplatin 10mg/m2 (dl-5), repeated every 3 weeks. Survivors were asked in 2011 to participate in this study on late toxicity, including assessment of laboratory tests, pulmonary function tests (PFT) and a semen analysis.

RESULTS: Between March 1998 and January 2009, 68 patients with GCTs received first line chemotherapy with this modified BEMP. Distribution of patients was as follows: Good prognosis (GP): 42, Intermediate and Poor-prognosis (IPPs): 26, stage I with High risk factors (HP): 6. The median follow-up was 75 months. The 2-years overall survival was 90%. The relapse rate was 13%. The main immediate adverse events reported grade III-IV were neutropenia (25%), anemia (1%), thrombocytopenia (1%), digestive (6%), infection (4%), decreased DLCO (4%) and trombembolic events (3%). Thirty four patients were assessable for the late toxicity of this regimen (18 patients in GP, 14 patients in IPP and 2 patients in HP). The 5-years overall survival was 82%. The analysis of late adverse effects revealed one patient developed a haematologic malignancy (myleodysplasia). Abnormal PFT was observed in 4 patients, and only 1 patient was clinically symptomatic. In post-treatment analysis, we evaluated the fertility of 30 patients. The fertility was preserved in 22 patients (73%). Twenty patients have realized a semen analysis after the chemotherapy, and azoospermia was observed in only 3 pts (15%). Among 10 patients remaining, 5 patients had children after the treatment.

Conclusion: Using bleomycin as a continuous infusion is feasible and seems to produce similar results in terms of response rates and overall survival compared to the classic BEMP chemotherapy regimen, with a total dose less important than standard. These results will be compared with those of conventional BEP.

Disclosure: All authors have declared no conflicts of interest.

MULTICYCLE HIGH-DOSE CHEMOTHERAPY WITH TI-CE REGIMEN FOR PATIENTS WITH RELAPSED/REFRACTORY GERM CELL TUMORS – A SINGLE INSTITUTION EXPERIENCE

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BACKGROUND: A large international phase III randomized trial (TIGER study) has been recently planned to compare the TI-CE multi-cycle high-dose chemotherapy (HDCT) with standard chemotherapy as salvage treatment for patients with relapsed germ cell tumors (GCT), but to date there are no reported experiences with this regimen other than the phase 2 study from MSKCC (Feldman et al – JCO 2010). We present preliminary results of our experience with TI-CE in relapsed/refractory GCT patients.

METHODS: From August 2009 to April 2012, patients with relapsed/refractory GCT received TI-CE comprising a mobilizing phase with paclitaxel and ifosfamide (TI) with leukapheresis of peripheral blood progenitor cells (PBPCs), followed by 3 HDCT courses with CE (carboplatin AUC 21 and etoposide 1200 mg/m2), with PBPC reinfusion. Biochemical filament (Zarzio) was used in the HDCT phase for all patients after PBPC reinfusion.

RESULTS: 26 patients (25 males, median age 34) started on TI, but 3 of them did not receive CE: two had rapidly progressive symptomatic brain metastases, the third one...
refused HDCT. Of 23 patients, 20 completed the TI-CE regimen and are evaluable, while 3 are still receiving treatment. There were no treatment-related deaths. The median number of days from the start of CE until recovery of neutrophils to 1,000/mm3 was 14. Twelve (60%) of the 20 evaluable patients achieved a complete remission (CR) (5 clinical CR, 5 pathological CR, 2 surgical CR), 5 had marker-negative partial remissions lasting 2, 2+, 6+ and 21+ months, and 3 progressed. After a median follow-up of 13 months (range, 2 to 33+), 15 (75%) evaluable patients are continuously progression-free. Of 4 mediastinal primary nonsemionomatous GCT, 2 achieved a CR (1 iCR and 1 pCR) lasting 7 and 12+ months, respectively.

Conclusions: Our experience confirms that the TI-CE regimen is safe and active, with a reasonable disease-free survival time of neutrophils after CE similar to that reported in the MSKCC study. Updated results will be presented at the meeting.

Disclosure: All authors have declared no conflicts of interest.

TERATOMA WITH MALIGNANT TRANSFORMATION (TMT) IN MEN WITH GERM CELL TUMORS (GCTs): RETROSPECTIVE STUDY OF 26 CASES FROM A SINGLE INSTITUTION

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Background: GCT is the most common solid tumor in young men. TMT is a rare entity. It occurs in less than 2% of GCTs and is associated with poor prognosis.

Methods: Between Jan 1993 and Jan 2012, we identified retrospectively all pts with GCTs with TMT treated at our institution and report here their characteristics, treatment and clinical outcome.

