7141 POSTER

Costs of adverse events management associated to the treatment of first-line metastatic renal cell carcinoma with bevacizumab + interferon alpha-2a compared with sunitinib in Spain

J. Puente[1], V. Calderero[2], X. García-Muro[3], J.M. Trigo[4], A.J. Castro[5], V. Martin-Escudero[5], M. Yebenes[6], M.A. Casado[6]. [1]*Hospital Clinico San Carlos, Servicio de Oncología, Madrid, Spain;* [2]*Hospital Universitario Miguel Servet, Servicio de Oncología, Zaragoza, Spain;* [3]*Institut Català d'Oncologia, Servicio de Oncología, Barcelona, Spain;* [4]*Hospital Universitario Virgen de la Victoria, Servicio de Oncología, Malaga, Spain;* [5]*Roche Farma SA, Pharmacoeconomics Dept, Madrid, Spain;* [6]*Pharmacoeconomics & Outcomes Research Iberia, Madrid, Spain*

Background: Both the combination of bevacizumab (BEV) + interferon alpha-2a (IFN) and sunitinib (SUN) have shown to prolong the time to progression-free survival when compared to interferon alpha alone in patients with metastatic renal cell carcinoma (mRCC). However, the type and frequency of adverse events (AEs) differ between these two options. The objective of the study was to evaluate the costs associated with the management of AEs in the current clinical practice when using BEV+IFN or SUN for mRCC, from the Spanish public hospitals perspective.
Methods: An economic decision analytic model was developed to compare the costs related to the management of all grade 3/4 AEs in patients with mRCC. Type and frequency of 40 AEs were collected from published trials (BEV+IFN: Escudier B. Lancet 2007; 370: 2103−11. SUN: Motzer RJ. N Engl J Med 2007; 356:115−24). The estimation of resources used related to the management of AE was made through an Oncology Expert Panel. Cost evaluation (€2009 values) included direct medical costs: outpatient visits, diagnostic and laboratory tests, hospitalizations, surgery, and medication. Unitary cost data were collected from the Spanish Database of Health Costs (e-Salud) and the Spanish Catalogue of Medicinal Products.
Results: Average cost of managing grade 3/4 AEs per patient was €568 for BEV+IFN and €940 for SUN, which represents a 40% cost saving with BEV+IFN (€371 per patient). The main drivers (representing approximately 83% of all costs) for SUN costs were related to the management of laboratory abnormalities, anaemia, mucosal inflammation, decline in ejection fraction, diarrhoea, thrombocytopenia, rash, epixtasis, and vomiting. In comparison, the main costs for BEV + IFN were associated to the management of gastrointestinal perforation, bleeding, proteinuria, venous thromboembolic event, anorexia and anaemia. The difference in costs between the two regimens was mainly due to a greater number of AE for SUN than for BEV+IFN, laboratory abnormalities, gastrointestinal perforation and bleeding.
Conclusion: The costs of managing grade 3/4 adverse events are substantially lower for BEV + IFN than those for SUN in patients with mRCC in Spain.

7142 POSTER

Immune tuning in renal cell carcinoma patients

A. Busse[1], A.M. Asemissen[1], A. Rietz[1], S. Ochsenreither[1], K. Zimmermann[1], A. Fusi[1], A. Schmittel[1], K. Miller[2], E. Thiel[1], U. Keilholz[1]. [1]*Charite Campus Benjamin Franklin, Med. Klinik III, Berlin, Germany;* [2]*Charite Campus Benjamin Franklin, Department of Urology, Berlin, Germany*

