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.

Materials and Methods: Epo-B was given as a 60-min infusion, 30 mins prior to a 30-min carboplatin infusion on day 1 q 21 days. Pharmacokinetic samples were taken on the first cycle. 25 patients were treated on this schedule at 4 dose levels (Epo-B doses of 30 + 40 mg/m2 + carboplatin AUC 5 + 6). Dose limiting toxicity (DLT) occurred at Epo-B 40mg/m2 + carboplatin AUC6 on this schedule with myelosuppression as the major toxicity. A further 14 patients were recruited onto an amended schedule with Epo-B doses split on days 1 and 8 q 21 days, carboplatin being given on day 1. DLT on this schedule was at carboplatin AUC 6 with Epo-B 25 mg/m2 d1 + 8. The preceding dose level (carboplatin AUC 6 + Epo-B 20 mg/m2 d1 + 8) was expanded and a total of 8 patients were treated.

Results: 39 patients (18 male/19 female/2 missing) were treated over 7 dose levels; 92% were WHO performance status 0 or 1 at entry; mean age 55 years (range 31-74). 56% patients had received prior chemotherapy (3 or fewer regimens) and 51% prior radiotherapy. The major toxicities were myelosuppression, myalgia and peripheral neuropathy. 73% of patients developed CTC grade 3/4 neutropenia during the course of their treatment, this was generally short lived and well tolerated, febrile neutropenia being reported in only 15% of cycles. 14% of patients developed grade 3/4 thrombocytopenia, despite using clinically active doses of carboplatin. Cumulative sensory neuropathy was observed, CTC grade 2 occurring in 23% of all patients and grade 3 in 18%. 11 patients withdrew from the study because of study drug toxicity, peripheral neuropathy was reported in all these patients. The regimen was active: partial responses were reported in 5 patients (2 breast, neuro-endocrine, unknown primary carcinomas and mesothelioma), 48% of patients showed disease stabilisation for more than 2 months.

Analysis of Epo-B plasma levels show that Cmax and AUC increase with dose, the volume of distribution is high and half-life is ~ 30 hours.

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Phase I studies with CERA (Continuous Erythropoiesis Receptor Activator), an innovative erythropoietic agent

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Background: CERA, an innovative erythropoietic agent with an extended serum half-life, has demonstrated a greater erythropoietic response than epoetin beta in animal models. Phase I studies were employed to investigate the pharmacokinetic and pharmacodynamic properties of CERA.

Materials and methods: Two single ascending dose (SAD) and two multiple ascending dose (MAD) studies were conducted in healthy volunteers (18-60 years). In the SAD studies, subjects were randomised to receive 1) single intravenous (IV) doses of CERA 0.4, 0.8, 1.6 or 3.2 μg/kg or placebo (n=38), or 2) single subcutaneous (SC) doses of CERA 0.1, 0.2, 0.4, 0.8, 1.6, 2.4 or 3.2 μg/kg or placebo (n=70). In the MAD studies, subjects were randomised to receive CERA 0.4, 0.8, 1.6 or 3.2 μ g/kg or placebo as 1) three doses IV at 3-week intervals (n=61), or 2) four doses SC at 2-week intervals (n=48).

Results: In the SAD studies, a potent dose-dependent erythropoietic response was observed with both IV and SC administration. Response to CERA was rapid; peak increases in reticulocytes occurred within 10 days and returned to baseline after 20 days. Mean reticulocyte response to CERA 0.4 μg/kg IV was increased by 119% vs baseline, suggesting that the minimum threshold for stimulation of erythropoiesis was less than the lowest dose used in the study. The highest study dose of 3.2 μg/kg IV produced a mean reticulocyte increase of 334%. The minimum threshold dose for stimulation of erythropoiesis after SC administration of CERA was 0.8 μg/kg, with a mean increase in reticulocytes of 262% at the highest dose. Soluble transferrin receptor levels also increased in a dose-dependent manner after both IV or SC injection, while serum ferritin and serum iron levels decreased. In the MAD studies, dose-dependent increases in reticulocyte response were also seen. Peak increases in reticulocytes occurred within 7 and 10 days for IV and SC dosing, respectively, and returned to baseline after 20 days. Repeated dosing did not appear to have a clinically relevant effect on the pharmacokinetics of CERA. CERA was generally well tolerated following both routes of administration in all studies.