Results: Twenty six patients (pts) with TMT were identified. Median age at initial diagnosis was 26 years (19–48). At initial diagnosis 20 pts had a gonadal primary (4 stage (sg) I, 8 sg II and 8 sg III) and 6 a mediastinal primary tumour (PMT). Six pts were classified as good prognosis, 5 as intermediate, 11 as poor according to the IGCCCG and 4 unknown. A teratoma component was described in the primary tumour of 22 out of the 25 pts with non seminomatous GCT. Only one pt had a pure seminoma (PMT). Four pts had TMT in their primary, 9 in resected post-chemotherapy, residual masses and 13 in a relapse. For these 13 pts, median time between initial GCT diagnosis and relapse as a TMT was 31.2 months (mo) (12.0–357.6). Various subtypes of TMT were observed: 10 adenocarcinomas, 4 neuroectodermal tumors, 6 rhabdomyosarcomas, 2 leiomyosarcomas, 1 blasterma, 1 angiogroma and 2 undefined sarcomas. Except 3 pts with sg I disease, all pts received first line cisplatin-based chemotherapy (CT). Surgery of residual masses was performed in 20 pts. Nineteen out of the 23 pts had initial clinical or surgical complete response (CR), 2 had a marker positive partial response and 2 had progressive disease. Iterative surgery for relapse was performed in 9 pts. Eight pts received CT according to TMT subtype and one achieved CR. With a median follow-up of 76.8 mo (9.5–369.0), 8 pts have died of disease (DOD), 1 has died of another cause, 2 are alive with disease and 15 alive without disease. Among the 8 pts DOD: 3 pts had PMT, 3 were sg III and 2 sg I; all relapsed and surgery was incomplete for 4 pts and 1 was inoperable. There was no difference between subtypes of TMT.

Conclusions: TMT is more frequent in GCTs with extensive disease, PMT and relapsed disease. Iterative and complete surgical resection is the mainstay of treatment. CT is usually palliative but sometimes gives long responses. CT is usually palliative but sometimes gives long responses. CT is usually palliative but sometimes gives long responses. CT is usually palliative but sometimes gives long responses.

Disclosure: All authors have declared no conflicts of interest.

A CYTOKINE AND ANGIOGENIC FACTOR (CAF) ANALYSIS IN PLASMA IN TESTICULAR GERM CELL TUMOR PATIENTS

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Background: Testicular germ-cell tumours (TGCTs) represent a model for the cure of cancer. Nonetheless, a small proportion of patients develop disease recurrence. We investigated cytokines and angiogenic factors (CAFs) in patients with TGCTs. We aimed to link the CAF profile to PFS and select candidate predictive and prognostic markers for further study.

Methods: In this ongoing translational study, plasma from 55 patients with TGCTs was collected. The concentrations of 51 plasma CAFs were measured pre-treatment (n = 47) and on day 22 (n = 30) using multiplex bead arrays (Human Group I and II cytokine panels and TGF beta by Bio-Plex 200 system (Bio-Rad Laboratories, Hercules, CA). We investigated the association between baseline levels of CAFs and clinico-pathological variables.

Results: We observed elevated level of transforming growths factor betai (TGF-b1), IL-2Ra, CXCL9, CXCL10, IFN-gama, macrophage inflammatory protein-1b (MIP-1b), and platelet-derived growth factor-BB (PDGF-BB) in seminoma patients compared to non-seminoma. Patients with poor prognosis according to IGCCCG had elevated pretreatment level of beta-nerva growth factor (NGF-b) and stromal cell-derived factor-1 (SDF-1a) compared to patients with good/intermediate prognosis. Patients with metastatic disease had elevated pretreatment level of stem cell growth factor beta (SCGF-b) and PDGF-BB compared to patients with stage I disease.

Conclusions: Using CAF profiling, we revealed differences in subgroups of TGCTs patients. We suggest that this platform may provide valuable insights into TGCTs biology, and could be useful in identification of new therapeutic targets.

Disclosure: All authors have declared no conflicts of interest.