Background: Immunosuppressive factors secreted by renal cell carcinoma (RCC) leads to the induction of regulatory T cells. The aim of the study was to determine the prognostic influence of interleukin (IL) 10 and transforming growth factor (TGF) β on mRNA and protein level and the frequency of Treg and IL10/TGFβ producing T cells of peripheral blood in a cohort of metastatic (m) RCC patients before receiving sorafenib treatment.
Material and Methods: Blood samples of 46 patients with histological proven mRCC were assessed before sorafenib treatment for their expression levels of TGFβ, IL10 and FoxP3 mRNA by quantitative RT-PCR. Serum levels of IL10 and active TGFβ were determined by ELISA. Frequency of different T cell subsets was analyzed by multicolour flow cytometry. Clinical features considered included ECOG performance status, hemoglobin, alkaline phosphatase, and calcium concentrations. Disease evaluation was performed every 8 weeks following RECIST criteria. Relationship between pre-treatment factors and survival were examined in univariate analyses and subsequently by multivariate analysis using a stepwise backward and forward Cox regression model.
Results: In contrast to FoxP3 the IL10 and TGFβ mRNA levels were significantly higher in RCC patients compared to healthy subjects ($p = 0.034$ and $p = 0.023$, respectively). CD4+CD25high/CD3+Treg cells were elevated in RCC patients compared to healthy subjects ($p = 0.008$) with a lower TGFβ positive fraction ($p = 0.002$). Serum levels of active TGFβ were reduced in RCC patients ($p < 0.001$), IL10 serum levels and IL10 production in T cells differed not significantly. Univariate analysis revealed a negative prognostic influence of IL10 on progression free survival (PFS) ($p = 0.04$) and overall survival (OS) ($p = 0.063$). Surprisingly, high TGFβ and FoxP3 expression level had a positive influence on PFS ($p < 0.001$ and $p = 0.047$, respectively) and OS ($p = 0.0002$ and $p = 0.031$, respectively). Frequency of Treg or IL10/TGFβ producing T cells or IL10/TGFβ serum levels had no prognostic influence. In the multivariate analysis including clinical features low ECOG and high TGFβ mRNA levels were independently associated with worse PFS ($p = 0.032$ and $p = 0.002$, respectively) and worse OS ($p < 0$ and $p = 0.01$, respectively).
Conclusion: RCC caused an immunosuppressive phenotype in peripheral blood characterized by increased mRNA, but not protein levels of IL10 and TGFβ. In contrast to IL10, high TGFβ mRNA levels were an independent good prognostic factor.

7143 POSTER

Safety and treatment (trx) patterns of angiogenesis inhibitors (AIs) in patients (pts) with metastatic renal cell carcinoma (mRCC): evidence from US community oncology clinics

S. Wang[1], J. Ivanova[2], L. Antras[1], E. Chang[1], P. Ramamurthy[1], S. Whittemore[1], B. Fortner[3], J. Scott[4], M. Neary[5], M. Duh[1]. [1]*Analysis Group Inc., Boston MA, USA;* [2]*Analysis Group Inc., New York NY, USA;* [3]*P4 Healthcare, Scientific Affairs and Provider Services, Lakeland TN, USA;* [4]*P4 Healthcare, None, Lakeland TN, USA;* [5]*GlaxoSmithKline, Global Health Outcomes - Oncology, Collegeville PA, USA*

Background: Safety and trx patterns of sunitinib (SU) and sorafenib (SOR) in mRCC had been previously reported using a retrospective chart review of 119 pts in 2 US tertiary centers (ESMO, 2008). Trx patterns may vary between hospital and office-based settings. The present study evaluated safety and trx patterns in a US community oncology setting.
Methods: Medical records were retrospectively reviewed for 250 mRCC pts treated at 18 community oncology clinics. Eligible pts were ⩾18 yrs and received ⩾1 prescriptions for SU (n = 131) or SOR (n = 119) as first AI. Proportions of pts with adverse events (AEs), and trx discontinuations (d/c), dose reductions, and interruptions due to AEs were computed.
Results: Median trx duration was shorter in community practice than in tertiary centers (SU: 5.9 vs 10.5 months (m); SOR: 5.5 vs 8.1m). Pts in both groups had on average about 5 all-grade AEs; 29.8% (SU) and 27.7% (SOR) had ⩾1 grade 3/4 AE. Most common all-grade AEs were fatigue/asthenia (SU) and skin rash (SOR), followed by diarrhea, nausea, and pain (Table). 61.8% of SU and 63.9% of SOR pts had ⩾1 trx modification due to AEs. Compared to tertiary centers, in community practice AEs resulted in higher rates of d/c (SU: 24.4% vs 17.5%; SOR: 31.1% vs 17.7%), dose reductions (SU: 32.8% vs 29.8%; SOR: 42.0% vs 25.8%), and interruptions (SU: 33.6% vs 19.3%; SOR: 37.8% vs 32.3%) due to AEs.
Conclusions: AE rates in mRCC pts treated with SU or SOR in community practice tended to be lower than in tertiary centers and/or clinical trials, which may be due to considerably shorter trx duration or to under-reporting of AEs related to differences in practice patterns. Rates of d/c, dose reductions, and interruptions due to AEs tended to be higher. This study provides evidence in office-based setting of unmet need for agents that may provide improved tolerability in mRCC.

