7131 POSTER

Optimizing the Sequencial Treatment of Metastatic Renal Cell Carcinoma (MRCC) − a Retrospective, Multicenter, Analysis of 40 Patients Treated With Either Sorafenib, an mTOR Inhibitor (mTORI) and Sunitinib, or Sunitinib, an mTORI and Sorafenib

C. Porta[1], C. Paglino[1], G. Procopio[2], R. Sabbatini[3], J. Bellmunt[4], M. Schmidinger[5], A. Bearz[6], A. Bamias[7], B. Melichar[8], I. Imarisio[1]. *[1]IRCCS San Matteo University Hospital, Medical Oncology, Pavia, Italy; [2]IRCCS National Cancer Institute Foundation, Department of Medical Oncology Unit 2, Milano, Italy; [3]University of Modena and Reggio Emilia, Department of Oncology Hematology and Respiratory Diseases, Modena, Italy; [4]University Hospital Del Mar, Medical Oncology Service, Barcelona, Spain; [5]Medical University of Vienna, Department of Medicine I and Cancer Center CLinical Division of Oncology, Vienna, Austria; [6]IRCCS Oncology Reference Center, Medical Oncology, Aviano, Italy; [7]Athens University Medical School, Department of Clinical Therapeutics, Athens, Greece; [8]Palacky University Medical School and Teaching Hospital, Department of Oncology, Olomouc, Czech Republic*

Background: Since the approval of 3 multikinase and 2 mTOR inhibitors (mTORI), an increasing number of mRCC patients have been empirically treated with a sequential treatment approach. However, the optimal sequential use of all these agents has yet to be estabilished. The purpose of this retrospective analysis was to assess the clinical benefit of 2 different sequential approaches, i.e., sorafenib, an mTORI and sunitinib, or sunitinib, an mTORI and sorafenib.
Material and Methods: This study was a retrospective analysis of 40 patients with mRCC treated between September 2005 and October 2010 at 6 European Centers. All patients were treated first-line with either sunitinib or sorafenib, followed by a second-line treatment with an mTORI (everolimus or temsirolimus), and, upon further progression, with the other multikinase inhibitor (sorafenib or sunitinib).
Results: 26 patients were treated with the sequence sorafenib-mTORI-sunitinib and 14 with the sequence sunitinib-mTORI-sorafenib. Baseline patient characteristics were similar between both populations in terms of age, ECOG Performance Status, Motzer's score, Fuhrman's grade, and presence of liver metastases. In the sunitinib-mTORI-sorafenib group, an higher incidence of non-clear cell mRCC were observed (5/14 *vs.* 0/26 in the sorafenib-mTORI-sunitinib group). The actuarial overall median PFS (not including inter-treatment periods) in the sorafenib-mTORI-sunitinib group and in the sunitinib-mTORI-sorafenib group were 21.9 and 22.8 months, respectively (Log-rank test: $p = 0.928$). In the sorafenib-mTORI-sunitinib group patient experienced a median PFS of 11.7 months at first-line, 5.1 months at second-line, and 9.1 months at third-line, while in the sunitinib-mTORI-sorafenib group the first-, second- and third-line PFS were 14.4, 4.3 and 3.9 months, respectively.
Conclusions: Even though biased by its retrospective nature and small sample size, this study suggests the absence of significant differences, in terms of median PFS, between patients treated with the two sequential modality considered. In particular, it is possible to assume that patients may be sensitive again to a multikinase inhibitor after a second-line treatment with an mTORI. The results of ongoing prospective studies will help us defining the best treatment sequence.
Acknowledgements: we gratefully thank the Biostatistician Dr. Carmine Tinelli, from I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy, for his precious help.

