534 POSTER

Ixabepilone, a novel tubulin interacting agent, given every other week in combination with irinotecan in patients with advanced malignancies: a phase i and pharmacokinetic study

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Background: Ixabepilone, a semisynthetic novel derivative of Epothilone B, is active against paclitaxel resistant and sensitive tumors. Myelosuppression and neuropathy were dose limiting in single agent phase **I**. This combination phase **I** study aims to establish the Maximal Tolerated Dose (MTD) of Ixabepilone with Irinotecan, characterize dose limiting toxicities (DLTs), the safety profile of the combination and describe antitumor activity.
Methods: Ixabepilone and Irinotecan were given intravenously, on days 1 and 15 of a 28-day cycle, to patients (pts) with advanced solid tumors previously treated with up to 3 prior chemotherapy regimens. Plasma levels of both drugs were measured on the first course.
Results: Thirty pts (median age: 52, ranging 26–71; male/female: 17/13; PS: 0–1) including 29 pts evaluable for toxicity received a total of 116 cycles of Ixabepilone/Irinotecan. Tumor types consisted of lung (7 pts), gynecological (6 pts) gastrointestinal (8 pts), breast (2 pts), and others (7 pts) cancers. Median number of prior chemotherapy regimens was 2.

Dose level	Ixabepilone (mg/m^2)	Irinotecan (mg/m^2)	# patients	DLTs
0*	20	120	6	1/6 Gr3 Neutropenia
1	15	150	3	0/6
2	15	180	6	1/6 Febrile neutropenia
3	20	180	3	0/6
4	25	180	6	1/6 Febrile neutropenia
5	30	180	6	1/6 Gr3 Diarrhea

* 1 patient had G2 neutropenia at D14 which would be a DLT before the protocol was amended to allow dose escalation with up to grade 2 ANC at Day 15.

While a protocol defined MTD has not been reached, dose level (DL) 3 (Ixabepilone 20mg/irinotecan 180mg) is being expanded as a potential recommended phase **II** dose based on cumulative neuropathy at higher doses (Gr 3 neuropathy: 1 pt at DL 3, 3 pts at DL 4 and 2 pts at DL5). The combination has antitumour activity with 4 partial responses in pts with non-small cell lung cancer (2), small-cell lung cancer (1), and carcinoma of unknown primary (1).
Conclusion: Ixabepilone 20 mg irinotecan 180 mg on days 1 and 15 of a 28-day cycle is the potential recommend dose. Final assessment will be presented at the meeting.

535 POSTER

Phase I study of a new Halichondrin B analog, E7389, administered by 1-hour IV infusion every 21 days

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E7389 is a synthetic analog of the biologically active portion of Halichondrin B and is currently in clinical studies. It is a novel tubulin-binding agent that inhibits tubulin polymerization into functional microtubules. This Phase **I** study was designed to determine the MTD, safety and pharmacokinetics (PK) using a 1-hour IV infusion on Day One of a 21 day-cycle.
13 patients (pts) with advanced solid tumors were enrolled at 2 centers. Median age was 61 (30–72). All patients were PS 0/1. Tumor types were lung adenocarcinoma (3), renal cell (3), gall bladder (1), bladder (1), sarcoma (1), pancreas (1), NSCLC (1), endometrial (1), prostate (1). Prior treatments included at most two prior chemotherapies. Doses ranged from 0.25 to 4 mg/m2.
Three out of 3 pts developed DLT at 4 mg/m2. All had febrile neutropenia, accompanied by grade (Gr.) 2 mucositis in one. The first pt. at the next lower dose (2.8) experienced febrile neutropenia. A Gr. 3 neutropenia attributed to extensive prior radiation occurred in every cycle (6) in one pt. treated at 1 mg/m2. The other drug-related toxicities reported were Gr. 1/2 and included anorexia, fatigue, nausea, anemia and thrombocytopenia (Gr. 1), increased alkaline phosphatase, increased ALT and hyperkalemia. The median number of cycles received was 2 (1–6). No response has yet been observed but 4 pts. had SD for 4 cycles or more. Enrollment is continuing.
Preliminary pharmacokinetics (N=10) were best described by a two-compartment model, in which there was rapid distribution, slow clearance, and prolonged elimination with a small fraction (5–12%) excreted unchanged into the urine. Average V_{ss}, CL, and MRT ranged from 53.2 to 218.5 L, 1.4 to 4.4 L/hr, 28.1 to 50.1 hours at the dose levels observed. The C_{max} and AUC increased in a dose-dependent manner between 0.25 and 1 mg/m^2. Higher dose levels are being studied. The ratios of C_{max} to $C_{trough,96hr}$ ranging from 0.33% to 1.5% as well as the calculated accumulation factor of 1 for all 10 subjects indicated that despite the prolonged elimination phase, repeated dosing is unlikely to cause drug accumulation with the regimen studied.
Updated information will be provided at the meeting. Phase **II** studies will be started upon completion of Phase **I**.