	SU (n = 131)			SOR (n = 119)		
AEs, n (%)	All Grades	Grade 3/4	⩾1 trx modification	All Grades	Grade 3/4	⩾1 trx modification
Fatigue/asthenia	55 (42.0)	7 (5.3)	28 (21.4)	41 (34.5)	2 (1.7)	15 (12.6)
Diarrhea	47 (35.9)	3 (2.3)	17 (13.0)	39 (32.8)	3 (2.5)	14 (11.8)
Nausea	36 (27.5)	2 (1.5)	18 (13.7)	31 (26.1)	2 (1.7)	12 (10.1)
Pain	31 (23.7)	5 (3.8)	5 (3.8)	29 (24.4)	4 (3.4)	6 (5.0)
Skin rash	13 (9.9)	1 (0.8)	4 (3.1)	42 (35.3)	7 (5.9)	27 (22.7)
Mucositis/stomatitis	27 (20.6)	2 (1.5)	12 (9.2)	19 (16.0)	4 (3.4)	11 (9.2)
Hand–foot syndrome	15 (11.5)	0 (0)	10 (7.6)	29 (24.4)	6 (5.0)	17 (14.3)
Vomiting	21 (16.0)	1 (0.8)	12 (9.2)	13 (10.9)	2 (1.7)	7 (5.9)

7144 POSTER

Predictive value and biologic significance of circulating tumor cells (CTC) in sporadic and von hippel lindau (VHL) renal cancer

S. Zovato[1], G. Opocher[2], E. Rossi[3], S. Indraccolo[3], A. Amadori[3], D. Pastorelli[1], G. Lombardi[1], M. Anglani[2], R. Zamarchi[3]. [1]*Istituto Oncologico Veneto-IRCCS, Medical Oncology, Padova, Italy;* [2]*Istituto Oncologico Veneto-IRCCS, Familiar Cancer Clinic, Padova, Italy;* [3]*Istituto Oncologico Veneto-IRCCS, Immunology and Oncologic Molecular Diagnostic Institute, Padova, Italy*

Background: Haematogenous spreading of tumor cells is a key step toward metastasis; the automated analysis of CTC by Cellsearch platform

represents an exciting improvement to serially investigate and accurately quantify these rare cells. At present, CTC count is indicated in the follow-up of metastatic breast cancer, colon rectal cancer and prostate cancer, so that cut-off values are now defined, predicting high risk of recurrence in metastatic disease. Moreover, variation in CTC can indicate a significant change in prognosis as early as the first treatment cycle and throughout the continuum of care. Preliminary reports indicate that CTC are present in patients with various metastatic carcinomas of epithelial origin with a wide range of incidences and frequencies but lack at presents extensively analysis of renal cell carcinoma (RCC) patients, both in sporadic and in VHL disease.

Materials and Methods: To investigate if RCC patients present CTC, we have designed a pilot study enrolling metastatic or advanced sporadic RCC patients and VHL patients, at diagnosis and naive for treatment. The first clinical objective of the study is to correlate CTC count with major prognostic factors determined at diagnosis. To gain further information on the biologic significance of CTC in patients with RCC both sporadic and VHL, we will also characterize the phenotypic profile of these cells, firstly regarding their metastatic potential. CTC and M30+ were measured in 12 consecutive patients affected by RCC and in 9 patients with VHL disease and renal cancer. CTC were measured in a group of healthy donors too. The study started at October, 2008 and is ongoing.