7132 POSTER

Impairment of Cognitive Functioning During Sunitinib or Sorafenib Treatment − a Cross Sectional Study

S.F. Mulder[1], D. Bertens[2], K.C.P. Vissers[3], C.J.A. Punt[1], P.F.A. Mulders[4], D.J. van Spronsen[5], R.P.C. Kessels[2], C.M.L. Herpen[1]. *[1]Radboud University Nijmegen Medical Centre, Department of Medical Oncology, Nijmegen, The Netherlands; [2]Radboud University Nijmegen Medical Centre, Department of Medical Psychology & Donders Institute for Brain Cognition and Behaviour, Nijmegen, The Netherlands; [3]Radboud University Nijmegen Medical Centre, Department of Anesthesiology Pain and Palliative Medicine, Nijmegen, The Netherlands; [4]Radboud University Nijmegen Medical Centre, Department of Urology, Nijmegen, The Netherlands; [5]Canisius Wilhelmina Hospital, Department of Internal Medicine, Nijmegen, The Netherlands*

Background: Impairment of cognitive functioning has been reported in several studies in patients (pts) treated with chemotherapy. So far, no studies have been published on the effects of the vascular endothelial growth factor receptor (VEGFR) inhibitors on cognitive functioning. We investigated the objective and subjective cognitive function of patients during treatment with VEGFR tyrosine kinase inhibitors (VEGFR TKI).
Material and Methods: Three groups of participants, matched on age, sex and education, were enrolled; 1. metastatic renal cell cancer (mRCC) or GIST pts treated with sunitinib or sorafenib for $\geqslant$ 8 weeks (n = 29); 2. not-systemically-treated mRCC pts (n = 19); 3. healthy controls (n = 30). Sixteen neuropsychological tests examining the main cognitive domains (intelligence, memory, attention and concentration, executive functioning and abstract reasoning) were administered by a neuropsychologist. Four questionnaires were used to assess subjective cognitive complaints, mood, fatigue and psychological wellbeing.
Results: No significant differences in mean age, sex distribution, education level or IQ were found between the three groups. In the VEGFR TKI group 22 pts received treatment with sunitinib and 7 with sorafenib; 25 pts had a diagnosis of mRCC and 4 of GIST. Pts on treatment with VEGFR TKI showed a significant impairment in memory and learning, executive functioning and abstract reasoning (all $p < 0.05$) compared with the healthy controls. The differences were modest to large (effect sizes Cohen's *d* ranging from -.48 to -.81) indicating that they are clinical relevant. Also, not-systemically-treated mRCC pts showed impairments on neuropsychological tests concerning memory, executive functioning and abstract reasoning, but on fewer tests than the VEGFR TKI group. No differences were observed between the VEGFR TKI group and the not-systemically-treated mRCC pts. No differences in the tests on attention and concentration were found between the three groups.
Conclusions: Our data demonstrate that the VEGFR TKIs sunitinib and sorafenib have a negative impact on cognitive functioning, specifically on memory and learning, and executive functioning. Patients treated with VEGFR TKIs have to be informed on this newly described adverse event.

7133 POSTER

Treatment (tx) Patterns and Toxicity of Angiogenesis Inhibitors in Patients (pts) With Advanced Renal Cell Carcinoma (RCC) in Spain

D. Castellano[1], M.S. Duh[2], E. Dial Suthoff[2], C. Korves[2], F. Vekeman[2], P. Ramamurthy[2], A. Mykletun[2], S. Lyon-Caen[2], M.P. Neary[2], J. Bellmunt[3]. *[1]Hospital 12 de Octubre, Servicio de Oncologia del Hospital, Madrid, Spain; [2]Analysis Group, Health Economics, Boston, USA; [3]Hospital del Mar, Solid Tumour Oncology (GU & GI) Medical Oncology Service, Barcelona, Spain*

