4502 ORAL

Phase 2 study of irinotecan and cisplatin in epidermoid carcinoma of the penis (EORTC 30992)

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Introduction: Despite considerable recent progress in reducing the morbidity of surgical treatment of carcinoma of the penis in recent years with the development of plastic surgery techniques for gland reconstruction and sentinel sampling, there has been little in the way of advances in chemotherapy since reports on the combination of 5FU and cisplatin or that of methotrexate bleomycin and cisplatin. For both combinations, the reported response rates were in the range of 25−30% with limiting toxicities for the latter combination. Prompted by reports of irinotecan synergising with a platinum analogue in colorectal cancer, the EORTC Genito-Urinary Tract Cancer Group undertook a phase 2 study of this combination in penile cancer patients with locally advanced disease or recurrence after treatment of local disease.
Patients and Methods: The study was designed according to Simon (Optimum) with the aim of excluding a response rate (CR+PR) <30% (alpha = 10%, power = 95%). 28 patients (pts) were needed, with an option to stop after 13 for inactivity. The treatment regimen consisted in cisplatin 80 mg/m^2 on day one and irinotecan 60 mg/m^2 on days 1, 8 and 15 of a 28 day cycle. Patients were treated either in the neoadjuvant setting for T3 or N1-N2 disease with a maximum of 4 cycles before surgery or up to 8 cycles for distant nodal N3 or metastatic (M+) disease.
Results: Recruitment started in August 2004 and 28 pts were recruited in 12 months, including 7 in neo-adjuvant setting. Two pts with advanced disease were ineligible. The median RDI for irinotecan and cisplatin was 89.1% and 101.1%, respectively. Toxicity of the treatment was mild with only 3 cases (11%) grade 3/4 diarrhoea and 3 cases of grade 3/4 neutropenic sepsis, all recovering rapidly. One patient stopped treatment early because of toxicity. The 26 eligible patients were assessed for response. There were 8 responses (2CR & 6PR) (30.8%, 80%CI: 18.8% – 45.1%); 6/15 (40%) in M0 disease, and 2/11 (18%) in M+ disease. Of the 4 PR pts undergoing histological verification after chemotherapy 2 showed no evidence of malignancy. The study did not demonstrate a response rate significantly larger than 30%.
Conclusion: Although this study was underpowered for subgroup analysis, the observation regarding M0 patients suggests that it might be worth to repeat this study in a larger cohort of patients in the neo-adjuvant setting with requirement of histological confirmation of response in all patients.

4503 ORAL

Sunitinib in metastatic renal cell carcinoma (mRCC): preliminary assessment of safety and efficacy in an expanded access trial with subpopulation analysis

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Background: Sunitinib is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs and PDGFRs, internationally approved for advanced ("1st" and "2nd") line RCC. The primary aim of this ongoing, international, open-label trial is to provide sunitinib to RCC patients (pts) with no access (due to ineligibility or other reasons) to the drug prior to regulatory approval in their countries.
Materials and Methods: Eligibility criteria were minimized to broaden the trial population. Pts who were >18 yrs with histologically-confirmed mRCC received oral sunitinib 50 mg/d in 6-wk cycles (4 wks on treatment [Tx], 2 wks off).
Results: As of Apr 1, 2007, 4423 pts were enrolled from 246 sites in 52 countries. Data are currently available on 2341 pts (median age, 59 [range: 19−85]; male/female, 74%/26%). Baseline demographics included 276 pts (12%) with non-clear cell histology; 182 pts (8%) with brain metastases (b-mets); 167 pts (7%) with prior antiangiogenic Tx; and 308 pts (13%) with ECOG PS > 2. Median duration of Tx and follow-up were 5.6 months (mo) (0.03−20.1) and 6.7 mo (0.03−17.9), respectively. Tx reductions and discontinuations occurred in 37.1% and 38.6% of the pts, respectively, and Tx discontinuation due to adverse events (AEs), in 4.3% of the pts. The most common treatment-related AEs were diarrhea (42% any grade, 4% grade 3/4), fatigue (39%, 9%) and nausea (37%, 2%). The incidence of diarrhea was 38% and 29% in pts with b-mets and PS > 2, respectively; corresponding numbers were 38% and 32% for fatigue, and 36% and 30% for nausea. In cytokine-refractory mRCC pts enrolled before Jun 30, 2006 (n = 1840), the estimated median progression-free survival (PFS) was 8.8 mo (95% CI: 8.3−9.9). PFS was longer in pts with clear cell vs. non clear cell histology (9.2 vs. 6.7 mo), absence vs. presence of brain metastases (9.3 vs. 5.5 mo), and MSKCC good vs. intermediate vs. poor prognostic criteria subgroup (12.9 vs. 8.1 vs. 4.2 mo). Median overall survival has not been reached.
Conclusions: In this large expanded access study, single agent sunitinib showed safety results similar to the registrational trials, with no clinically relevant difference in pts with PS > 2 and in pts with b-mets as compared to the overall population. The efficacy results are in line with the known efficacy profile of sunitinib and provide useful data for specific unfavorable RCC patients subgroups (b-mets, non clear cell histology, PS > 2) that were not or poorly represented in previous trials.