536 POSTER

A Phase 1 study of Epothilone B analog BMS-247550 in combination with carboplatin in recurrent and/or refractory solid tumors

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Background: BMS-247550 is a semi-synthetic analog of the natural product epothilone B. BMS 247550 belongs to a novel class of non-taxane microtubule stabilizing agents obtained from the fermentation of a cellulose-degrading myxobacterium, *Sorangium cellulosum*.
Material and methods: BMS-247550 is administered by a 1-hour infusion on days 1, 8 and 15 of each 28 day cycle. Subjects received pretreatment with diphenhydramine, ranitidine and dexamethasone prior to each infusion. The starting BMS-247550 dose was 10 mg/m^2 with planned dose escalation in successive cohorts of 3–6 subjects. Carboplatin was administered on day 1 to achieve an AUC=6. Enrollment at the maximum tolerated dose (MTD) was expanded to allow collection of tumor biopsies in at least ten subjects to determine pretreatment expression of survivin.
Results: A total of 26 subjects have been enrolled onto this study. The maximum administered dose was 15 mg/m^2 of BMS-247550 in combination with carboplatin AUC=6. At this dose level two of five subjects experience dose-limiting hematologic toxicity, which halted dose-escalation. Enrollment was then started at a dose of BMS-247550 12.5 mg/m^2, which ultimately proved to be the maximum tolerated dose. Tumor biopsies were obtained in at least ten subjects at this dose level. The survivin protein levels ranged between 1.7 to 34.5 ng/mg of protein, as determined by an ELISA. In 5 of the 10 samples, where both protein and mRNA transcript levels (by QPCR) of survivin were determined, survivin/histone H3 mRNA copy ratio ranged between 0.01 to 0.52, which in each sample did not correlate with the survivin protein level.
Conclusions: The MTD of this regimen is 12.5 mg/m^2 of BMS247550 weekly $\times$ 3 in combination with Carboplatin AUC=6 when administered every 28 days.
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537 POSTER

Multidrug-resistant tumors treated with Epothilone B in combination with clinically relevant doses of ionizing radiation

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Background: Treatment with ionizing radiation (IR) in combination with microtubule inhibitors like taxanes represents a favourable radiochemotherapeutical approach against various tumor entities. However treatment with taxanes is often limited by taxane-related toxicities and furthermore taxanes are less effective in tumors overexpressing the P-glycoprotein efflux pump. EPO906, a novel microtubule inhibitor, retains full activity in multidrug-resistant tumor cells. Here we have investigated combined treatment of EPO906 with IR in vitro and in vivo against human, treatment-resistant adenocarcinoma cells.
Material and Methods: The effect of the combined treatment with IR and Epothilone B (EPO906, Novartis Oncology) or Paclitaxel was tested *in vitro* with the multi-drug-resistant (P-glycoprotein (PgP)-overexpressing) and