Background: This study evaluated the frequency of and reasons for tx modifications and frequency of adverse events (AEs) among pts with advanced RCC treated with anti-angiogenic agents in Spanish clinical practice.
Materials and Methods: Medical records, not part of a disease-based registry, from adult pts with advanced RCC who received sunitinib [SU] (N = 60), sorafenib [SOR] (N = 23), bevacizumab (N = 6), or temsirolimus (N = 1) as 1st-line tx from 1/1/2005 to 9/15/2010 were retrospectively reviewed at 2 large oncology centers in Spain. Kaplan–Meier survival analysis was used to estimate tx duration. Proportions of pts with and reasons for tx modifications (discontinuation, interruption, dose reduction) were determined. Proportion of pts with all grade and grade 3/4 AEs were also determined.
Results: Only results for SU and SOR with sufficient sample sizes are presented. 26.7% (SU) and 13.0% (SOR) of pts had prior immunotherapy, 73.3% (SU) and 60.9% (SOR) of pts had history of nephrectomy, and 50.0% (SU) and 43.5% (SOR) of pts had metastasis at $\geqslant$2 sites. 83.3% of SU pts and 91.3% of SOR pts started tx at recommended dosing levels. Median 1st-line tx duration for all pts was 5.6 months for SU and 11.5 months for SOR. 1st-line tx discontinuation occurred in 91.7% (SU) and 69.6% (SOR) of pts. 40.0% of SU pts and 43.5% of SOR pts experienced grade 3/4 AEs and an average of 5.5 (SU) and 2.7 (SOR) all-grade AEs were experienced by each pt. Most common all grade AEs were mucositis or stomatitis (73.3% of SU pts; 43.5% of SOR pts), fatigue (70.0% of SU pts; 47.8% of SOR pts), diarrhea (43.3% of SU pts; 34.8% of SOR pts) and hand-foot syndrome (43.3% of SU pts; 39.1% SOR pts). AEs led to tx modification in 55.0% of SU pts and 73.9% of SOR pts (Table). 55.6% of SU pts who discontinued due to AEs did so within 12 weeks of tx initiation.

Tx Modifications, n (%)	SU (n = 60)	SOR (n = 23)
Pts with tx discontinuation	54 (90.0)	16 (69.6)
Due to progressive disease	40 (66.7)	14 (60.9)
Due to AEs	9 (15.0)	1 (4.3)
Pts with tx interruption	27 (45.0)	15 (65.2)
Due to AEs	26 (43.3)	13 (56.5)
Pts with dose reduction	24 (40.0)	11 (47.8)
Due to AEs	20 (33.3)	8 (34.8)
Pts with $\geqslant$1any of the above tx modifications	59 (98.3)	22 (95.7)
Due to AEs	33 (55.0)	17 (73.9)

Conclusions: Pts treated with both SU and SOR experienced high rates of tx modifications due to AEs. Further analysis is needed to understand the impact of these tx modifications on clinical outcomes. Results from this real-world clinical practice study suggest a need for more tolerable treatments for advanced RCC.

7134 POSTER

Updated Safety and Efficacy Results for Sunitinib From a Global, Expanded-Access Trial in Metastatic Renal Cell Carcinoma (mRCC)

M. Gore[1], C. Porta[2], S. Bracarda[3], L. Crinò[4], R. Hawkins[5], G. Bjarnason[6], S. Oudard[7], S.H. Lee[8], T.M. Kim[8], C. Szczylik[9]. [1]*The Royal Marsden Hospital NHS Trust, Cancer Medicine, London, United Kingdom;* [2]*IRCCS San Matteo University Hospital Foundation, Medical Oncology, Pavia, Italy;* [3]*Ospedale San Donato, Medical Oncology, Arezzo, Italy;* [4]*Azienda Ospedaliera di Perugia, Medical Division, Perugia, Italy;* [5]*Christie Hospital NHS Trust, Medical Oncology, Manchester, United Kingdom;* [6]*Sunnybrook Odette Cancer Centre, Medical Oncology, Toronto, Canada;* [7]*Hôpital Européen Georges Pompidou, Medical Oncology, Paris, France;* [8]*Seoul National University Hospital, Internal Medicine, Seoul, Korea;* [9]*Military Medical Institute, Oncology, Warsaw, Poland*