EXPERIENCE WITH SINGLE AGENT ADJUVANT CARBOPlatin FOR STAGE I SEMINOMA — A RETROSPECTIVE ANALYSIS

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The cure rate for stage I seminoma is above 99%, and current adjuvant strategies aim to maintain this favorable result with less therapy related toxicity. Adjuvant therapeutic options include irradiation of the para-aortic lymph nodes, single agent carboplatin and surveillance. There is an increased risk of relapse in case of tumor size > 4 cm and rete testis infiltration, so as a risk adapted strategy, to patient with these risk factors, adjuvant therapy can be advised. We retrospectively analyzed the data of our patients, who received adjuvant carboplatin for stage I seminoma in order to assess the safety and efficacy of this treatment. From November 2006 till the end of 2011, 275 patients were treated or intended to treat with two courses of adjuvant carboplatin in the dose of area under the curve 7 after orchietomy. One hundred and thirty two patients (48%) had tumors > 4 cm, 131 patients (47.6 %) had ≤ 4 cm, and we had no data of 12 patients (4.4%). The tumor invaded the rete testis in 103 patients (37.4 %), the rete testis was tumor-free in 70 patients (25.4 %) and data was not available in 102 patients (37.2%). We had data for both risk factors in 166 patients (60%). Fifty one patients (30.7%) had two risk factors, 72 of them (43.3%) had one, and 43 patients (26%) had no risk factors. Ten patients received...
only one course of carboplatin. We experienced grade 3 side effects in 4 patients (vomiting, low platelets, neutropenia, deep vein thrombosis). No toxicity of higher grade developed. Seven patients relapsed. All relapses occurred in the retropelvic lymph nodes. In two patients, the retropelvic lymph node metastases were discovered after the first cycle of carboplatin, so these cases are not considered real relapses, but rather the mistake of the initial staging. To conclude, single agent carboplatin proved to be a safe and effective treatment. The risk adapted strategy is not consistent with our everyday practice. We aim to improve the quality of the initial staging to avoid false stage I assessments. We also have to promote the more accurate pathologic examination of the specimens to be able to correctly inform the patients on the risk of relapse and thus enable them to make a fully informed decision on their adjuvant treatment.

Disclosure: All authors have declared no conflicts of interest.

| PROGNOSTIC SIGNIFICANCE OF EPIDERMAL GROWTH FACTOR RECEPTOR OVEREXPRESSION AND CHROMOSOME 7 POLYSOMY IN CLEAR CELL RENAL CELL CARCINOMA |

Background: Clear cell renal cell carcinoma (ccRCC) is the most common histological subtype of renal cell carcinoma. In patients with ccRCC several prognostic markers have been suggested, including epidermal growth factor receptor (EGFR) expression and chromosome 7 polysomy (C7p). Cancer cells addicted to EGFR bear activated mutations in the EGFR gene, and these mutations are useful in predicting susceptibility of ccRCC to EGFR inhibitors. The aim of this study was to evaluate the prognostic value of EGFR overexpression and C7p.

Patients and methods: Archival specimens, coupled with clinical and survival data of 34 patients (20 men, 14 women, median age 58, range 42–79 years) who had undergone radical nephrectomy for ccRCC were analyzed. Immunohistochemistry and fluorescence in situ hybridization (FISH) specimens were sections of formalin-fixed paraffin-embedded tissue. EGFR expression was detected as membranous and cytoplasmic staining of neoplastic cells > 1%, and a ratio between gene/centromeric signals of more than two was considered to indicate gene amplification. Mean number of centromeric signals per nucleus was also scored to evaluate C7p.

Results: The age did not differ significantly (p = 0.79) between men and women. Overall, the median survival was 46 months (range 5–150 months). C7p was confirmed. The relationship with gender (R = 0.87, p < 0.01) was confirmed. The relationship with gender (R = 0.41, p = 0.21), while the relationship with gender (R = 0.87, p < 0.01) was not confirmed. In our single-center study, women with ccRCC had an overall better survival than men. EGFR was not a useful predictor of outcome, while C7p may have a prognostic significance.

Disclosure: All authors have declared no conflicts of interest.

| ANGIogenic AND SIGNALLING PROTEINS CORRELATE RESISTANCE AND SEQUENCE OF TREATMENT IN RENAL CELL CANCER |

Background: The multi-tyrosine kinases inhibitors and the mammalian target of rapamycin (mTOR) inhibitors have dramatically changed the management of metastatic renal cell carcinoma (RCC). However, a relevant issue in RCC treatment is still the lack of a biological and molecular rationale able to establish the most effective sequence of the different therapeutic options available.

Methods: To address this issue, we systematically assessed the effect of different agents, alone or in sequence, on the growth, expression and secretion of key angiogenic and signalling proteins involved in tumor growth and resistance to treatment, in a panel of human RCC cell lines with different VHL status and in tumors xenografted in nude mice.

