7152 POSTER

Interim Analysis of a Non-interventional Study of Everolimus After Failure of the First Anti-VEGF Therapy

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Background: To date, six targeted agents have been approved for the treatment of metastatic renal cell carcinoma (mRCC). Their role and place as part of a sequential treatment concept is subject to an ongoing debate and data beyond clinical trials is limited. Everolimus (EVE) is approved and recommended for the treatment of mRCC after failure of the first anti-VEGF therapy. Here, we report for the first time prospective non-interventional second-line data on EVE in routine use after failure of anti-VEGF therapy.
Material and Methods: A prospective, single arm, open label, multi center non-interventional study for patients with mRCC was initiated in Germany in 08/2009 to determine efficacy defined as time between first EVE intake until disease progression due to any cause (TTP) and patient related quality of life as measured by EORTC-QLQ-C30. Accrual is still ongoing. After 100 patients had been enrolled, a pre-planned interim analysis was conducted.
Results: Included were the first 113 patients enrolled at 59 German sites. The safety population consisted of 99 patients with documented EVE treatment. Median time since diagnosis of RCC was 3.5 years and median time since diagnosis of mRCC was 1.9 years. 88% of patients had prior nephrectomy. Before receiving EVE, most patients had received sunitinib (78%). The main reason for switching to EVE was progression on previous treatment (86%). Median time to progression (TTP) was 9.7 months (95% CI: 6 months; n.d.). A total of 230 AEs occurred in 61% of patients including 18 serious adverse drug reactions in 12 patients (12%). The nature of the AEs corroborated the safety profile of EVE. Median Karnofsky performance status (KPS) across all visits was $\geqslant$80% and median time to deterioration of KPS by 10% was 9.1 months. 44% of patients received third-line treatment after EVE (75% TKI). 80% of treating physicians attested EVE favorable tolerability, coinciding with high therapy compliance of patients as assessed by physicians and patients' diaries (>80%).
Conclusions: This non-interventional study on EVE in the treatment of RCC after prior failure of anti-VEGF therapy confirms its safety and efficacy in an early treatment setting. With this ongoing study, promising data on EVE treatment after failure of anti-VEGF therapy in the routine setting were obtained. Final results are eagerly awaited.

7153 POSTER

Treatment (trx) Modalities After a Front Line Targeted Therapies in Patients (pts) With Metastatic Renal Cell Carcinoma (mRCC)

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Background: New targeted therapies (TT) have been approved for metastatic renal cell carcinoma (mRCC) in the past 5 years, based on large multicenter randomized phases III trials. Median overall survival (OS) in these studies ranged from 19 to 26.4 months (mths). Whether this OS is also observed in routine practice has not been reported. We report here the experience of Institut Gustave Roussy (IGR) in France.
Methods: Data from all mRCC patients (pts) who were treated at IGR from 2005 to 2009 with first line TT (sunitinib (SU), sorafenib (SO), bevacizumab (B), temsirolimus or everolimus pooled together as mTOR) were analyzed. Only pts with subsequent follow up have been kept for this study. Pts were considered as eligible for 2nd line analysis if not progressive or still on first line treatment. Outcome of pts in terms of overall survival (OS), number of subsequent therapies have been analyzed.
Results: 264 pts, median age 62 y, median follow-up 37 months (mths) were treated with TT with a median OS of 25.5 mths. Median OS with SU (131), SO (59) or B (66) containing regimen are respectively 26.3, 16.3 and 29.5 mths. Only 8 pts received mTOR as first line. Among 199 pts eligible for 2nd line, 55% for SU (51/93), 51% for SO (26/51) and 73% for B (35/48) respectively received a 2nd line. A 3rd line was given to 53%, 31% and 46%, respectively for SU, SO and B. In those pts who received more than one line, median OS is respectively 16, 16.4 and 19.3 mths. Interestingly, when we split pts in 2 periods (2005–2006 and 2007–2009), there is no difference in OS ($p = 0.86$) or in % of 2nd and 3rd lines.
Conclusions: Median OS in pts treated with targeted therapies for mRCC exceeds 2 years. More pts treated with B could receive 2nd line therapy, with a trend to better OS. Update and characteristics of pts and treatments will be presented at the meeting.

