7162 POSTER

A Pan-European Study of Treatment (trx) Patterns and Toxicity of Angiogenesis Inhibitors in Patients (pts) With Advanced Renal Cell Carcinoma (RCC)

A. Levy[1], C. Porta[2], R. Hawkins[3], J. Bellmunt[4], J. Wagstaff[5], P. Donnellan[6], M.P. Neary[7], S.P. Sarda[8], F. Vekeman[8], M.S. Duh[8]. *[1]Institut Gustave Roussy, Department of Medicine, Villejuif, France; [2]IRCCS San Matteo University Hospital Foundation, Internal Medicine and Medical Oncology, Pavia, Italy; [3]University of Manchester, School of Cancer and Imaging Sciences, Manchester, United Kingdom; [4]Hospital del Mar, Solid Tumour Oncology Section, Barcelona, Spain; [5]South West Wales Cancer Institute, Medical Oncology, Swansea, United Kingdom; [6]University College Hospital Galway, Medical Oncology, Galway, Ireland; [7]GlaxoSmithKline, Global Health Outcomes − Oncology, Collegeville, USA; [8]Analysis Group Inc., Healthcare, Boston, USA*

Background: Multicenter studies provide valuable information regarding trx patterns and outcomes for rare cancers. Trx modalities and toxicities of sunitinib (SU), sorafenib (SOR), and bevacizumab (BEV) for advanced RCC in clinical practices across 5 Western European countries in 2005–2010 are reported here.
Material and Methods: Medical records, not part of a disease based registry, were retrospectively reviewed for 746 RCC pts in 11 tertiary oncology centers. Pts were ⩾18 years, had diagnosis of advanced RCC, received SU (n = 532), SOR (n = 159; 1 with IFN), or BEV (n = 55; 21 with IFN or temsirolimus) as first anti-angiogenic trx. Prior trx with cytokines, chemotherapy, and radiotherapy was permitted. Data were collected on all adverse events (AEs) and trx modifications, including trx discontinuation (d/c), interruption, and dose reduction. Trx duration was estimated using Kaplan–Meier analysis.
Results: Mean age ranged from 59 (y) (BEV) to 63 y (SOR). Over 74% of pts in each group were males. 31.4% (SU), 52.2% (SOR), and 61.8% (BEV) pts were cytokine pre-treated. The 2 most common any grade AEs were SU (fatigue: 61.3%, mucositis/stomatitis: 46.4%), SOR (hand-foot syndrome [HFS]: 44.7%, diarrhea: 43.4%), and BEV (fatigue: 47.3%, pain: 18.2%). Median trx duration was 10.5 months (m) for SU, 8.1 m for SOR, and 7.7 m for BEV. Among pts with trx d/c due to AEs, common AEs associated with d/c were: SU (fatigue: 61.1%), SOR (HFS: 37.5%), and BEV (fatigue: 44.4%). For SU and SOR, trx d/c within 18 weeks for any reason was 31.9% and 23.7%, respectively, with 51.8% and 43.8% of these due to AEs. Rates of trx modifications are in Table.
Conclusions: In this large chart review study, it was found that fatigue and HFS were major contributors to trx d/c, and 87−95% of pts experienced at least 1 trx mod, more than half due to AEs for oral agents (56% SU and 53% SOR). Early trx d/c was common and often due to AEs. Newer agents with better tolerability will broaden trx options.

Trx Modifications, n (%)	SU (oral) N = 532	SOR (oral) N = 159	BEV (IV) N = 55
Trx d/c	366 (69)	137 (85)	44 (80)
Due to progressive disease[a]	181 (44)	82 (62)	14 (39)
Due to AE[a]	72 (18)	16 (12)	9 (25)
Trx interruption[a]	130 (32)	36 (27)	5 (14)
Due to AE[a]	101 (25)	32 (24)	4 (11)
Dose reduction	235 (44)	45 (28)	4 (7)
Due to AE[a]	152 (37)	41 (31)	3 (8)
⩾1 any of the above modifications	507 (95)	150 (94)	48 (87)
Due to AE[a]	228 (56)	71 (53)	14 (39)

[a]Data from one site were not available. Denominators for proportions were: 409 (SU), 133 (SOR), and 36 (BEV).