Results: We demonstrated that sunitinib, sorafenib and everolimus are equally active as single agents in inhibiting cell proliferation, signal transduction and VEGF secretion, both in vitro and in tumors grown in mice. Pre-treatment of tumor cells with sunitinib reduced the response to subsequent sunitinib and sorafenib but not to everolimus. Lack by sunitinib of a persistent inhibition of key proteins including HIF-1, VEGF and MAPK anticipates onset of resistance in xenografted tumors. After first line sunitinib, second line everolimus was more effective than sorafenib or sunitinib rechallenge to interfere with critical signalling proteins and VEGF and Interleukin-8 secretion, translating into an advantage in the long-lasting inhibition of tumor growth and significant prolongation of mice survival.

Conclusions: Our study demonstrates that angiogenic and signalling proteins predict treatment failure with sunitinib and that the use of mTOR inhibitor everolimus in second line is substantiated by a persistent control of proteins responsible for RCC growth and resistance to treatment.

Disclosure: All authors have declared no conflicts of interest.

| COMPLIANCE WITH SUNITINIB TREATMENT IN PATIENTS WITH RENAL CELL CANCER |

Introduction: Sunitinib (SUN) is one of the standard treatment options for metastatic renal cell cancer (mRCC). There are several possible reasons for non-compliance to the prescribed doses: oral intake of the drug, side effects and the existence of multiple dosage forms. Prescribers are not always aware of this non-compliance.

Methods: In Belgium SUN can only be delivered by the hospital pharmacy. This allows calculation of the used versus the prescribed dose. Based on these data, the minimum number of non-compliant weeks per patient was calculated.

Results: 34 incident patients were considered, treated in the Ghent University Hospital between 2007–2012. The total number of treatment weeks for this patient group was 1079 (ranging between 1 and 108 weeks). A total of 850 weeks were suitable for analysis. 14 out of these 34 patients (41.2%) had at least one week in their treatment period of non-compliance (insufficient number of pills), with the percentage of time of treatment non-compliance in these individual patients ranging from 2–40 % of the total treatment time, the average being 19 % of the weeks. The group with one or more weeks of non-compliance were the patients with the longest SUN intake: 47.2 versus 20.8 months of intake. On the other hand 5/34 patients (14.7%) received considerably more pills from the pharmacy than their treatment regimen warranted.

Conclusions: In our single-center database of patients treated by SUN for mRCC, we demonstrated that over 40% of the patients were possibly non-compliant with their prescribed SUN dose. This occurred more frequently in long-term treatment. Given the average non-compliance time in this subgroup (19% of the weeks) we can conclude that this might significantly influence overall survival and response to treatment. We thus advocate a tighter control of drug prescription and delivery, which could result in detection of non-compliance more rapidly.

Disclosure: S. Rottey: Advisory board Pfizer, Novartis, Bayer, GSK Research grant Pfizer, Bayer. All other authors have declared no conflicts of interest.

| COMPARATIVE EFFICACY OF SUNITINIB VERSUS SORAFENIB AS THE FIRST-LINE TREATMENT FOR PATIENTS WITH METASTATIC RENAL CELL CARCINOMA |

Background: Sunitinib has been recommended as the primary treatment in the patients with metastatic renal cell carcinoma (mRCC) among the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin kinase inhibitor (VEGFR TKI). However, there are no published clinical data that compared directly the efficacy of targeted agents in the first line setting. This study investigated the efficacy and toxicity of sorafenib and sunitinib as primary treatment for patients with mRCC.

Methods: To compare the efficacy and toxicities between sorafenib and sunitinib, clinical database was used to identify all patients with mRCC treated with VEGF TKIs in Asan Medical Center from April 2005 to March 2011. Among 304 patients,
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The patients in the sorafenib group were older than those in the sunitinib
Results: respectfully.

Sorafenib showed comparable efficacy to sunitinib and demonstrated
sorafenib vs. sunitinib = 0.94, p = 0.774)
Multivariate analysis showed that first-line VEGF TKI did not affect OS (hazard ratio
bone and liver metastases were independent prognostic factors affecting OS.
Multivariat analysis showed that first-line VEGF TKI did not affect OS (hazard ratio

Conclusion: Sorafenib showed comparable efficacy to sunitinib and demonstrated
fewer and less severe toxicities in the treatment of mRCC patients.
Disclosure: All authors have declared no conflicts of interest.