7154 POSTER

Hypothyroidism and Macrocytosis as Surrogate Markers for Response and Survival in Patients With Advanced Renal Cell Carcinoma Treated With Sunitinib as First-line Therapy

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Background: Sunitinib, a multi-target tyrosine kinase inhibitor, is considered as a standard first-line treatment for advanced renal cell carcinoma. Some analytical abnormalities, such as thyroid dysfunction or macrocytosis, could be surrogate markers for sunitinib efficacy, as reported in previous studies.
Material and Methods: From January-2006 to January-2010 we collected consecutive patients with advanced renal cell carcinoma who received sunitinib as first-line therapy for advanced renal cell carcinoma for at least three cycles. Patients with thyroid function abnormalities or macrocytosis before initiation of sunitinib were excluded. For every patient we reviewed data about appearance of thyroid disfunction, new-onset macrocytosis, best response achieved with sunitinib, relapse-free survival (RFS) and overall survival (OS).
Results: A total of 34 patients were included. Patients with hypothyroidism showed a clear trend to better PFS, although not statistically significant (66 vs 30 weeks, $p = 0.190$); in the same way, the benefit observed in OS was also non-statistically significant (140 vs 90 weeks, $p = 0.192$). There was also a trend for correlation of hypothyroidism and a higher probability of achieving a complete or partial response ($\chi^2 = 0.097$).
Patients with new-onset macrocytosis showed a marked advantage for better progression-free survival, statistically significant (68 vs 30 weeks, $p = 0.02$). There was also a clear benefit in overall survival in patients who developed macrocytosis during treatment with sunitinib (170 vs 69 weeks, $p = 0.001$). Patients with new-onset macrocytosis had a greater probability of showing a complete or partial response with sunitinib therapy ($\chi^2 = 0.007$).
Conclusions: Although limited by the small size of this study, new-onset macrocytosis can be a surrogate marker for response and survival in metastatic renal cell carcinoma treated with sunitinib as first-line therapy. Data regarding hypothyroidism seem to point in the same way, but this study did not reach statistical significance for this issue. These findings will be re-analyzed with longer follow-up and including new patients from other collaborating centres to confirm these data.

7155 POSTER

Is Epidermal Growth Factor Receptor R497K Polymorphism in Renal Cell Carcinoma a Molecular Marker of Advanced Disease?

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Background: Renal cell carcinoma (RCC) is the most common cancer in the adult kidney, accounting for 5% of all malignancies and is considered the most lethal urological cancer. Epidermal growth factor receptor (EGFR) is a member of HER/ErbB family of receptors tyrosine kinases affecting cell proliferation, differentiation, tumour growth, inhibition of apoptosis, migration and angiogenesis. EGFR is a major transducer of mitogenic signals involved in cancer pathogenesis and progression. Its activity is mainly elevated in most human solid tumours leading to progression. A functional polymorphism (*R497K*) was described in *EGFR* gene responsible for a G-to-A leading to an Arg-Lys substitution in codon 497 in the extracellular domain within subdomain IV of the EGFR. This transition has been associated with an attenuated receptor function. Genetic functional variants, which influence EGFR function, may have impact in RCC development/prognosis. Our purpose was to investigate the association between *EGFR R497K* functional polymorphism and RCC clinicopathologic features.
Material and Methods: DNA was extracted from peripheral blood cells of 170 patients histopathologically diagnosed with RCC. Genotyping of *R497K* polymorphism was performed by PCR-RFLP. The odds ratio (OR) and its 95% confidence interval (CI) were calculated as a measure of the association between *EGFR R497K* genotypes and clinicopathologic features.

Results: The frequency of the GG, GA and AA genotypes were 58.2%, 31.2% and 10.6%, respectively. We found that GG/GA genotypes were present in 96.6% of cases with advanced disease (stages III-IV) and in 85.6% of cases with early disease (stages I-II) and these differences were statistically significant (OR = 4.8, $P = 0.026$). After adjustment for gender and age ($\leqslant$62 years), we observed that the G allele were statistically significant associated with advanced disease (OR = 5.1, $P = 0.035$).
Conclusions: Individual differences in cellular microenvironment and in signalling pathways activation may influence cancer development and tumour behaviour. Our preliminary results, suggest that *R497K* functional polymorphism is associated with advanced disease probably because the genetic variant *EGFR 497K* has attenuated functions in ligand binding, growth stimulation, tyrosine kinase activation and induction of proto-oncogenes compared with *EGFR 497R* variant. This genetic profiling may help define higher risk groups and design new target and individualized therapies.