Background: Sunitinib demonstrated a manageable safety profile and encouraging efficacy in an expanded-access trial (ClinicalTrials.gov, NCT00130897; Pfizer) in which it was provided to trial-ineligible patients (pts) with mRCC in countries where regulatory approval had not yet been granted (Gore et al, 2009). We sought to evaluate whether the demonstrated efficacy and safety was consistent with extended follow-up.
Methods: Pts aged ⩾18 years with treatment-naïve or previously treated mRCC received oral sunitinib on the approved 50 mg/day 4-week-on/2-week-off schedule. Eligibility criteria were minimized to broaden the trial population. Safety was assessed regularly and tumour measurements were done as per local standard practice using RECIST-defined response. Analyses included all pts who received ⩾1 dose of sunitinib.
Results: As of March 2011, 4,572 pts were enrolled of whom 4,533 had received treatment, including 7% with brain metastases, 14% Eastern Co-operative Oncology Group performance status (ECOG PS) ⩾2, 12% non-clear cell RCC, and 33% aged ⩾65 years; traditionally poorer prognosis pts. Median treatment duration was 7.6 months; treatment was ongoing in 169 pts (4%). 4,084 pts (90%) had discontinued, reasons for which included lack of efficacy (34%), death (24%) and adverse events (13%). The most common treatment-related adverse events of any grade were diarrhea (47%), fatigue (40%), nausea (36%), decreased appetite (31%), mucosal inflammation (29%), stomatitis (28%), hand–foot syndrome and vomiting (both 27%), dysgeusia (25%), hypertension (24%), thrombocytopenia (23%) and asthenia (22%). The most common treatment-related grade 3/4 adverse events were fatigue (9%), thrombocytopenia (8%), hand–foot syndrome and asthenia (both 7%), hypertension and neutropenia (both 6%), and diarrhea (5%). In 3,361 evaluable pts, the overall objective response rate (ORR) was 19% (n = 651) with subgroup ORR as follows: baseline brain metastases (30 of 218 [14%]), ECOG PS ⩾2 (33 of 309 [11%]), non-clear cell RCC (41 of 374 [11%]), and age ⩾65 years (188 of 1,031 [18%]). Overall median progression-free survival was 9.7 months (95% CI: 9.1, 10.4) and overall survival was 18.4 months (95% CI: 17.4, 19.4).
Conclusions: The results from this large expanded-access trial in mRCC in a real-world setting confirm the safety and efficacy of sunitinib in a broad population. The sunitinib adverse event profile was manageable and consistent with that previously reported.

7135 POSTER

Treatment of Metastatic Renal Cancer With High-dose Interleukin-2 After Targeted Therapy Can Be Given Safely and Can Produce High Rates of Response Including Complete Remissions

R. Hawkins[1], K. Sikand[2], J. Shanks[2]. [1]*Christie Hospital NHS Trust, Medical Oncology, Manchester, United Kingdom;* [2]*Christie Hospital NHS Trust, Pathology, Manchester, United Kingdom*

Background: High-Dose Interelukin-2 (HD IL2) remains a good option for treatment of metastatic renal cancer. As a first-line treatment, in carefully selected patients, it can produce high rates of response (response rate 50%) with around 50% of these being complete remissions (Shablak A et al., J Immunotherapy 2011, 34(1): 107–122). Its use after targeted therapies is controversial and there are reports of increased toxicity, particularly an increased incidence of cardiovascular toxicity (and possibly a reduced response rate (Cho DC et al., J Immunotherapy 2009, 32(2): 181–520).
Methods: Here we present the outcomes of six patients treated with first-line immunotherapy with HD-IL2 after targeted therapy. Four had been treated with sunitinib alone and two had been treated with the sequence sunitinib followed by sorafenib and then everolimus. The histological characteristics of the tumours all fitted into the "favourable" group as defined previously by us and all had high levels of expression of CAIX (>80%). All had a satisfactory baseline stress echo and all had an interval of at least 8 weeks from last dose on TKI to start of HD-IL2. The patients ranged from 42 to 65, all had only one or two organ sites of disease and all were ECOG PS 0/1.
Results: Toxicity is indistinguishable from that of patients without prior treatment and no patient needed inotropic support or admission to intensive care. The number of doses given per cycle was also similar to that in unpretreated patients. Overall the response rates are excellent − 4/6 have had RECIST defined response. Three of these are complete remissions and the fourth is in complete remission after surgical resection of residual disease. The current duration of follow-up is relatively short but to date no responding patient has progressed with follow up of 15+, 12+, 12+, 10+ months. The responses have been particularly striking following treatment with multiple drugs with both patients being in complete remission.
Conclusions: Overall, HD IL2 is a viable and effective salvage treatment in carefully selected renal cancer patients who have previously failed treatment with targeted therapy. Updated results will be presented.

