no shift of pharmacokinetic parameters from week 1 to week 6 rendering dose adjustment under therapy unnecessary.

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Pharmacokinetics and metabolism of fulvestrant after oral, intravenous and intramuscular administration in healthy volunteers

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Background: Fulvestrant (Faslodex™) is an estrogen receptor (ER) antagonist indicated for the treatment of hormone receptor-positive advanced breast cancer in postmenopausal women progressing on prior anti-estrogen therapy.

Materials and methods: In separate studies, male or postmenopausal female volunteers received [^{14}C]-fulvestrant either as a single oral (po) dose of 400 mg (n=6), a single intravenous (iv) infusion of 10 mg (co-administered with plasma; n=8), or a single intramuscular (im) injection of 18 mg (n=7). The pharmacokinetics of total radioactivity and unchanged drug were assessed for up to14 d. Metabolites in plasma and excreta were investigated.

Results: Following iv infusion of fulvestrant (C_{inf} 121 ng/ml), there was rapid distribution leading to low levels of fulvestrant in plasma at 2 h post-infusion (approx. gmeans, 16.0 and 13.0 ng/ml in male and female volunteers, respectively). The concentration/time profiles of fulvestrant in males and females were very similar up to 24 h after infusion (gmean $AUC_{(0-t)}$, 223.0 and 197.0 ng.h/ml, respectively). After po administration, bioavailability was very low with minimal fulvestrant plasma concentrations (median T_{max} 0.75 h, gmean C_{max}, 9.0 ng/ml). Total exposure to fulvestrant, as determined by gmean $AUC_{(0-t)}$, was 15.2 ng.h/ml. Following im administration, absorption of fulvestrant was slow (T_{max} 8-24 h, gmean C_{max}, 14.6 and 13.3 ng/ml in male and female volunteers, respectively) and prolonged (apparent $t_{1/2}$ λ z 26-30 h) with detectable levels remaining 7 days post dose. Total exposure to fulvestrant, as determined by gmean $AUC_{(0-t)}$, was 555.0 and 646.0 ng.h/ml in male and female volunteers, respectively. Differences between the concentration of fulvestrant in plasma and circulating total radioactivity, particularly after oral administration, suggested rapid metabolism of the parent compound. Total ^{14}C was excreted slowly, almost entirely in the feces. In each case $\geq$ 90% of the dose was recovered, although rate of excretion varied with route of administration in the order po (7-10 d)>iv>im (21 d).

Conclusion: These data suggest that im injection is an appropriate method for administration of fulvestrant.

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Phase I combination study of oral vinorelbine (VRL) and oral cyclophosphamide (CTX) in patients with metastatic breast cancer (MBC)

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Background: VRL and CTX have proven activity in MBC and are orally available. Both have a cytochrome P450-mediated metabolism which justifies the search for drug-drug interaction.

Material and methods: This phase I study is evaluating oral VRL, given on days 1 and 8, and oral CTX from days 2 to 15, every 3 weeks, in patients (pts) failing one line of chemotherapy for MBC. On days 1, 7 and 8 the pharmacokinetics (PK) of both drugs are assessed to explore drug interactions. VRL, deacetylvinorelbine (DVRL), CTX and phosphoramide mustard (PM) are assayed. Dose limiting toxicities (DLTs) are evaluated during the first cycle (cy) and defined as grade (gr) 4 neutropenia for 7 days, gr 3 thrombocytopenia, febrile neutropenia, neutropenic infection, one week toxicity-related delay in starting cy 2, any delay in the administration of VRL or CTX due to toxicity, any gr 3/4 non-haematological toxicity except asthenia and inadequately treated nausea/vomiting.

Results: To date 18 pts have been included at 3 dose levels (DL) of VRL/CTX: DL1 (60/80 mg/m*), DL-1 (50/80 mg/m*) and DL-2 (50/100 mg/m*). Age ranged from 39 to 74 years. Metastatic sites were liver, skin, pulmonary, bone, or local recurrences. Four out of 5 pts at DL1 experienced DLT, consisting in a one-week delay of cy 2 due to neutropenia. At DL-1 none of the 6 enrolled pts developed DLT. Only one gr 3 diarrhoea appeared at DL-2. Main non-haematological toxicities at these 3 DLs during 46 cy were: gr 1-2 nausea (16 pts, 37 cy), vomiting (11 pts, 15 cy), fatigue (6 pts, 19 cy), diarrhoea (11 pts, 18 cy, including gr 3 once in 2 pts), paresthesia in 2 pts for 8 cy with one gr 3 episode once, and gr 1 alopecia in 6 pts for 16 cy.

