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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.

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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.

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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