4504 ORAL

A phase II study of continuous daily administration of sunitinib in patients with cytokine-refractory metastatic renal cell carcinoma (mRCC) – final results

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Background: Sunitinib malate (SUTENT®) is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3 with demonstrated antitumor and antiangiogenic activity. In two, multicenter phase II trials of pts with cytokine-refractory mRCC, 42% of pts achieved an investigator-assessed objective response rate (ORR; pooled analysis, n = 168) and a median progression-free survival (PFS) of 8.2 mo, when given sunitinib 50 mg/d on a 4/2 schedule (4 wks on treatment, 2 wks off) [Motzer et al., JAMA 2006; 295: 2516–24]. Here we report the mature results of an open-label, multicenter phase II study to evaluate the efficacy and safety of single-agent sunitinib when administered in a continuous dosing regimen of 37.5 mg/d to pts with cytokine-refractory mRCC.
Methods: Eligibility criteria included histologically proven mRCC with measurable disease, failure of 1 prior cytokine regimen, ECOG PS 0/1 and adequate organ function. Pts were randomized to receive sunitinib at a starting dose of 37.5 mg/d in the morning (AM) or evening (PM). Based on tolerability, individual doses were subsequently titrated to 25 or 50 mg/d. RECIST-defined ORR was the primary endpoint. Secondary endpoints included PFS, adverse events (AEs) and quality of life (QOL) measures.
Results: A total of 107 pts were randomized to AM (n = 54) or PM (n = 53) dosing and, as of February 2007, have been on study for a median of 6.9 mo (range 0.4–13.4). 70 pts have discontinued, 50 (47%) due to progression, 19 (18%) due to AEs, and 1 due to consent withdrawal. Continuous dosing at 37.5 mg/d has been maintained in 38 pts (36%). Dosing was reduced to 25 mg/d in 47 pts (44%) due to grade 2/3 AEs, the most frequent being asthenia (12%), hand–foot syndrome (HFS; 8%) and diarrhea (5%). The most commonly reported ($\geqslant$5% of pts) grade 3/4

AEs were hypertension (10%), asthenia (9%), HFS (9%), anorexia (8%) and diarrhea (6%). No differences were observed between pts receiving AM vs. PM dosing. RECIST-defined ORR was 20% by investigator assessment, with 43 pts (40%) achieving clinical benefit of ⩾6 mo of stable disease. Median PFS is 8.3 mo. QOL results will be presented.
Conclusions: Sunitinib 37.5 mg/d administered on a continuous dosing schedule has a manageable safety profile and shows promising clinical benefit as second-line therapy in mRCC, with a median PFS similar to that observed on the 4/2 schedule. This regimen may warrant further study for use in combination studies.

4505 ORAL

A population pharmacokinetic/pharmacodynamic (PK/PD) analysis of exposure–response for sunitinib in metastatic renal cell carcinoma (mRCC)

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Background: Sunitinib malate (SU) is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, and PDGFRs, approved multinationally for the treatment of advanced RCC. SU has previously shown substantial antitumor activity in mRCC [Motzer et al. JCO 2006; Motzer et al. JAMA 2006; Motzer et al. NEJM 2007]. The current analysis used a population PK/PD approach to examine the relationship between SU or total drug (TD; SU+SU12662 [active metabolite]) exposure and response in these studies.
Materials and Methods: PK and efficacy data were collected from 2 prior phase II trials of cytokine-refractory mRCC (N = 148) and phase III trial of treatment-naive mRCC (N = 44). SU starting dose was 50 mg/d, administered in 6-wk cycles (4 wks on followed by 2 wks off treatment), but modifications to 37.5, 25, or 62.5 mg/d were allowed based on tolerability and response. Plasma concentrations of SU and SU12662 were fitted to a 2-compartment population PK model and used to estimate the area under the curve at steady state (AUCss) for SU, SU12662, and TD. AUCss for SU and TD were used in subsequent PKPD analyses to examine the relationship between drug exposure and partial response (PR) rates, time to tumor progression (TTP), overall survival (OS), or tumor volume changes.
Results: For cytokine-refractory pts, the probability of PR increased as exposure to SU or TD increased. The odds-ratio suggested a 2.6-fold increase in PR frequency for each unit increase in AUCss. High SU and TD AUCss were also associated with a trend toward longer TTP and OS. A tumor growth dynamics model was used to describe changes in tumor volume as a function of AUCss for both cytokine-refractory and treatment-naive pts treated with SU. Clinical trial simulations based on this model and assuming perfect pt compliance predicted 62% of pts would achieve a PR with SU 50 mg/day.
Conclusions: For SU-treated pts with advanced mRCC, the probability of PR was significantly correlated with SU and TD AUCss. Elevated exposure was also associated with longer TTP and OS. A tumor growth dynamics model suggested that increased exposure to SU was associated with clinical benefit for pts with either cytokine-refractory or treatment-naive mRCC.