COULD THE SAFETY PROFILE OF EVEROLIMUS BE DIFFERENT IN DIFFERENT CANCERS? FONDAZIONE IRCCS ISTITUTO NAZIONALE TUMORI (INT) EXPERIENCE IN RECURRENT CELL CARCINOMA, NEUROENDOCRINE TUMORS (NETS) AND BILIARY-TRACT CANCERS
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Background: Everolimus is an inhibitor of the mammalian target of rapamycin
(mTOR), a kinase which plays a key role in cellular processes. The toxicity profile
of antiangiogenic therapies lacks disease specificity; while few data on everolimus are
available.
Methods: We retrospectively analyzed data about safety profile of everolimus in patients
(pts) with different cancer treated in our Institution: 21 pts with metastatic renal cell cancer (mRCC), 20 pts with biliary tract cancer, 12 pts with pancreatic neuroendocrine tumors (NETs).
All pts were pre-treated with 1 standard treatment (Tirsoxine Kinase Inhibitors/chemotherapy/somatostatine analogs +/- chemotherapy, respectively) at least and received everolimus at 10 mg od continuously.

Results: mRCC pts: median age 64 years (53-78), median treatment exposure 6.8 months (3-20); previous treatments (1/2/3/28)% (47%/23%) respectively AEs: mucositis (68%, 1 pt G3), hypertriglyceridemia (56%; 20 G3), hypercholesterolemia (43%, 1 pt G3), rash (31% 1 pt G3), pneumonia (10% all G1), no haematological AEs;
Biliary tract cancer pts: median age 61 years (48-74), median treatment exposure 4.6 months (2-10), previous treatments (1/2/85%) (15% respectively) AEs: thrombocytopenia (60%, 3 pts G3), fatigue (39%, 2 pts G3), mucositis (25% no G2), 20% rash (no G3) NETs pts: median age 57 (38-76), median treatment exposure 8.1 months (3-12); previous treatments (1/2/45%) (55% respectively) AEs: fatigue (2 pts G3), neutropenia 35% (1 pt G3), mucositis 25% (2 no G3), 12% rash (no G3), thrombocytopenia 15% (no G3), hypercholesterolemia 12% (no G3), hyperglycemia 8% (no G3) Dose reductions from 10 mg to 5 mg; 26% in mRCC, 27% in biliary cancers, 25% in NETs Drug interruptions(< 3 day): 8% in RCC, 5% in biliary, 7% in NETs Drug withdrawn due to AE: nobody.

Conclusions: Everolimus is safe and well tolerated. AEs seem to be maintained
across the different baseline disease. However the differences in the frequencies of the same AEs observed suggest a potential impact of previous treatment on Everolimus tolerability. May be interesting to study the inter-individual and the oncotype variability of everolimus in terms of different activities of the drug efflux pump P-glycoprotein. Moreover the metabolism of cytochrome P450 and the polymorphism in his gene could be further investigated.
Disclosure: All authors have declared no conflicts of interest.

EVEROLIMUS IN THE SEQUENCE AFTER FAILURE OF VEGFR-DIRECTED THERAPY IN MRCC - A RETROSPECTIVE ANALYSIS
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In a retrospective NIS, 81 patients receiving everolimus after failure of VEGFR
directed therapy have been analyzed in regard to response, duration of treatment and
subsequent therapies. In total, the data of 81 patients (57 m, 24 f) with 93 ccRCC and
6% nRCC (1% undefined) have been analyzed. The median age was 58 years
(23-78 y). 36% had synchronous and 63% metachronous metastases. According to
the MSKCC score at initial diagnosis, 24% have been “favorable”, 26% “intermediate”, 7% “poor prognosis” and in 43% there was no initial prognostic score defined by the treating physicians. The major locations of metastases have been lung
(56.8%), lymph nodes (34.6%), skeleton system (17.3%), 36% of the patients had
A REVIEW OF RADIOLOGICAL ASSESSMENT RESPONSE IN METASTATIC RENAL CELL CARCINOMA TREATED WITH ANTIANGIOGENIC THERAPY- ARE WE HITTING THE TARGET?

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Background: Targeted therapy has changed the treatment landscape of metastatic renal cell carcinoma (RCC) in the last years. However, despite the positive results with antiangiogenic drugs in the treatment of metastatic RCC, the evaluation of response to these therapies remains undefined. This study aimed to review different proposed radiologic methods used for response evaluation with antiangiogenic agents in RCC.

Methods: A no systematic literature review using electronic databases PubMed/MEDLINE, EMBASE, Cochrane Library and LILACS with the terms “renal cell carcinoma”, “response criteria” and “targeted therapy” and its variables.

