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A phase I clinical trial of the matrix metalloproteinase inhibitor, marimastat, administered concurrently with carboplatin, to patients with relapsed ovarian cancer

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Objectives of Study: The aim of this phase 1b study was to define the safety and tolerability of escalating doses of marimastat in combination with carboplatin.

Methods and Patients: Patients with histologically-proven epithelial ovarian cancer who have previously responded to a platinum-based chemotherapy have been recruited. Marimastat dose levels studied were 2, 5, 10, 15 or 20 mg bd po with a minimum of 3 patients per dose group.

Results: 16 evaluable patients have received a total of 64 cycles of chemotherapy. Eight patients have completed the 6 cycles of carboplatin (AUC 6; 21 day intervals). Seven patients reported marimastat-related musculoskeletal toxicity during the carboplatin course. In one of the patients the severity was such that activity was restricted and in one other patient an interruption in marimastat therapy was necessary. There was no evident difference in musculoskeletal side effects at different doses. All adverse events were graded according to the NCI common toxicity criteria. No grade 4 toxicities have been reported. Grade 3 toxicities reported include thrombocytopenia (6 reports), neutropenia (1 report), vomiting (1 report) and lethargy (1 report). All other toxicity was mild and consistent with administration of carboplatin alone. Preliminary response data using serological criteria (Rustin et al., 1996) and/or radiological criteria suggests a response in 4 of the 8 completed patients.

Conclusion: This is the first study involving marimastat in combination with carboplatin in ovarian cancer. From the data obtained to date, marimastat does not appear to increase the incidence or severity of chemotherapy-related adverse events. Patient recruitment is continuing and updated safety and response data on over 20 patients will be presented. The combination of marimastat and carboplatin appeares to be well-tolerated and justifies a phase II, randomised, placebo-controlled study.

1112 POSTER*

Pharmacokinetics and oral bioavailability of 9-amino-camptothecin PEG1000 capsules

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Purpose: Preclinical studies indicated enhanced antineoplastic activity of 9-aminocamptothecin (9AC) when administered as a chronic treatment. In view of this observation, the pharmacokinetics (PK) and oral bioavailability (F) of 9AC PEG1000 capsules were evaluated in patients with solid tumors.

Methods: 9 Patients with histologic proof of malignant solid tumor (median age: 60; median ECOG PS: 1; 4 M/5 F) were randomized to receive either 1.5 mg/m^2 of 9AC p.o. on day 1 and 1.0 mg/m^2 of 9AC i.v. on day 8 or vice versa. Serial plasma samples were taken upto 55 h after dosing, and analyzed for the presence of 9AC lactone and carboxylate forms by RP-HPLC.

Results: Interconversion of the lactone and carboxylate forms rapidly reached an *in vivo* equilibrium, with the active lactone accounting for <10% of total drug at steady state. 9AC lactone demonstrated rapid oral absorption, with peak levels at 1.2 h and a mean k_a of 2.9 h^{-1}. Elimination half-lifes were not significantly different between administration routes for both drug forms. The overall F revealed moderate interpatient variation, and ranged between 28.3–69.3%, indicating significant systemic exposure to the drug.

Conclusion: Compared to other camptothecin analogs, *viz.* topotecan and GG211, 9AC has a higher F which may be an advantage with potential pharmacodynamic (PD) importance. At present, a phase I study with oral 9AC is in progress to assess the PK/PD and its clinical utility.

1113 POSTER*

Phase I and pharmacokinetic study of Xeloda™ (capecitabine) in combination with docetaxel

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Introduction: Xeloda™ is a rationally designed oral tumour-activated and tumour selective fluoropyrimidine carbamate with proven activity in colorectal and breast cancers. As Xeloda™ and docetaxel have different mechanisms of action and non-overlapping toxicities, this study was designed to evaluate the MTD, safety profile and pharmacokinetics (PK) of the combination.

Materials and Methods: Docetaxel was administered d1 of a 3 wk cycle (with co-meds), with Xeloda™ on d1–14. 16 patients (8 M, 8 F), median age 58 (range 34–74) and KPS ≥ 70 with tumours (6 colorectal, 3 ACUP, 2 breast, 1 each of NSCLC, oesphageal, melanoma, bladder and adenocystic carcinoma) refractory/resistant to conventional chemotherapy have received 56 cycles of this combination in 3 cohorts. Co 1, 75 mg/m^2 docetaxel (4 pts), Co 2, 85 mg/m^2 docetaxel (6 pts) and Co 3, 100 mg/m^2 docetaxel (6 pts), each with Xeloda™ 825 mg/m^2 b.i.d.

Results: 1 pt in Co 2 experienced CTC gd III mucositis. 1 DLT (neutropenic fever) has been seen in 1 pt in Co 3. Gd IV uncomplicated neutropenia (afebrile and <7 d duration) was seen in all cohorts. Other (gd II) toxicities included diarrhoea and mucositis, hand-foot syndrome with onycholysis, skin toxicity, nausea, fatigue and conjunctivitis. 2 pts have completed 6 cycles, 2 pts were delayed due to skin/GI toxicity, 1 pt required dose reduction (Co 1) of both drugs.

Pharmacokinetics: To assess docetaxel PK, blood samples were taken on d1 (with Xeloda™) and d22 (without Xeloda™). $AUC_{0-\infty}$ values averaged 2.53, 3.72, and 4.38 μg/ml for 75, 85 and 100 mg/m^2 docetaxel respectively, consistent with linear PK. Mean clearances of 28.2 ± 7.9 (d1) and 27.2 ± 7.8 L/h/m^2 (d22) indicate no effect of Xeloda™ on the PK of docetaxel.

Responses: 2 PRs (breast cancer pts in Co 1 and Co 2) have been observed.

Conclusion: The next phase is escalation of Xeloda™ to 1000 mg/m^2 b.i.d plus docetaxel 100 mg/m^2, doses which represent 80% and 100% respectively of the recommended single agent doses.

1114 POSTER*

Phase I study of the biodistribution, pharmacokinetics and immunogenicity of ^{111}In-hCTMO1 (CDP671) ± predosing with unlabelled hCTMO1 in patients (pts) with lung cancer

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^{111}In-hCTMO1 is an engineered human radiolabelled monoclonal antibody (Ab) to polymorphic epithelial mucin (PEM), a glycoprotein over-expressed on the surface of SCLC & NSCLC cells. This study was designed to confirm previous safety data and to study biodistribution of ^{111}In-hCTMO1 in pts with lung cancer. In part 1, pts received an IV infusion of 1 mg/kg ^{111}In-hCTMO1. In part 2, following a dose of 1 mg/kg unlabelled Ab (to saturate free PEM binding and reduce liver uptake of labelled Ab) pts received 0.1 mg/kg ^{111}In-hCTMO1. Toxicity was recorded using WHO criteria. Plasma levels of hCTMO1 were measured. Immunogenicity was studied by measurement of specific IgG anti IgM titres. Biodistribution was measured by whole body planar imaging. 21 pts received Ab, 8 after predosing. Median age 66 (44–76); M 18, F 3; SCLC 3, NSCLC 18. Infusions were well tolerated, 1 pt had a rigor after ^{111}In-hCTMO1. Mean $t_{1/2}$ was 44 hours. Biodistribution (% total dose/organ) was:

	Liver	Kidney	Tumour image seen
Without pre-dosing	23.8	1.0	9/12 evaluable pts
With pre-dosing	17.7	1.8	4/7 evaluable pts

Pre-dosing with cold antibody reduced liver uptake in the split dosing part of the study. In a forthcoming therapy study, hCTMO1 will be used conjugated with a cytotoxic drug.