Conclusions: In phase I studies, CERA demonstrated potent, prolonged dose-dependent erythropoietic activity when administered both IV and SC. Phase II studies of CERA administered in several extended dosing intervals to patients with cancer are ongoing.

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A phase I and pharmacokinetic study of oral administration of SU5416 in patients with advanced solid tumors.

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SU5416 is a small molecule inhibitor of VEGF-mediated signaling through Flk-1/KDR, a receptor tyrosine kinase expressed on endothelial cells. SU5416 suppresses tumor growth when administered intraperitoneally (25 mg/kg/day) or orally (100 mg/kg/day) in xenograft models. We conducted a study to assess the safety and bioavailability of oral SU5416 in patients with advanced malignancies. The oral formulation consisted of a Nanocrystal Colloidal Dispersion (NCD), the IV administration was a Cremophor-based liquid formulation. The recommended IV dose is 145 mg/m^2. Fourteen patients (8M/6F;median age 51) with advanced and extensively pretreated solid organ tumors were enrolled. All patients received a single dose of 75mg IV on Day 1 and oral SU5416 under one of four different treatment schedules (single, weekly, twice weekly, daily) starting on Day 8.

Thirteen patients (93%) experienced treatment-related adverse events; the most common side effects were vomiting (43%), nausea, injection site pain (29%), abdominal pain, injection site burning and pain NOS (21%). Four patients (29%) experienced adverse events with intensity severe or greater; one patient died during the study due to fatal asphyxia. No clinically significant laboratory abnormalities were observed.

Following IV administration of SU5416, peak SU5416 concentrations were generally observed 15 minutes after the beginning of the infusion. Thereafter, the concentration declined with a mean half-life of 43.5 minutes. The IV pharmacokinetics (PK) was very similar to those observed in previous studies. Oral SU5416 revealed generally lower plasma concentrations during Days 15, 21/22 as compared to Day 8. By Day 15, a number of patients SU5416 concentrations were below the level of detection. Mean concentrations (C) of oral SU5416 were approximately 12-fold lower than those observed following IV infusion. C following a single oral dose of NCD SU5416 were seen at 67 minutes. The mean bioavailability for a single dose and weekly, twice weekly and daily dosing of NCD SU5416 on Day 8 were 18.9%, 20.6%, 20.7% and 36.8%, respectively. However, there was a large interpatient variability ranging from 1.3% to 68%.

Further development of oral NCD SU5416 was not pursued, because it was unlikely that effective plasma concentrations could be achieved with it. This could most likely be due to clearance induction of SU5416. The study is part of the basis for the decision not to pursue the development of oral SU5416. It confirmed the difficulty to achieve constant plasma concentrations with this drug. The study revealed important information for the future development of this class of compounds.

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A phase I study to determine the safety and pharmacokinetics of intravenous administration of SB715992 on a once weekly for three consecutive weeks schedule in patients with refractory solid tumors.

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Mitotic kinesins play exclusive and essential roles in assembly and function of the mitotic spindle and represent novel targets for development of therapeutics against cancer. SB-715992 is the first mitotic KSP inhibitor to enter clinical trials. SB-715992 is a unique and potent inhibitor of KSP (HsEg5), a mitotic kinesin that is essential for assembly of a functional mitotic spindle and is preferentially overexpressed in malignant cells. SB-715992 is 70,000-fold more selective for KSP than other members of the kinesin family, and disrupts the assembly of functional mitotic spindles, thereby causing cell cycle arrest in mitosis and subsequent cell death. Since KSP functions exclusively in mitosis and is not expressed in terminally differentiated neurons, SB-715992 is not expected to produce neurotoxicity. However, these preclinical findings need to be confirmed in clinical studies. In preclinical efficacy studies in a broad range of human tumor xenografts, doses of SB-715992 substantially below the maximum tolerated dose produce prominent growth inhibition, tumor regression, and cures. In the current study, toxicity, feasibility and pharmacology of SB-715992 administered as an IV infusion once a week for 3 consecutive weeks is being evaluated in pts with advanced solid malignancies. At least 2 pts are being treated at each dose level, and doses are escalated from the