Results: A total of 53 articles were identified, of which 12 were selected and 41 excluded. After evaluation of the references of the 12 selected studies, two new studies were included. The 14 studies were published from August 2009 to October 2011, 11 of them using computed tomography as a method of response evaluation, one with doppler ultrasound and two others with positron emission tomography. A total of 927 patients were studied. The drugs used for analysis in the different studies were sunitinib, sorafenib, bevacizumab, and interferon alfa, but sunitinib and sorafenib are variably present in all studies. The retrospective design was the basis for the end points analyzed and the best evaluated method comparison was time to disease progression (TTP) or progression-free survival (PFS). All studies had RECISt as the assessment parameters (control). Proposed new methods of radiographic response criteria in this context were present in 11 studies (78%). In 3 studies (21%) only one radiologist reviewed the images, in the other at least 2 radiologists participated in the evaluation. Most studies evaluated a small number of patients and 8 studies (57%) included more than one antiangiogenic drugs in its analysis.

Conclusion: Antiangiogenic drugs are considered standard therapy in the treatment of metastatic RCC. Phase III trials are needed to validate the best radiological response criteria in this context, new proposed methods should be incorporated as secondary end-points in future prospective trials.

Disclosure: All authors have declared no conflicts of interest.
Background: On the basis of a few published data, sunniitib and soranefib can be administered safely to patients (pts) with metastatic renal cell carcinoma (mRCC) and end-stage renal disease on haemodialysis (HD). Aim of this study was to investigate the safety and efficacy of temsirolimus and everolimus in pts with mRCC on HD.

Patients and methods: Between September 2007 and February 2012, 13 pts with mRCC undergoing HD were treated with temsirolimus and everolimus in 6 Italian Institutions. We retrospectively reviewed the medical records of these pts to evaluate the doses of mTOR inhibitors administered, the tolerability and the activity of the treatment.

Results: Gender: 9 males/4 females; median age: 63 years (range 47–79). All pts were undergoing HD, in 7 cases for bilateral nephrectomy; the time interval between the start of HD and the start of mTOR inhibitors treatment was 37 months. Everolimus was administered in 12/13 pts daily in 5 pts and 2 pts received temsirolimus at 25 mg weekly. Everolimus was administered as second-line treatment in 4 pts, as third and fourth-line in two pts; temsirolimus was given as first-line treatment to 4 pts, as second-line to one patient and as third-line to 2 pts. No unexpected adverse events (AE) (AIE) and no grade 4 haematological or non-haematological toxicity were reported. The most common grade 1–2 non-haematological treatment-related AEs were fatigue (9/13 pts), dyslipidemia (4/13 pts), oral mucositis in 2/13 pts. A grade 3 dyspea due to interstitial pneumonia led to treatment discontinuation. The most frequent grade 1–2 haematologic toxicity was anemia (10/13 pts). None of the patients had to change the number of dialysis sessions during mTOR inhibitors treatment. None of the pts experienced an objective response while a disease stabilization was observed in 7 pts. At the time of the analysis, 7 pts had died, 5 pts were disease progression. The estimated median progression-free survival (PFS) of this cohort of pts was 6.1 months.

Conclusions: In this small retrospective series of pts the incidence of AEs was as expected, and a prolonged PFS was observed. The use of temsirolimus and everolimus is not contraindicated in pts with mRCC and severe renal impairment on HD.

Disclosure: All authors have declared no conflicts of interest.
Aims: A retrospective analysis to evaluate the toxicity profile, protocol completion rate, tumor response rate, and disease free interval in patients undergoing chemoradiotherapy with muscle-invasive bladder cancer.

Materials and methods: Following transurethral resection of the tumor in patients with Stage T2-T4a bladder cancer, induction chemotherapy with paclitaxel and cisplatin / gemcitabine and cisplatin was administered for two–three cycles. Thereafter radiotherapy with low dose chemotherapy was administered with weekly review. Adjuvant chemotherapy based on the neoadjuvant protocol was given to all patients.

Results: Between May 2005 to April 2008 total of 109 patients database were available for review. Paclitaxel and cisplatin chemotherapy resulted in mildly grater grade 3-4 acute toxicity, mainly gastrointestinal (25%) as compared with gemcitabine and cisplatin 17%. Four cycles of adjuvant chemotherapy were completed per protocol or with minor deviations in 45% of the patients in both the arms together. Late bladder radiation toxicity was evaluated in 47 patients with >/= 2 years of follow-up. Of these 47 patients, 3 experienced self-limited, late grade 3 bladder toxicity. The post induction complete response rate was 81% and 76% in the Paclitaxel and cisplatin group and gemcitabine and cisplatin group respectively. At a median follow-up of 39.4 months, the disease free survival was 69% and 71%, respectively.

Conclusions: These favorable tumor response rates with possible increased bladder preservation rates suggest that this treatment regimen deserves further study.

Disclosure: All authors have declared no conflicts of interest.

