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Phase I and Pharmacokinetic Study of RPR116258A, a Novel Taxane Derivative, Administered Intravenously over 1 Hour Every 3 Weeks. *A. D. Goetz, L. J. Denis, E. K. Rowinsky, L. Ochoa, K. Molpus, B. Deblonde, D. Semiond, M. Besenval, A. W. Tolcher; Institute for Drug Development, San Antonio, TX; Aventis Pharma, Washington DC*

RPR116258A, a semisynthetic and potent taxane derivative, is a weak substrate for P-glycoprotein and able to cross the blood brain barrier. These features confer broad antitumor activity in tumor models, including mdr-1 cell lines. This clinical phase I study evaluates the safety and pharmacokinetic (PK) profile of RPR116258A administered as 1-hour infusion every 3 weeks in minimally-pretreated patients (pts) with advanced cancer. No prophylactic anti-emetics or treatment to prevent hypersensitivity reactions were permitted at cycle 1. Fourteen pts (9 males/5 females; median age 64 yrs [32–80]; median PS 0 [0–2]) have been enrolled and 49 treatment courses were evaluable at dose levels of 10 (3 pts), 15 (6 pts), 20 (3 pts) and 25 mg/m^2 (2 pts). The main toxicity was short-lasting neutropenia Gr 4 in one patient at 25mg/m^2 and Gr 3 diarrhea in patients at 15 (1 pt) and 25 mg/m^2 (1 pt) that was well controlled by loperamide. Minor Gr 1 or Gr 2 toxicities included diarrhea (3 pts), fatigue (3 pts), nausea (3 pts), vomiting (2 pts), neutropenia (5 pts), thrombocytopenia (1 pt), and neurosensory disorders Gr 1 (1 pt). Neither hypersensitivity reactions or fluid accumulation has been observed. Plasma samples were obtained up to 72 hrs post-infusion at cycles 1 and 2 and showed a three-phasic elimination profile. Preliminary mean (± SD) PK parameters indicated a high total body clearance (CL) of 30.5 (±11.7) L/h/m^2, a large volume of distribution (V_{ss}) of 1438 (±701) L/m^2 and a long terminal half-life of 55 (± 29) hours. Intrapatient variability of CL over 2 cycles was low (25%). One unconfirmed partial tumor response has been reported in a TCC bladder cancer patient and minor responses have been reported in patients with prostate cancer (1) and osteosarcoma (1). In conclusion, the novel taxane RPR116258A is well tolerated at the studied dose levels up to 25 mg/m^2. Preliminary PK results indicate a long terminal half-life justifying the intermittent dosing schedule every 3 weeks.

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Phase I Clinical and Pharmacokinetic (PK) Trial of the Novel Taxane BMS-184476 Administered as a 1-Hour IV Infusion in Combination with Cisplatin Every 21 Days. *M. L. Gallagher, J. P. Stevenson, W. Sun, D. Vaughn, S. M. Hahn, D. G. Haller, K. Hiller, C. Tarby, D. Sonnichsen, S. Nason, G. Gallant, P. J. O'Dwyer; University of Pennsylvania, Philadelphia, PA; Bristol-Myers Squibb, Princeton, NJ; University of Pennsylaniva, Philadelphia, PA*

BMS-184476 is a 7-methylthiomethyl ether derivative of paclitaxel that displays in vitro potency at nM concentrations against paclitaxel-resistant human tumor cell lines with MDR mediated by P-glycoprotein and altered tubulin, and exhibits efficacy superior to paclitaxel against human tumor xenografts, producing significantly greater cures. Given the known synergy between taxanes and cisplatin in vitro and their clinical activity, we performed a phase I trial of BMS-184476 as a 1-hour IV infusion followed by cisplatin every 21 days. 24 patients with a range of solid tumors and good performance status have received 84 cycles of therapy. BMS dose has ranged from, 40 - 60 mg/m2 with cisplatin fixed at 75 mg/m2. At the planned final dose level of BMS-184476 60 mg/m2 and cisplatin 75 mg/m2 we observed DLT in the form of Gr 3/4 diarrhea (2 pts), Gr 3 N/V (5 pts) and Gr 4 neutropenia 5 days (1 pt). We subsequently instituted a prophylactic regimen of ondansetron, dexamethasone, metoclopramide and prn loperamide and observed no further DLT in 6 additional pts. Mild to moderate peripheral neuropathy (Gr 1/2, 4 pts) has been infrequent as was alopecia. Clinical responses include 3 PRs (mesothelioma, esophageal ca, H+N ca), 2 MR (cholangioca, mesothelioma) and 4 SD. Preliminary cycle 1 PK analyses reveal dose-proportional increases in plasma BMS-184476 Cmax and AUC values, detailed below (SD). BMS-184476 60 mg/m2 and cisplatin 75 mg/m2 are recommended for further evaluation on this schedule, using antiemetic prophylaxis. The lack of significant peripheral neuropathy allowed prolonged dosing in responding pts. Antitumor activity was observed in range of tumor types, and BMS-184476 PK parameters were not significantly different from single-agent studies at similar doses.

