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)

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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

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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

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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,

there was a significant association between tx interruption and OS and any tx change and OS. In the sensitivity analysis, increased risk for OS remained statistically significant for these tx changes.
Conclusions: For SU and SOR pts, tx changes due to AEs may have a detrimental impact on OS. Limitations of the study include retrospective data collection.

7137 POSTER

Safety and Efficacy of Everolimus in Patients With Non-clear Cell Renal Cell Carcinoma Refractory to VEGF-targeted Therapy – a Subgroup Analysis of the REACT Expanded-access Program

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Background: Approximately 25% of all renal cell carcinomas (RCCs) have non-clear cell histology. Metastatic non-clear cell RCC (mncRCC) is characterized by resistance to treatment and poor overall survival. While the recent advent of targeted therapies has provided improved treatment options for patients with metastatic clear cell RCC, effective therapies for patients with mncRCC remain limited. The REACT (RAD001 Expanded Access Clinical Trial in RCC) study was initiated to provide patients with mRCC of any histology refractory to VEGF-targeted therapy access to everolimus in advance of regulatory approval.
Material and Methods: The open-label, international, expanded-access program REACT (Clinicaltrials.gov: NCT00655252; Trial sponsor: Novartis Pharmaceuticals) enrolled patients with measurable or nonmeasurable mRCC of any histology who were intolerant of, or progressed while on, VEGFR-TKI therapy. Patients received 10 mg everolimus daily. The primary study objective was to evaluate the long-term safety of everolimus, as determined by overall incidence of grade 3/4 and serious adverse events (AEs). Tumour response to everolimus was assessed by local investigator according to RECIST. A subgroup analysis of safety and efficacy in patients with mncRCC was performed.
Results: A total of 1367 patients were enrolled from July 2008 to June 2010; of these, 75 patients (5.5%) had mncRCC. Median everolimus treatment duration in the mncRCC subgroup was 12.14 weeks (range, 0.9–49.0 weeks), as compared with 14.0 weeks (range, 0.1–83.7 weeks) for the overall REACT population. Most commonly reported grade 3/4 AEs in the mncRCC subgroup included: anemia (17.3%), dyspnea (10.7%), pleural effusion (9.3%), fatigue (8.0%), and hyperglycemia (6.6%). Best overall response for the mncRCC subgroup was 1.3% partial response and 49.3% stable disease, as compared with 1.7% and 51.6% for the overall population.
Conclusions: The duration of everolimus treatment in patients with mncRCC was slightly lower than that of the overall REACT population, and nearly 50% of these patients achieved disease control on treatment. Everolimus was well tolerated in this patient subgroup, with no new safety issues identified and a comparable AE profile to that of the overall study population. Our results represent the first data reported on the safety and efficacy of everolimus in patients with mncRCC, and support further evaluation of everolimus in these patients.

7138 POSTER

High Rate of Complete Remission (CR) Using Two Sequential, Dose-dense Regimens of Cisplatin, Gemcitabine, and Paclitaxel (CGP) Followed by HD-MVAC in Patients With Metastatic Bladder Cancer (mBC)