Results and Conclusions: Preliminary data obtained indicate that:

– Over 80% and over 70% of RCC samples, sporadic and VHL respectively, present CTC; no CTC were detected in healthy donors;
– The quote of live versus apoptotic CTC extensively differ between the two cohorts of patients (sporadic RCC and VHL);
– 50% of sporadic RCC patients presented 100% of apoptotic CTC, whereas in VHL patients the same percentage of apoptotic CTC was found in 66% of the cases.

7145 POSTER

Evaluation of safety, tolerability and activity: a registry for Temsirolimus-treated patients with advanced or metastatic renal cell carcinoma (aRCC) in the usual health care setting

H. Pelz[1], G. Krekeler[1], L. Bergmann[2], J. Roigas[3], T. Steiner[4], M. Kosch[1], P.A. Loeschmann[1]. *[1]Wyeth Pharma GmbH, Medical Department, Münster, Germany; [2]Johann Wolfgang Goethe-University, Medical Center, Frankfurt, Germany; [3]Vivantes-Hospital am Urban, Urology, Berlin, Germany; [4]Friedrich-Schiller-University, University Hospital Urology, Jena, Germany*

Background: In Nov 2007, the mTOR-inhibitor Temsirolimus (TEMS) was approved in the EU for the first-line treatment of patients with aRCC who have at least 3 of 6 prognostic risk factors. A pivotal study had demonstrated significantly increased overall survival with TEMS in poor risk aRCC compared to the former standard Interferon (10.9 mo vs 7.3 mo). A pre-registration compassionate use program (CUP) for patients with aRCC confirmed the known safety profile of TEMS. However, the low incidence of reported serious adverse events (SAE) even in the CUP (8 SAE during about 2200 applications) reflects the low level of spontaneous SAE reporting in oncology in general. To better identify the true safety profile of newly approved drugs, collection of data on pharmacovigilance in the post-approval period is essential. Hence a non-interventional trial appears to be adequate.

Methods: To prospectively evaluate TEMS in the usual health care setting we started a registry for TEMS-treated patients with aRCC. Primary objective is the evaluation of TEMS's safety profile. Secondary objectives include the tolerability and activity of TEMS as well as the profile, comorbidity and characteristics of patients and sequence of systemic therapies in aRCC. Inclusion criteria are a histologically confirmed aRCC treated with TEMS and written informed consent by the patient.

Results: With regulatory and ethic committee's notification the registry started in Germany in Feb 2008. The registry is set up and managed by Wyeth's medical department in collaboration with a scientific advisory board. Up to the end of March 2009 73 active centers have recruited 176 patients. Preliminary documentation is available for 106 patients (79 male, 26 female), median age 66.9 yrs (40.4–86.7), median Karnofsky index 80% (40–100%). 56 patients experienced 191 AE, including 23 pts with 51 SAE (13 of them considered related, 38 not related by the treating physician). Clear cell carcinomas represent the predominant histological subtyp (74.5%) in the study-population.

Conclusions: To further evaluate the safety, tolerability and efficacy of TEMS in the treatment of aRCC in the post-approval period and also due to the low level of spontaneously reported SAE in oncology Wyeth started a registry for TEMS-treated patients in aRCC. Thus far, patient population represents the expected pattern regarding distribution of age, sex and histology. Updated results will be presented in September.

7146 POSTER

Metastatic renal cell carcinoma: a comparative effectiveness assessment of first-line bevacizumab + Interferon alpha-2a vs sunitinib

G.H. Mickisch[1], B. Schwander[2], S. Walzer[3]. *[1]Center of Operative Urology Bremen, Department of Urology, Bremen, Germany; [2]AiM GmbH - Assessment in Medicine, Outcomes Research, Schopfheim, Germany; [3]F. Hoffmann-La Roche Pharmaceuticals AG, PBSE, Basle, Switzerland*

Background: Bevacizumab (BEV) + Interferon alpha-2a (IFN-α) [1] and sunitinib (SUN) [2] have shown significant increase in progression free survival (PFS) compared to IFN-α in first-line metastatic renal cell carcinoma (mRCC) therapy. There is no head-to-head evidence available comparing both regimens, however there is an increasing need to assess and compare the relative efficacy in order to offer a transparent basis for reimbursement purposes.