7156 POSTER

HIF1a 1772C/T Polymorphism and Prognosis in Renal Cell Carcinoma

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Background: Hypoxia inducible factor (HIF-1) is a key regulator of the genes involved in the cellular response to hypoxia. Overexpression of HIF-1 has been implicated in the pathogenesis of renal cell carcinoma (RCC) and it is argued that polymorphisms of the HIF1A gene may confer susceptibility to RCC. Purpose: To assess the impact of HIF1A functional polymorphism on RCC progression and prognosis.
Material and Methods: The HIF1A 1772C/T (rs11549465) single nucleotide polymorphism was evaluated in a retrospective cohort study of sporadic RCC patients (n = 179) treated at Instituto Português de Oncologia do Porto from 1999 to 2009. Genomic DNA was extracted from peripheral blood samples. Genotyping was performed by Real-Time PCR allelic discrimination method. Recurrence/progression and cancer-specific survival (CSS) were the clinical outcomes studied. The associations of the HIF1A genotypes with clinicopathological prognostic factors and recurrence/progression were analyzed by the chi-square or Fisher tests. Genotypes influencing survival were compared using Cox proportional hazard regression. CSS was estimated by Kaplan–Meier curves and differences were compared using the Breslow test.
Results: None of the genotypes (CC, CT or TT) were significantly associated with ECOG *performance status* (PS), tumour size, tumour extension, Fuhrman grade, lymph node invasion, distant metastasis, TNM stage, histological necrosis or vessel permeation. The T allele was more frequent in patients with ECOG PS 1 than in those with ECOG PS 0 (OR 1.77; 95% CI 0.91–3.40; p = 0.07). The TT genotype and T allele were associated with recurrence/progression (p = 0.042 and p = 0.02, respectively). The CT and CT+TT genotypes were tend associated with unfavorable CSS (HR 2.79; 95% CI 0.88–8.82; p = 0.08 and HR 2.76; 95% CI 0.93–8.22; p = 0.07, respectively). Patients with CT and CT+TT genotypes showed worse CSS than those with the CC genotype (p = 0.012 and p = 0.018, respectively). CSS rates at 5-years were 88.1% vs 83.9% and 76.6% for the CC vs the CT and CT+TT genotypes, respectively.
Conclusion: These results suggest that HIF1A 1772C/T polymorphism may have effects on RCC progression or prognosis, possibly through altered HIF-1 transcription activity.

7157 POSTER

INT70/09 Phase II Study of Pazopanib (PZP) Monotherapy for Patients (pts) With Relapsed/refractory Urothelial Cancer (UC) − Updated Results