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Background: Currently, CGP and HD-MVAC are the most active regimens against bladder cancer. According to Norton and Simon, we tested the hypothesis that the administration of two sequential non cross-resistant dose-dense chemotherapy regimens, may target different cancer cells, avoid drug resistance, improve response rate and complete response.
Materials and Methods: This is a single institution phase II trial. Eligibility included histological diagnosis of mBC, PS 0−2 (ECOG), adequate organ function and no previous systemic regimens. Patients were treated with 4 cycles of CGP dose-dense (Gemcitabine 1000 mg/m^2 d 1, Paclitaxel 140 mg/m^2 d 1, Cisplatin 70 mg/m^2 d 2 plus PegFilgrastim 6 mg on day 3, every 2 weeks) followed by 4 cycles of M-VAC (Methotrexate 30 mg/m^2 d 1,Vinblastine 3 mg/m^2 d 2, Doxorubicin 30 mg/m^2 d 2, Cisplatin 70 mg/m^2 d 2 plus Pegfilgrastim 6 mg on day 3 every 2 weeks). All were evaluated with CT scan at the baseline, after 4 cycles, at the end of chemotherapy and then every 3 months for two years and 6 months thereafter. The primary end point was the response rate. The trial was designed to detect a 100% improvement of CR rate from 15% with traditional CGP to 30% with our approach.
Results: 21 consecutive pts were included, 19 were evaluable. Male were 80%; median age 66 years; median PS was 90 (60–100). Metastatic sites included retroperitoneal nodes, lung, liver and bone. Bajorin risk factors was 0 in 33%, 1 in 40%, 2 in 27%. All pts were hospitalized for three days and received chemotherapy with generous hydration and supportive therapy. After the first 4 cycles of CGP we observed 11.1% CR, 55.5% PR, 16.6% SD and 16.6% PD. With the 4 sequential cycles of HD- MVAC the response was enhanced in 33% of the patients with a global 32% CR, 31% PR, 11% SD and 26% PD. Main grade 3−4 toxicity included asthenia (33%), neutropenia (26%), febrile (6.6%), thrombocytopenia (6.6%), mucositis (13.3%), electrolite disorders (15%). All patients with RP recurred whereas 5/6 patients with CR maintained the NED status after 2+, 9, 10+, 15+,16+, 28+.
Conclusions: The sequential use of CGP and HD- MVAC demonstrates significant clinical activity in the first line treatment of mBC.Toxicity was accetable. Approximately one out of three patients gets a durable RC. A longer follow-up is needed in order to see if some patients are cured.

7139 POSTER

Sunitinib for RCC in a Public Brasilian Institution: Predictive Factors of Major Toxicity

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Sunitinib is an oral drug with inhibitory activity over VEGF TK, as well as other TKs associated with the platelet-derived growth factor receptor and c-kit oncogene. Molecular pathways appear to be critical for RCC growth, metastatic progression and angiogenesis. Based on data derived from a large prospective randomized trial, sunitinib has emerged as a front line standard of care for the majority of patients with metastatic renal-cell carcinoma (RCC) deemed not suitable for high-dose IL-2. This trailblazing activity has been balanced though with some rather morbid and burdensome toxicities seen in real daily practice. These patients usually have clinical features which may interact and aggravate these adverse events.
Material and Methods: The aim of our study was to look for those clinical features which could predict undue toxicities responsible for dose reduction or interruption of treatment. We retrospectively reviewed the records of patients with advanced RCC treated with sunitinib from September of 2008 to march of 2011 at the Instituto do Câncer do Estado de São Paulo.
Results: From the initial seventy-four patients, 10 were excluded because of upfront dose-reduction, leaving 64 patients treated with conventional sunitinib dose and schedule (50 mg once daily for 4 weeks, every 6 weeks). The majority of patients had clear-cell histology (only 3 non-clear cell) with median age of 55 years; 77% had an ECOG of 0 to 2; 46 of 64 had an debulkying nephrectomy; median OS was 16.5 m; response rate by RECIST 1.1 was 26.5% in evaluable patients. Seventy-one percent of patients required dose reduction due to non-manageable toxicity (grade 3 or 4). Clinical factors that were associated with dose reduction by univariate analysis by student's t-test were weight <65 kg ($p = 0.026$), body surface area ($p = 0.031$), low IMC ($p = 0.019$) and estimated creatinine clearance less than 60 ml/min ($p = 0.047$ analysis by coefficient $\chi 2$). By multivariate analysis, only weight <65 kg remained statistically significant ($p = 0.021$).
Conclusion: Sunitinib's clinical activity in our daily practice emulates the one seen in clinical trials but most of our patients required dose reduction during treatment due to major toxicities. Except for body weight, there were no demographic factors or clinical variates independently associated with possible increased drug exposure and dose-limiting toxicities. Identification of clinical, genetic and demographic factors associated with increased adverse events is of interest and should be addressed in future studies.