7163 POSTER

Evolution of Overall Survival in Renal Cell Carcinoma (2000−2008) − Results From a Swedish Population-based Study

T. Wahlgren[1], J. Kowalski[2], S. Lundstam[3], U. Harmenberg[4], P. Sandström[4], M. Jakobsson[5], R. Sandin[5], B. Ljungberg[6]. *[1]Pfizer AB, Oncology, Sollentuna, Sweden; [2]Pfizer AB, Biostatistics, Sollentuna, Sweden; [3]Sahlgrenska University Hospital and the Sahlgrenska Academy University of Gothenburg, Department of Urology, Gothenburg, Sweden; [4]Karolinska University Hospital and Karolinska Institutet, Department of Oncology-Pathology, Stockholm, Sweden; [5]Pfizer AB, Global Health Economics and Outcomes Research, Sollentuna, Sweden; [6]Umeå University, Department of Surgical and Perioperative Sciences Urology and Andrology, Umeå, Sweden*

Background: Renal cell carcinoma (RCC) treatment has evolved rapidly over the past decade and recent advances of targeted therapies have greatly improved patient prognosis. However, survival data from population studies reflecting advances in clinical practice are sparse, as are insights regarding factors influencing overall survival (OS).
Methods: This register study assessed OS in patients with RCC and metastatic RCC (mRCC) diagnosed before (2000–2005) and after (2006–2008) the introduction of targeted therapies, as well as factors influencing OS in mRCC. Three Swedish national health registers were used: the Swedish Cancer register (diagnosis and death records), the National Patient Register (records of in-/out-patient data), and the Swedish Prescribed Drug Register (records of prescribed and dispensed drugs). In total, 8,009 patients diagnosed with RCC between 2000 and 2008 were identified in the Cancer register and individual patient data were merged from the other registers. 3,243 patients (40%) developed metastasis between 2000 and 2009. Multivariate analysis was performed using a Cox proportional hazards model, including estimation of adjusted OS. The regression model included the following covariates: age, gender, geographical region, institution size, nephrectomy, period of diagnosis, and tyrosine kinase inhibitor (TKI) prescription.
Results: RCC patients diagnosed between 2006 and 2008 demonstrated an improvement in OS compared with patients diagnosed between 2000 and 2005 (median adjusted OS: not reached vs. 46.7 months, respectively [HR = 0.72, 95% CI: 0.67–0.77; P < 0.001]). A similar improvement was found in mRCC patients (median adjusted OS: 16.1 vs. 10.9 months, respectively [HR = 0.76, 95% CI: 0.69–0.83; P < 0.001]). For mRCC patients, females compared with males (HR = 0.9, 95% CI: 0.81–0.99), large compared with small institutions (HR = 0.86, 95% CI: 0.79–0.93), nephrectomy (HR = 0.32, 95% CI: 0.29–0.35), diagnosis between 2006 and 2008 (HR = 0.76, 95% CI: 0.69–0.83), and a TKI prescription (HR = 0.82, 95% CI: 0.73–0.93) were all factors significantly associated with longer OS.
Conclusion: An improved OS for both the RCC and mRCC cohorts was demonstrated for the period 2006–2008 compared with 2000–2005. This confirms a change in therapeutic and diagnostic attitudes in RCC over recent years. Although the observed survival advantage is multifactorial in origin, contribution of targeted therapies is highly probable.

7164 POSTER

Adjuvant Treatment for Resected Renal Cell Carcinoma (RCC): Are All Strategies Equally Negative? Meta-analysis of Randomized Trials (RCTs)

F. Massari[1], E. Bria[1], D. Giannarelli[2], M. Milella[3], F. Cognetti[3], G. Tortora[1], G. Pappagallo[4], C. Porta[5]. *[1]Azienda Ospedaliera Universitaria Integrata, Oncologia Medica d.U., Verona, Italy; [2]Regina Elena National Cancer Institute, Biostatistics, Roma, Italy; [3]Regina Elena National Cancer Institute, Medical Oncology, Roma, Italy; [4]Ospedale Civile, Epidemiologia-Sperimentazioni Cliniche, Mirano (VE), Italy; [5]Fondazione IRCCS Policlinico San Matteo, Oncologia Medica, Pavia, Italy*