4506 ORAL

A large open-label, non-comparative, phase III study of the multi-targeted kinase inhibitor sorafenib in European patients with advanced renal cell carcinoma

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Background: A phase III trial showed that sorafenib (400 mg twice daily) doubled PFS and produced a 39% improvement (non-significant) in overall survival relative to placebo in previously treated patients with clear cell renal cell carcinoma (RCC). The objectives of the present trial were to make sorafenib available to European patients until regulatory approval and collect safety and efficacy data from a large and unselected study population.
Methods: This non-randomised, open-label study included male and female patients, ⩾18 years of age, with an ECOG PS 0–2 and a life expectancy >2 months. Patients had to be unsuitable for, or have failed, prior cytokine therapy. Controlled, asymptomatic brain metastases were allowed. Patients received continuous therapy with sorafenib 400 mg twice daily until disease progression, intolerable toxicity, or withdrawal of consent. Dose increases were not permitted. Recruitment was planned to continue until regulatory approval of sorafenib for advanced RCC. Study assessments were conducted at baseline and then monthly. Adverse events were graded according to NCI CTCAE v3.0 criteria. Tumour assessment and radiological evaluation were conducted within 28 days prior to the start of sorafenib therapy, and then according to local standards of care, but at least every 3 months.
Results: Over 1,150 patients were recruited in 11 European countries. Approximately 75% of patients were male. Median age at enrolment was 62 years. At baseline, ECOG PS = 0 in 38%, 1 in 45% and 2 in 17% of patients; approximately 73% of patients had tumour lesions in the lungs, 32% in bone, 32% in lymph nodes, 27% in the liver and 23% in the kidneys. Approximately 10% had not had the primary tumour resected. Approximately 24% had no prior therapy and were included because they were unsuitable for cytokine treatment. Tumour histology included clear cell (78%), papillary (11%) and chromophobe (3%). Sarcomatoid features were noted in tumour samples from 6% of the patients. At a median follow up of >10 months, approximately 40% of the patients remained on study drug. In addition to the efficacy and safety data for the study as a whole, subgroup analyses will be performed for prior treatment, performance status, tumour histology and location of metastases.

4507 ORAL

Axitinib (AG-013736; AG) in patients (pts) with metastatic clear cell renal cell cancer (RCC) refractory to sorafenib

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Background: Sunitinib and sorafenib, receptor tyrosine kinase inhibitors (TKIs) of VEGF and PDGF receptors (VEGFR, PDGFR), are FDA-approved treatments for advanced RCC. AG is a potent inhibitor of VEGFR 1, 2 & 3 and showed substantial efficacy in a previous phase II study in pts with cytokine refractory RCC (Rini et al., ASCO 2005). The activity of AG in metastatic RCC patients refractory to prior TKI therapy is of clinical interest.
Methods: Pts with sorafenib-refractory metastatic RCC were enrolled in this multicenter, open-label, phase II study. Eligibility criteria included measurable disease, ECOG performance status of 0 or 1, controlled CNS metastases (if present) and adequate organ function. All pts received a starting dose of AG 5 mg orally BID, titrated according to tolerance. The primary endpoint was RECIST-defined objective response (OR) with a null hypothesis of OR ⩽8% versus ⩾20% under the alternative hypothesis. Pts underwent radiographic staging at baseline and every 8 weeks and were treated until progressive disease or unacceptable toxicity.
Results: All planned 62 pts have been enrolled. Median age of pts was 60 years (range 35–77); 42 pts (68%) were male; 60 pts (97%) had prior nephrectomy. All pts had received prior sorafenib and 14 pts also received prior sunitinib. Median final AG dose was 5 mg (range, 2–10 mg). Partial response (PR) was observed in 9/62 evaluable pts (14%; 95% CI: 7–26%), stable disease in 23 pts (37%), and 15 pts (24%) experienced progressive disease. 51% of patients overall experienced tumor shrinkage. With a median follow-up of 7.4 months (95% CI: 4.7–8.7 months), the median progression-free survival (PFS) was not reached, but preliminary analysis indicates overall median PFS > 7.7 months. One of 14 patients with prior sorafenib and sunitinib treatment had a PR, with median PFS > 6.2 months in this sub-group. Grade 3 and 4 treatment-related adverse events included fatigue (13%), hypertension (11%), hand–foot syndrome (11%), diarrhea (5%) and dyspnea (5%). Overall, 22 pts remain on study.
Conclusions: AG has substantial antitumor activity in pts with sorafenib-refractory metastatic RCC. Toxicity is as expected with a VEGFR TKI and generally manageable.