Material and Methods: On the basis of the pivotal phase III trials, widely accepted indirect comparison methods [3–5] were applied focusing on PFS. The unadjusted investigator-assessed PFS hazard ratio (HR) for BEV + IFN-α vs IFN-α (0.63) and for SUN vs IFN-α (0.52) have been used as the basis of the analysis. To enable valid indirect comparison, the IFN-α control arms of both trials have been standardised. Taking into account published evidence, sensitivity analyses on the effects of down-dosing and patient compliance have also been applied in order to re-evaluate PFS outcome.

Results: The base case unadjusted indirect comparison resulted in a non-significant PFS difference of SUN vs BEV + IFN-α (HR: 0.82; 95% CI: 0.64, 1.06; p = 0.13). Standardising the IFN arms and simulating SUN down-dosing and patient compliance fortifies the base case findings of non-significant PFS difference: the adjusted indirect PFS comparison HR of SUN vs BEV + IFN-α varied from 0.98 to 1.17, which may suggest a tendency in favour of BV + IFN-α. Results were most influenced by IFN-α control arm adjustment, followed by patient compliance and down-dosing.

Conclusion: BEV + IFN-α is similarly efficacious to SUN in terms of PFS based on a comparative effectiveness evaluation in first-line mRCC therapy. These findings imply that other treatment decision criteria such as tolerability need to be considered.

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7147 POSTER

Efficacy and safety of long-term use of sorafenib: final report of a phase II trial of sorafenib in Japanese patients with unresectable/metastatic renal cell carcinoma

H. Akaza[1], S. Naito[2], T. Tsukamoto[3], M. Murai[4], K. Fukino[5]. *[1]Institute of Clinical Medicine University of Tsukuba, Department of Urology, Ibaraki, Japan; [2]Graduate School of Medical Science Kyushu University, Department of Urology, Fukuoka, Japan; [3]School of Medicine Sapporo Medical School, Department of Urologic Surgery and Andrology, Sapporo, Japan; [4]International Goodwill Hospital, Hospital Director, Yokohama, Japan; [5]Bayer Yakuhin Ltd, Medical Advisor Medical Affairs, Osaka, Japan*

Background: Results of the landmark TARGET study indicated that sorafenib, an oral multi-kinase inhibitor, is a safe and effective treatment for advanced renal cell carcinoma (RCC). By blocking cell growth and angiogenesis pathways, sorafenib significantly improves progression-free survival (PFS) and overall survival (OS) in patients (pts) with advanced RCC. Few analyses, however, have evaluated the long-term effects of sorafenib. Here we present efficacy and safety data from a phase II trial and extension study of pts with unresectable/metastatic RCC.

Materials and Methods: 131 pts with unresectable/metastatic RCC in Japan were treated with sorafenib 400 mg BID in a single-arm, phase II trial and extension study conducted from Nov 2004 through Jul 2008. All pts had undergone nephrectomy and cytokine therapy prior to study enrollment.

Results: Efficacy data is shown in the data table. In the 25 pts with a partial response (PR), the median time to response and duration of response were 12.0 weeks and 59.9 weeks, respectively. Notably, 6 of these pts achieved PR ⩽40 weeks after the start of sorafenib treatment. Drug-related adverse events (AEs) were observed in 127 pts (96.9%). However, most AEs were CTCAE grade 1–3. Drug-related grade 4 AEs were observed in 20 pts (15.3%), including high levels of lipase in 9 pts (6.9%), hyperuricemia in 4 pts (3.1%), and high levels of ALT in 3 pts (2.3%). Sorafenib was discontinued in 29 pts (22.1%) due to AEs, including