Background: Adjuvant treatment with cytokines (CK) or vaccines (VAX) or other (chemotherapy, radiotherapy) for surgically removed localized RCC did not meaningfully improve outcome according to the available evidences, regardless of treatment administered. Nevertheless, in light of the current introduction of targeted agents, the different mechanism of action of the adopted drugs may hide a differential effect on outcome. A literature-based meta-analysis was performed to explore this issue.
Methods: Event-based Relative Risk Ratios (RRs) with 95% confidence intervals (CI) were extracted and cumulated according to a random-effect model from papers or presentation. Differences in 5-year relapse-free survival (RFS, primary end-point) and 5- and 2-year overall survival (OS), and 2-year RFS were explored. Testing for heterogeneity was performed as well. In order to determine eventual differential effect according to treatment (CK versus VAX versus Other), interaction was calculated ('quantitative' interaction with diamonds on the same side of the plot, 'qualitative' when diamonds on opposite sides).
Results: Eleven trials (2,956 pts) were gathered; 9 (1,948 pts), 6 (1,639 pts) and 6 (1,209 pts) were evaluable for 5-yrs RFS, 2-yrs RFS/OS and 5-yrs OS, respectively. The patient population ranged from 47 to 918 pts. A significant interaction ('quantitative' for CK versus Other; 'qualitative' for VAX versus CK or Other) according to treatment in the main outcome was found, as shown in the table.

Outcome	Sample	HR (95% CI)	p-value	Het. (p)	Interaction (p)
5-yrs RFS	Overall	1.12 (0.98, 1.27)	0.088	0.023	**0.035**
	CK	1.12 (0.98, 1.29)	0.085	0.76	
	VAX	0.91 (0.50, 1.66)	0.78	0.04	
	Other	1.23 (0.64, 1.35)	0.53	0.05	

No significant interaction was found in 2-yrs RFS (Overall RR 1.06, 95% CI 0.93, 1.20, p = 0.35; interaction p = 0.14), 5-yrs OS (Overall RR 1.23, 95% CI 1.01, 1.50, p = 0.039; interaction p = 0.11), or 2-yrs OS (Overall RR 1.11, 95% CI 0.91, 1.34, p = 0.28; interaction p = 0.58). Heterogeneity was

significant in all subgroups, with the exception of the CK sub-population (the larger sample).
Conclusions: Although the overall negative impact of adjuvant treatment upon the natural history of RCC, the significant 'qualitative' interaction between VAX and CK suggests an underlying differential effect, which requires deeper investigations.

7165 POSTER

Sunitinib (SU) Pharmacokinetic (PK)–Pharmacodynamic (PD) Modeling With Respect to Safety and Efficacy Endpoints in Asian Patients With Gastrointestinal Stromal Tumour (GIST) or Renal Cell Carcinoma (RCC) in Pursuit of a Therapeutic Window

R. Khosravan[1], G. Mugundu[1], N. Agata[2], E. Ueda[2], T. Nishida[3], H. Akaza[4]. *[1]Pfizer Oncology, La Jolla, USA; [2]Pfizer Japan Inc, Tokyo, Japan; [3]Osaka Police Hospital, Department of Surgery, Osaka, Japan; [4]Univerity of Tokyo, Department of Strategic Investigation on Comprehensive Cancer Network, Tokyo, Japan*