So far no responses were noted, but 4 out of 12 evaluable patients showed disease stabilisation. Preliminary PK analysis did not reveal drug-drug interaction between VRL and CTX (DL1/DL-1). The AUCs of VRL on day 1 (without concomitant CTX) and day 8 (with CTX) were not significantly different. DVRL blood concentrations were low and remained within the same range on days 1 and 8. The AUCs of CTX and PM were comparable between days 7 and 8. Exposure to the drugs was similar in all pts, and there was no difference between pts who developed DLTs and the others.

Conclusions: The combination of oral VRL and oral CTX is feasible. No drug-drug interaction between both drugs has been detected up to now. DL-2 has an acceptable toxicity. A 4-week regimen is being studied.

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Phase 1 study of CT-2103/carboplatin in patients with solid tumors

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Background: CT-2103 (XYOTAX™) is a tumor-targeted taxane designed to concentrate selectively in tumors, which potentially may result in superior efficacy, safety and symptom control compared with standard taxane therapy. Conjugation of paclitaxel to poly-L-glutamate enhances aqueous solubility and eliminates the need for Cremophor, resulting in a convenient 10-min infusion. This phase 1 study is designed to determine the maximum tolerated dose (MTD) of CT-2103 in combination with carboplatin (Cb) in patients (pts) with refractory solid tumors.

Materials and methods: CT-2103 is administered in escalating doses per cohort of 3 pts every 21 days as a 10-min IV infusion followed by Cb 30-min IV infusion. Toxicity and response are assessed according to NCI CTC and RECIST. Twenty-two pts have been treated.

Results: Data is available for 17 pts: non small cell lung cancer (4 pts), esophageal adenocarcinoma (1), ovarian cancer (2), breast cancer (1), thyroid (2), squamous cell carcinoma of the head and neck (2), pancreatic (2), colon (1), renal cell (2). Dose levels included: CT-2103 175 mg/m^2 / Cb AUC 5 (3 pts); CT-2103 210 mg/m^2 / Cb AUC 5 (3); and CT-2103 210 mg/m^2/Cb AUC 6 (7); CT-2103 225 mg/m^2/Cb AUC 6 (6); CT-2103 250 mg/m^2/Cb AUC 6 (3). Pts received 1-9 cycles. Disease assessments available for 12 pts. Nine of 12 pts (75%) achieved disease control (partial response [PR], 2 pt + stable disease [SD] for > 10 weeks, 7 pts). Both pts with ovarian cancer had a PR. One of these pts had a 60% reduction in tumor size, completed 9 cycles (discontinued treatment due to grade 3 neuropathy), a decrease in CA-125 from 11,724 to 16 ng/mL. The 2nd ovarian pt has a 75% reduction in tumor size, has completed 6 cycles, and is still on study. Clinically significant drug-related grade 3/4 toxicities were neutropenia (7 pts), thrombocytopenia (6) and febrile neutropenia (1). This toxicity profile is consistent with that of Cb. CT-2103/Cb is well tolerated. The cycle 1 MTD in heavily pretreated patients is 225 mg/m^2/AUC6. The predominant dose-limiting toxicities were neutropenia and neuropathy.

Conclusions: Evidence to date demonstrates anticancer activity. Based on these results and the safety/activity seen in single-agent studies, the Gynecologic Oncology Group is developing a randomized phase 3 trial comparing CT-2103/Cb with paclitaxel/Cb in pts with newly diagnosed, advanced ovarian cancer.

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A phase I and pharmacokinetic study of BMS-247550 in combination with carboplatin in advanced solid malignancies

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Background: BMS-247550 (Epo-B) is a semi-synthetic analogue of epothilone B which has shown antitumour activity in phase I trials. Here we report the final data from a phase I trial of Epo-B and carboplatin in patients with advanced solid malignancies.