Table: 884

<table>
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<th>PIN</th>
<th>Adenocarcinoma</th>
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<td>68 yrs 71 yrs (37-85)</td>
<td>66 yrs 66 yrs (51-82)</td>
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<td>Bladder cancer: - stage I-II - stage III IV</td>
<td>12 pts (27%) 32 pts (73%)</td>
<td>9 pts (38%) 15 pts (63%)</td>
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<td>Perioperative treatment for bladder cancer</td>
<td>5 / 35 pts (4 pts unknown)</td>
<td>9/19 pts (5 pts unknown)</td>
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<tr>
<td>Perineural and/or lymphovascular invasion</td>
<td>17/43 pts (1 unknown)</td>
<td>8/24 pts</td>
</tr>
<tr>
<td>Positive margins after cystectomy</td>
<td>3 pts</td>
<td>5 pts</td>
</tr>
<tr>
<td>3 yrs overall survival (CI 95%)</td>
<td>41.6% (24.8-58.4%)</td>
<td>77.2% (57.3-97.0%)</td>
</tr>
<tr>
<td>5 yrs overall survival (CI 95%)</td>
<td>41.6% (24.8-58.4%)</td>
<td>57.9% (21.9-93.8%)</td>
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</table>
All authors have declared no conflicts of interest.

Early diagnosis and to provide a proper systemic treatment up-front. NSE serum levels may help to achieve an early diagnosis and to provide a proper systemic treatment up-front.

Despite its chemosensitivity, SCCUT showed an aggressive clinical course and poor prognosis in our series. Bladder origin SCCUT may have a better prognosis than those from prostate origin. NSE serum levels may help to achieve an early diagnosis and to provide a proper systemic treatment up-front.

Results: Retrospective analysis of 14 pts with a median follow-up of 40 months (m). Median age at diagnosis was 30 (18-43) years. Pathologic evaluation of the testis tumor revealed mixed NSTGCT with teratomatous elements in 11/14, and pure teratoma in 1. Embryonal carcinoma was presented in 12/14. Royal Marsden staging classification was: IAA: 2; IIB: 7; IIC: 2; IIIR: 1; IYB: 1; IVC: 1. All pts received a median of 4 cycles of BEP and had a complete serum marker response after induction CHT. RP masses showed a partial response in 8 and stable disease in 6 pts. Median size of the post-CHT retroperitoneum masses was 2.5 cm (1-10). Histologic examination showed fibrosis or necrosis in 4 (28%) and mature teratoma in 10 (64%) pts. Toxicity: Median days of hospitalization were 4 (2-9). 5 pts showed decrease of at least 2 points in hemoglobin, not requiring transfusion support. Chylous ascites was reported in 1 and an infected pelvic hematoma in another 1 pts. 2 pts developed ejaculatory dysfunction. Only 1 patient experienced an early relapse (3 m after RPLND) requiring salvage laparotomy. Pathology of the RP mass in this case reported a growing teratoma. All pts are alive and presently free of disease.

Conclusion: In our series, in a Hospital with long expertise in RF surgery, laparoscopic RPLND provided a low rate of complications and RF relapses, reducing morbidity compared to historical series with open procedures.

Disclosure: All authors have declared no conflicts of interest.
Pathway has been proposed to play a major role in ACC, we aim to test the clinical
other tyrosin kinases, the fibroblast growth factor receptor (FGFR). Since this
Background:
Madrid, SPAIN,3Medical Oncology Department, Instituto Clara Campal, Madrid, SPAIN,2Madrid, Hospital Madrid Norte San Chinarro Centro Integral Research, National Cancer Institute, Bratislava, SLOVAK REPUBLIC, 2Clinical Research, National Cancer Institute, Bratislava, SLOVAK REPUBLIC, 2Medical Oncology, St. Elisabeth Cancer Institute, Bratislava, SLOVAK REPUBLIC
Our preliminary data suggests that, Everolimus is safe and well tolerated
grade 3, and dose reduction was needed. One patient progressed early, while three
Results:
GCTs have been eligible. E has been administered at a dose of
one platinum regimen in case of platinum-refractory disease or primary mediastinal
chemotherapy or surgery and who failed at least two platinum-based regimens or
serological proof of relapsed GCTs, who were not amenable to be cured by
Everolimus (E) in pts with refractory GCTs. The primary objective is to determine
arm, two-staged phase II study aimed to evaluate the efficacy and toxicity of
In December 2011, National Cancer Institute of Slovakia launched a one
GCTs suggests that these pts would have greater benefit from mTOR inhibition.
Methods: In December 2011, National Cancer Institute of Slovakia launched a one arm, two-staged phase II study aimed to evaluate the efficacy and toxicity of Everolimus (E) in pts with refractory GCTs. The primary objective is to determine the efficacy of E in pts with refractory GCTs. The pts with radiological and/or serological proof of relapsed GCTs, who were not amenable to be cured by chemotherapy or surgery and who failed at least two platinum-based regimens or one platinum regimen in case of platinum-refractory disease or primary mediastinal non-seminomatous GCTs have been eligible. E has been administered at a dose of 10mg daily until progression or unacceptable toxicity.
Results: From December 2011, 4 patients have been enrolled. Median age of patients is 28 years. All patients were pretreated with at least 3 cisplatin-based therapy, three patients were absolute cisplatin refractory, progressed directly on cisplatin-based therapy. We observed no unexpected toxicity. One patient experienced pneumonitis grade 3, and dose reduction was needed. One patient progressed early, while three patients are still on treatment for 1 +, 3+ and 5+ months.
Conclusion: Our preliminary data suggests that, Everolimus is safe and well tolerated drug in patients with GCT. Efficacy data is warranted.
Disclosure: All authors have declared no conflicts of interest.