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Background: Discouraging results have been reported in relapsed/refractory UC with the use of either single-agent or combination therapy (Rx), including targeted Rx. In 2nd line setting, median progression-free (PFS) and overall survival (OS) approximate 3 and 6 months, respectively, then having a dramatic fall in 3rd line and beyond. On 10/2010 we reported preliminary, yet encouraging, results of a phase II trial with PZP, a multitargeted drug with distinct anti-angiogenic activity (ESMO 2010, LBA#23). An update of the trial is presented.
Methods: Eligibility included histologically confirmed UC failing $\geqslant$1 CDDP-based Rx for metastatic disease (perioperative Rx excluded). PZP 800 mg once daily until disease progression or unacceptable toxicity was planned. Both CT scan and PET/CT scan were set at baseline and q4weeks thereafter. An optimal 2-stage Simon's design was applied with the 1st stage recruiting 21 pts and, if $\geqslant$2 responses, a full enrollment of 41 pts. RECIST v.1.1 was used; response-rate (RR) was the primary endpoint.
Results: 36 pts were enrolled from 02/10 to 03/11 (28 males, 8 females). Median age was 64 yrs (42−79). 13 pts (36%) had UC of the upper urinary tract and 23 had a bladder primary tumour. 33 pts had multiple disease sites (median 3, range 1−5). Median number of prior cytotoxic agents was 3 (2−8), of prior Rx lines was 2 (1−4) and median number of prior platinum-based cycles was 5 (2−13). 30 pts (83%) had undergone major surgery, 10 pts had received RT. 30 pts had visceral metastases (hepatic in 17 pts). Median baseline ECOG PS was 1 (0−2). 4 pts (11%) had a confirmed RECIST-defined partial response (PR), 26 had a stable disease (83% clinical benefit). 19 pts (53%) had a clear necrotic evolution of multiple metastases and/or a decreased SUV at PET consistent with PR. Of the 34/36 pts having 2 months minimum follow up, median PFS and OS were 3 months (1−11) and 6 months (2−11), respectively. G3 hypertension occurred in 2 pts while G1−2 asthenia in 13, diarrhoea in 5, anemia and hand-foot syndrome in 3 pts each and G2 increase of liver transaminases in 2 pts. No discontinuations/dose reductions were needed.
Conclusions: Activity and potential efficacy of PZP is demonstrated in very highly pre-treated UC pts. Though the PR-rate by RECIST is low, half of pts had a densitometric/metabolic response, the majority of pts had a clinical benefit and PFS-rate is promising (approaching pure 2nd line results). This is consistent with the mechanism of action of PZP, and highlight the need for new criteria or modifications to existing ones to assess response of angiogenesis inhibitors. Final efficacy and safety outcomes with biomarker analysis will be available in 09/2011 (Cancer.gov registry number: NCT01031875).

7158 POSTER

Impact of Targeted Therapies on Muscle Loss and Adipose Tissue in Metastatic Renal Cell Carcinoma (mRCC)

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Background: We previously reported that sorafenib (So) can induce severe muscle depletion (sarcopenia) in RCC. Whether adipose tissue is also involved and whether this phenomenon is due to VEGF inhibition or involves other pathway is unclear. In order to understand the physiopathology of body composition changes with targeted therapies we investigated different drugs, including other VEGF inhibitor (sunitinib [Su]) and mTOR inhibitor (everolimus [E]).
Methods: All patients with mRCC enrolled in 3 previously reported studies: RECORD 1 (E vs placebo [P]), TARGET (So vs. P), and Su continuous dosing were analyzed. Patients were eligible if at least 2 CT scans were available. CT analysis, which has high precision and specificity for evaluation of specific muscles, was used to define change in total skeletal muscle. The 3rd lumbar vertebra was chosen as a landmark. Images were analyzed using Slice-O-Matic software V4.3. Subsequently, tissue cross-sectional areas (cm^2) were computed.
Results: 147 patients (78% male) were evaluable: 36 on E, 37 on So, 36 on Su and 38 on P. Mean durations of treatment were; 136, 172, 142, 117 days respectively on E, So, Su, P. At baseline obesity or overweight were frequent: 42% (P); 55% (E); 55% (So); 66% (Su). Placebo patients had stable body weight (mean$\pm$SD) (+0.9$\pm$3.7 kg), with no changes in muscle mass or adipose tissue. By contrast, patients lost body weight (mean$\pm$SD): −3.5$\pm$5.6 kg, −2.5$\pm$3.8 kg; −3.1$\pm$4.4 kg respectively on E, So, Su. Patients lost skeletal muscle compared with placebo group −3$\pm$8% for E ($p = 0.1$), −5$\pm$8% for So ($p < 0.0001$) and −4$\pm$5% for Su ($p = 0.001$). Interestingly, there were no differences between groups. Muscle loss rate (cm^2/day) was similar for the 3 groups respectively 0.042; 0.045, 0.044 for E; So; Su. No significant changes for adipose tissue were reported: 16$\pm$143% for E; −1$\pm$19% for So; 2$\pm$21% for Su. All combined, after 5 months of treatment, 86 patients were on progressive disease and 33 on stable disease. Loss of adipose tissue but not loss of muscle mass was significantly linked to progressive disease (p = 0.01).
Conclusions: The 3 therapies, everolimus, sorafenib and sutent are responsible for muscle wasting and surprisingly muscle wasting rate is