Background: SU (SUTENT®) is an oral multitargeted tyrosine kinase inhibitor, approved multinationally for the treatment of advanced RCC, imatinib-resistant or -intolerant GIST, and well-differentiated pancreatic neuroendocrine tumour. We explored SU PK–PD relationships with respect to safety and efficacy endpoints to determine a therapeutic window for SU in Asian patients with GIST and RCC.
Methods: We analyzed pooled PK–PD data from two completed Japanese phase 2 studies (N = 81 combined; NCT 00457743, NCT00254540; Pfizer) in patients with GIST (SU 25 mg, 50 mg or 75 mg on intermittent schedule) and RCC (SU 50 mg on intermittent schedule) using NONMEM® V7.0. We initially built a PK model (2-compartments with 1st order absorption and elimination) to describe SU PK data. Subsequently, different sequential semi-mechanistic or mechanism-based (i.e., transit compartments with feedback loop [TCF] or indirect response [IDR] with E_{max} or sigmoid E_{max} drug effect) PK–PD models were built and compared for selection of a PK–PD model to describe each PD endpoint; these models were internally validated by Visual Predictive Check using PsN and Xpose.
Results: Key PK–PD model characteristics or parameter estimates are shown in the table below. There appeared to be great inter-patient variability in, and overlap between, the exposure–response curves for safety endpoints and that of the efficacy endpoint.
Conclusions: We could not identify a therapeutic window for SU in Asian patients with GIST and RCC. SU dose modification based on individual ppatient safety/tolerability appears to be the best approach to ensure maximum SU plasma exposure and efficacy, consistent with the SUTENT® label recommendation.

PD Endpoint	PK-PD Model	EC_{50} Mean (CV) ng/mL (%)	g Mean
Safety			
Absolute neutrophil count	TCF	6.91 (146)	1(F)
Platelet count	TCF	55.7 (27)	5.22
Lymphocyte count	IDR	98.6 (NE)	3.09
LVEF	IDR	1050 (180)	1(F)
Diastolic blood pressure	IDR	318 (44)	1(F)
AST	TCF	74.7 (NE)	4.66
Efficacy			
SLD	IDR	80.1 (248)	1(F)

CV: coefficient of variation; EC_{50}: SU concentration at which 50% of the maximum effect is achieved; F: fixed; g (Gamma): Hill coefficient; LVEF: left ventricular ejection fraction; NE: not estimable; SLD: sum of the largest diameters of target tumours.

7166 POSTER

Validation of the Prognostic Score System for Survival in Patients (pts) With Relapses of Metastatic Nonseminomatous Germ Cell Tumours (mNGCT) After Induction Chemotherapy (iCT)

M. Fedianin[1], A. Tryakin[1], D. Kanagavel[1], T. Zakharova[2], I. Fainstein[3], K. Figurin[4], U. Sergeev[3], A. Garin[1], S. Tjulandin[1]. *[1]Blokhin's Russian Cancer Research Center, Clinical Pharmacology and Chemotherapy, Moscow, Russian Federation; [2]Blokhin's Russian Cancer Research Center, Pathomorphology, Moscow, Russian Federation; [3]Blokhin's Russian Cancer Research Center, Radiosurgery, Moscow, Russian Federation; [4]Blokhin's Russian Cancer Research Center, Urology, Moscow, Russian Federation*

Background: The International Prognostic Factors Study Group published a new prognostic classification for pts with relapses of GCT at the end of 2010. Scores prognostic system is presented at JCO 2010;28:4906–4911. This classification was validated on the data of 138 pts with relapses of NGCT.
Materials and Methods: We analyzed the data of 698 CT-näive pts with mNSGCT, who were treated in our department from 1986 to 2006 with etoposide- and cisplatin-based regimens (EP, BEP, C-BOP-3BEP and T-BEP) followed by resection of residual tumours. Pts with mature teratoma syndrome were excluded from analysis. With median follow-up time 32 (range, 3–215) months 181 (26%) pts had relapsed. The salvage CT was administered in 138 pts. 71 (51.7%) out of 138 were treated with ifosfamide-cisplatin-based CT. Mediastinal localization of primary GCT was revealed in 10.1% pts. According to the IGCCCG criteria: 26/138 (18.8%) pts had good prognosis, 47/138 (30.4%) − intermediate prognosis, and 65/138 (47.1%) − poor prognosis. One metastatic site was revealed in 71/138 (51.1%) pts. Complete and marker-negative response reached in 101/138 (73.2%) pts, 51/138 (36.9%) pts underwent surgical resection of residual masses.
Results: Early relapses (<2 years) were seen in 121/138 (87.7%) pts (the most of them was cisplatin-sensitive − 81/121 (67%) pts), 17/138 (12.3%) pts had late relapses (all of them were marker-positive). Median f.-up after relapse was 19 months (range 3–191). According new prognostic classification for pts with relapses: 33/138 (23.9%) pts were in the low risk group (0 scores), 44/138 (31.9%) − intermediate risk group (1 score), 18/138 (13%) − high risk group (2 scores), 43/138 (31.2%) − very high risk group (3 cores). Two-year PFS and 3-year OS for each group are presented in the table. The classification properly distributed pts into prognostic groups. However pts outcome in our study was worse than originally reported. That could be explained by differences in pts' characteristics: only half of them received ifosfamide in salvage CT and 28% of relapses were platinum resistant.

