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Phase I study of an all-oral combination of vinorelbine (VRL) and cyclophosphamide (Ctx) as second line treatment in patients with metastatic breast cancer (MBC)

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Vb is a semi-synthetic vinca-alkaloid that binds to specific sites on tubulin and prevents their polymerisation and assembly. The agent has proven activity in MBC. Recently an oral formulation became available. We perform a phase I study combining oral VRL with oral Ctx, in patients failing one line of chemotherapy for metastatic breast cancer. VRL is given at escalating doses, starting at 60 mg/m^2 given at day 1 and day 8 of a three-week cycle. Ctx is scheduled at escalating doses, starting at 80 mg/m^2 from day 2 till day 15. Day 1, 7 and 8 pharmacokinetics of both drugs allows assessment of potential interaction. VRL, its main metabolite deacetylvinorelbine (DVRL), Ctx and phosphoramide mustard (PM) are assayed. DLT is defined as grade 4 neutropenia for 7 days or more, grade 3 thrombocytopenia, febrile neutropenia, any delay in the administration of VRL or Ctx due to toxicity, any grade $>$ 2 non-hematological toxicity except alopecia, asthenia, and inadequately treated nausea/vomiting. Currently 11 patients, age 38-74, median WHO performance score 1, range 0-2. have been entered. Metastatic sites are liver, skin, pulmonary, bone, or local recurrence. Four of 5 patients treated at dose level 1 (Vb 60 mg/m^2 day 1 + 8, Ctx 80 mg/m^2 day 2 - 15) experienced DLT, involving delay of administration due to neutropenia (3 pts.), and neutropenic fever (1 pt.). At the lower dose level (VRL 50 mg/m^2, Ctx 80 mg/m^2) 6 patients were enrolled. Until now no DLT was recorded at this dose level. Further non-haematological toxicities observed at both dose levels were nausea grade 1-2 in 7 pts. (63%); fatigue grade 1-2 in 6 pts. (54%) One patient with extensive liver metastasis had an increase of ASAT, grade 3 (grade 2 at baseline), probably due to disease progression. So far no responses were noted, but until now 5 out of 11 patients showed disease stabilisation. Preliminary pharmacokinetic analysis revealed no drug-drug interaction between VRL and Ctx. The AUC's of VRL at day 1 (without concomitant treatment of Ctx) and day 8 were identical. DVRL blood concentrations were low and remained within the same range on day 1 and 8. The AUC's of Ctx and PM were comparable between day 7 and 8. Exposure to the drugs was similar in all patients, and there were no differences between patients who developed DLT and the others.
Conclusion: The combination of oral VRL and oral Ctx is feasible. So far no drug-drug interaction between both drugs has been observed.

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Phase I and pharmacokinetic study of BMS-247550 in combination with carboplatin in patients with advanced malignancies

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BMS-247550 is a semi-synthetic analogue of the natural product epothilone B which promotes microtubule stabilisation. Preclinical studies demonstrate broad spectrum antitumour activity, including in paclitaxel insensitive cell lines. The combination of paclitaxel and carboplatin has been successfully used in a number of cancer types; this study was designed to investigate the feasibility and safety of the analogous combination, BMS-247550 with carboplatin. BMS-247550 followed by carboplatin was given intravenously every 3 weeks to patients with advanced solid tumours treated with 2 or fewer prior chemotherapy regimens. Pharmacokinetics of both drugs were measured on the first course. 25 patients were treated at 4 dose levels - combining BMS-247550 30 or 40 mg/m^2 with Carboplatin AUC 5 or 6 (Calvert Formula). A total of 91 courses were given. Transient CTC grade 4 neutropaenia was noted at all dose levels and was dose limiting at 40mg/m^2/AUC6 (2/2 patients with complicated grade 4 neutropaenia). The major non-haematological toxicities were myalgia on day 4 and cumulative peripheral neuropathy. 7 patients withdrew from the trial because of neurotoxicity, grade 2/3 sensory neuropathy after at least 3 courses but grade 3 motor neuropathy in one patient on the first course. The regimen was active with 3/25 confirmed partial responses (breast, neuroendocrine and unknown primary carcinomas) and 12 patients having disease stabilisation and clinical benefit from treatment. Maximum tolerated dose was BMS-247550 40mg/m^2 with carboplatin AUC 5. Data from single agent BMS-247550 studies suggested that d1 and 8 dosing might be better tolerated and permit higher dose intensity. An amended regimen of Carboplatin d1 and BMS-247550 d1 + 8 is being investigated and patients are being recruited at a dose of AUC 5/20mg/m^2 $\times$2 with evidence of less myelosuppression seen on this schedule. The activity and safety of the combination of BMS-247550 and carboplatin in this study justify further development of the combination. Updated results from the day 1 day 8 schedule will be presented including pharmacokinetic endpoints.

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A Phase I trial of ABT-751, a novel microtubulin inhibitor

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ABT-751 is a novel oral antimitotic agent that binds to the colchicine site on tubulin and inhibits polymerization of microtubules. Disruption of new microtubules leads to arrest in the cell division cycle and induction of apoptosis. There are currently no colchicine-site agents approved for cancer chemotherapy. ABT-751 has demonstrated anti-tumor activity against a variety of syngeneic and human xenograft tumor models including colon, lung, stomach, breast, and nasopharyngeal cancer models, and is also active *in vivo* against vincristine-, cisplatin- and 5-fluorouracil-resistant cells. ABT-751 is not a multiple drug resistance (MDR) substrate. A phase I trial of orally administered ABT-751 given daily $\times$ 7 every 3 weeks was instituted to determine the dose limiting toxicity (DLT), maximum tolerated dose (MTD) and pharmacokinetics on both a qd and bid schedule. A total of 15 patients have been studied to date. Doses of 200 and 250 mg po qd $\times$ 7 were found to be tolerable. DLT was seen in 2/6 patients (neuropathy and ileus) at the qd dose of 300 mg/d. One of 3 patients studied to date at the 125 mg po bid $\times$ 7d dose developed a supraventricular arrhythmia. This occurred 17 days after ABT dosing and is thought unlikely to be drug related.

Table 1: Toxicity

Dose Level	Pts Studied	Maximum Cycle 1 Toxicity (# of pts)			
		<Gd1	Gd2	Gd3	Gd4
200 mg qd	3	1	2	–	–
250 mg qd	3	2	1	–	–
300 mg qd	6	1	3	2	–
125 mg bid	3	2	–	1	–

Grade 2 toxicities noted to date include constipation, fatigue, nausea, vomiting, myalgias, and anemia. Myelosuppression has not been noted. Pharmacokinetic studies were performed on day 7 of therapy.

Table 2: Pharmacokinetics on Day 7

Dose	Cmax	Cmin	AUC 0-24
300 mg (N=4)	14V2 :g/ml	0.5V0.2 :g/ml	51V21 :g * hr/ml
200 mg (N=3)	7V2 :g/ml	0.3V1 :g/ml	42V2 :g * hr/ml

Tmax averaged 3 hrs and half-life 4 hrs. Average duration of therapy has been 9.7 weeks (range 1-19 wks). No objective responses have been noted to date.
Conclusions: 1. DLT of ABT-751 on a qd $\times$7 appears to be neuropathy (peripheral and ileus). 2. The MTD on a qd $\times$ 7 schedule is 250 mg/d. 3. ABT-751 is rapidly absorbed and eliminated; there is no evidence of drug accumulation with multiple dosing. 4. Accrual is continuing on the bid schedule as the MTD has not yet been defined.