Phase II study of dovitinib in first line metastatic or (non resectable primary) adrenocortical carcinoma (ACC). SOGUG study 2011-03
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Background: Dovitinib is a novel targeted therapy, that has proven to inhibit, among other tyrosin kinases, the fibroblast growth factor receptor (FGFR). Since this pathway has been proposed to play a major role in ACC, we aim to test the clinical efficacy of dovitinib in this tumor.
Methods: An open label phase II trial has been designed in patients with advanced non-resectable ACC. The objective will be to obtain at least a 15% response rate according to RECIST criteria. Taking as a basis the two-stage Gehan model, 15 patients would need to be included in the first stage to demonstrate a treatment efficacy of at least 15%. Sample size calculation was done based on the following parameters, probability of Type I error α = 0.05, power of the test (1 - β) = 0.8. Main inclusion criteria are advanced non-resectable disease and no prior therapy (other than mitotane). Since this is an extremely unfrequent disease 7 institutions, members of the SOGUG (Spanish Oncology Genitourinary Group), will participate. The active support of a big collaborative group will guarantee candidate patients to be referred to such institutions. So far 6 patients have already been included. Starting January 26th 2012 recruitment is scheduled to last around 12 months. Updated data regarding population of study and toxicity will be presented at the ESMO meeting. A translational research, including whole exon analysis, will be performed in order to improve our scarce knowledge of ACC.
Conclusion: All authors have declared no conflicts of interest.

Patient preference for tivozanib hydrochloride or sunitinib in the treatment of metastatic renal cell carcinoma (mRCC): Taursus study
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Purpose: Tivozanib hydrochloride is a potent, selective, long half-life inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3. Inhibition of VEGF-driven angiogenesis is known to reduce vascularization and tumor growth. Currently, sunitinib is most commonly used as first-line treatment in patients with mRCC. Previous Phase II and Phase III studies have demonstrated the promising efficacy and safety of tivozanib in patients with mRCC. The primary objective of this study is to compare patient preferences for tivozanib or sunitinib. Secondary objectives include assessing overall safety and tolerability, frequency of dose modifications, and quality of life in patients treated with tivozanib and sunitinib. Study design: This Phase II, randomized, double-blind, multinational, crossover study will compare the preference of mRCC patients for tivozanib or sunitinib as treatment for metastatic disease. Recruitment of 160 patients is planned. Patients will be randomized to tivozanib 1.5 mg/d for 12 weeks (wks) (Cycle = 3 wks on, 1 wk off) or sunitinib 50 mg/d for 12 wks (Cycle = 4 wks on, 2 wks off). After a washout period, patients will cross over to the alternate treatment (sunitinib or tivozanib).
Methods: After 12 wks of treatment, tumor response will be assessed using Response Evaluation Criteria In Solid Tumors (version 1.1). Patients are expected to cross over to the second treatment for 12 wks; however patients with a significant clinical response (defined as ≥50% tumor reduction or complete response for non-measurable disease) will be given the option to continue the first treatment if they choose. Patients with Grade 3/4 adverse events may have a dose interruption of ≤2 wks to manage toxicities, after which they may continue at the same or reduced dose; dose reductions to 1.0 mg/d for tivozanib and 37.5 mg/d for sunitinib will be allowed. After the second 12-wk period, patients’ drug preferences, based on a questionnaire, and their tumor response will be assessed and reviewed prior to a final tumor assessment.
Conclusion: The double-blind design of this study will enable comprehensive assessment of patient preference for tivozanib and sunitinib as treatment for mRCC.

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