Prognostic category	Score	N = 138 (100%)	HR (95% CI)	P	2-Year PFS	3-Year OS
Low	0	33 (23.9%)			30%	43%
Intermediate	1	44 (31.9%)	1.1 (0.6−1.9)	0,13	18%	29%
High	2	18 (13%)	1.4 (0.7−3.1)	0,02	6%	24.5%
Very high	3	43 (31.2%)	2.6 (1.6−4.8)	<0.0001	0%	7.2%

Conclusion: The International Prognostic Factors Study Group classification for patients with relapsed mNGCT was successfully validated in independent pts cohort and recommended to use in daily practice.

7167 POSTER

Prognostic Factors for Overall Survival (OS) of Patients (pts) With Locally Advanced (LA) or Metastatic (m) Urothelial Carcinomas (UC) Following Platinum-based Combination Chemotherapy (CT) at Georges Pompidou Hospital (GPH) Between 2001 and 2009

E. Dina Bell[1], C. Takouchop[1], Y. Gornadha[1], J. Gachet[1], E. Kempf[1], F. Scotté[1], E. Fabre-Guillevin[1], J. Medioni[1], R. Elaidi[1], S. Oudard[1]. *[1]HEGP, Service Oncologie, Paris Cedex 15, France*

Background: The study was undertaken to identify clinical and biological pre-treatment prognostic factors of OS after platinum-based combination CT in LA or mUC pts.
Materials and Methods: A retrospective study was designed and clinical, biological, histopathological and therapeutic data were recorded before CT of 77 LA or mUC pts at GPH, Paris, France. Objective responders (OR) were defined as those with complete or partial response and non-responders (NR) as those with progressive or stable disease at the end of first-line CT in the metastatic setting. OS was estimated between date of initiation of first-line CT and date of last follow-up or death. Correlations with OS after CT were analysed using univariate and multivariate analyses.
Results: Sex ratio was 4 men/1 woman, mean age±SD: 66±8.7 years. Median (Range) OS: 11.0 (0.2–59.8) months. 85% of pts had ECOG PS <1. Mean ± SD of haemoglobin was 12.0±1.8 g/dl. Median (Range) of AST, ALT, Alkalin Phosphatase and CRP was 20 (10–132) U/L, 20 (1–172) U/L, 75 (7–320) U/L and 36.5 (1–273.3) mg/l, respectively. 83% pts had mUC and others had a LAUC disease. Among pts, 36 received CT in either neoadjuvant/adjuvant setting (n = 9/27 pts). Type of metastasis was liver, lung, bone and lymph nodes in 22, 32, 22 and 54% of pts, respectively. OR were 33%. With univariate analysis, response to CT, AST level, presence of metastasis and number of organ involved (in mUC pts) were significantly associated with OS. Other biological factors and ECOG PS were not significantly associated with OS because pts had mainly normal values at the initiation of CT. Upon multivariate analysis, only presence of metastasis [HR = 5.0, CI95% (1.2–21.2)], abnormal AST [HR = 2.4, CI95% (1.11−5.0)] and lack of response to the first-line CT [HR = 3.2, CI95% (1.4−7.7)] were main adverse prognostic factors (APF) for OS. Pts with more than 1 APF had significant poorer OS (8.8 vs 24.1 months, p < 0.001) [HR = 5.6, CI95% (2.7–11.9)].
Conclusion: Presence of metastasis, abnormal AST and lack of response at the first-line of CT can predict poor prognostic of LA or mUC pts. Compared to pts with 0−1 APF, those with more than 1 APF had a worse OS. These factors could be used to stratify pts in prospective clinical trials.