7136 POSTER

The Association Between Treatment (tx) Modifications Due to Adverse Events (AEs) and Overall Survival (OS) in Patients (pts) With Advanced Renal Cell Carcinoma (RCC) Treated With Sunitinib and Sorafenib: Results From a Multi-country Study in Europe

S. Oudard[1], C. Porta[2], D. Castellano[3], R. McDermott[4], P. Nathan[5], J. McCaffrey[6], M.P. Neary[7], C. Korves[8], E. Dial Suthoff[8], M.S. Duh[8]. [1]*Hôpital Européen Georges Pompidou, Medical Oncology, Paris, France;* [2]*IRCCS San Matteo University Hospital Foundation, Internal Medicine and Medical Oncology, Pavia, Italy;* [3]*Hospital 12 de Octubre, Medical Oncology, Madrid, Spain;* [4]*Adelaide & Meath Hospital, Medical Oncology, Dublin, Ireland;* [5]*Mount Vernon Cancer Centre, Medical Oncology, Middlesex, United Kingdom;* [6]*Mater Misericordiae Hospital, Medical Oncology, Dublin, Ireland;* [7]*GlaxoSmithKline, Global Health Outcomes Oncology, Collegeville, USA;* [8]*Analysis Group Inc., Healthcare, Boston, USA*

Background: Tx modifications due to AEs are frequent among advanced RCC pts treated with angiogenesis inhibitors. This study evaluates the association of these changes with OS among advanced RCC pts in European clinical practice.
Materials and Methods: Medical records, not part of a disease-based registry, from 542 adult pts with advanced RCC who received sunitinib [SU] (N = 409) or sorafenib [SOR] (N = 133) as first anti-angiogenesis tx from 1/1/2005 to 9/15/2010 were reviewed at 11 large oncology centers in France, Ireland, Italy, UK and Spain. Tx changes were defined as pts having experienced SU or SOR tx discontinuation, interruption or dose reduction due to an AE. Cox proportional hazards (PH) model and a landmark analysis (at 24 weeks; 30 weeks in a sensitivity analysis) were used to evaluate survival differences between pts with and without tx change due to AE. Landmark analysis was corrected for the "guarantee time" bias, a false-positive association between tx changes and longer survival. Each model was adjusted for age, gender, number metastatic sites, country, prior immunotherapy, AE during landmark period, time from RCC diagnosis to tx initiation; each model was adjusted to meet the PH assumption. Adjusted hazard ratio (HR) of death for pts with vs without tx change due to AEs were determined.

SU (n = 309)		SOR (n = 113)	
Tx change due to AE	$HR_{adjusted}$ (95% CI)	Tx change due to AE	$HR_{adjusted}$ (95% CI)
Discontinuation yes(y) = 15, no(n) = 294	3.44 (1.42–8.34)	Discontinuation y = 4, n = 109	Not estimable
Reduction y = 78, n = 231	0.96 (0.60–1.55)	Reduction y = 14, n = 99	2.13 (0.80–5.62)
Interruption y = 58, n = 251	1.42 (0.90–2.23)	Interruption y = 21, n = 92	2.56 (1.07–6.12)
Any change y = 112, n = 197	1.31 (0.86–2.00)	Any change y = 31, n = 82	2.94 (1.39–6.24)

Results: 309 SU and 113 SOR pts who did not have death/censor before the landmark period were eligible for analysis; of them, 112 and 31, respectively, had a tx change due to AE during the landmark period. For the more common AEs such as fatigue, diarrhea, nausea, hand foot syndrome, mucositis/stomatitis and skin rash, the majority were reported as possibly/probably treatment-related. In general, tx changes due to AE had negative impact on OS. For SU (Table), there was a strong and statistically significant association between tx discontinuation and OS. Analysis of discontinuation was not conducted for SOR due to limited data. For SOR,