Dose (mg/m^2)	N	CMAX (ng/mL)	AUC(24h) (ng·h/mL)	CLT (mL/min/m^2)	THALF (h)	VSS (L/m^2
40	6	943 (365)	1732 (425)	218 (84)	43 (17)	545 (129)
50	3	1498 (217)	2375 (491)	253 (69)	24 (3)	327 (81)
60	7	1541 (474)	2509 (527)	275 (88)	27 (10)	409 (157)

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A Phase I and Pharmacokinetic (PK) Study of the Novel Taxane BMS 184476 Administered as a 1-Hour Intravenous (IV) Infusion Weekly. *M. Beeram, M. Hidalgo, G. Rodriguez, K. Molpus, R. Drengler, A. Tortora, L. Smith, C. Tarby, L. Ochoa, S. Choe, A. Tolcher, G. Gallant, E. Rowinsky; Institute for Drug Development, Cancer Therapy and Reserarch Center; The University of Texas Health Science Center at San Antonio, San Antonio, TX; Bristol-Myers-Squibb, Wallingford, CT*

BMS 184476 is a novel taxane with greater potency and a broader spectrum antitumor activity than paclitaxel in preclinical modes. Furthermore, BMS 184476 is more soluble in aqueous solutions than pacliltaxel, requiring 68% less Cremophor EL®, which may render shorter IV administration schedules more feasible and and/or decrease the requirement for premedication to prevent hypersensitivity reactions. The maximum tolerated dose (MTD) of BMS-184476 administered as a 1-hour IV infusion every 3 weeks is 60 mg/m2, with an unacceptably high incidence of neutropenia, mucositis, and diarrhea at higher doses. Based on distinct differences in the toxicologic profiles of the taxanes on weekly schedules, the feasibility and PK behavior of BMS 184476 administered as a 1-hour IV infusion on an uninterrupted weekly schedule is being evaluated. To date, 24 patients (median age, 56, median ECOG PS - 1) have received 63 three-week courses of BMS 184476 at doses of 20, 25, 30, 35, and 40 mg/m2.weekly. Dose-limiting toxicity (DLT), consisting of grade 4 neutropenia with fever (1 pt) and prolonged neutropenia requiring a treatment delay exceeding 2 weeks (1 pt) occurred in 1 heavily-pretreated (HP) and 1 minimally-pretreated (MP) pt at the 40 mg/m2 dose level. In addition, 1 of 8 pts treated at the 35 mg/m2 dose level developed grade 3 diarrhea associated with dehydration and syncope. MP and HP pts are currently being treated at the 40 and 35 mg/m2, dose levels respectively. Preliminary PK parameters determined in 14 patients treated at dose levels of 20–35 mg/m2 revealed a proportional increment in Cmax and AUC0–24 that ranged from 429 – 1054 nM and from 867 nM.h to 1458 nM.h. Mean t 1/2, Cl, and Vss ranged from 31.3 to 51.6 hours; 167 to 349 ml/ min/ m2; and 514 to 744 L/m2 respectively. These results indicate that BMS-184476 administered on weekly IV schedule is well tolerated. At the 35 & 40 mg/m2 dose levels, which are projected to be the MTDs for HP and MP pts, respectively, the dose intensity is 1.75 and 2-fold higher than the MTD on the every 3-week schedule, but further studies are required to determine the clinical significance of this observation.

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Phase I Study of BMS-188797, a New Taxane Analog Administered Weekly in Patients with Advanced Malignancies. *R. Advani, G. A. Fisher, C. Jambalos, A. Yuen, C. Cho, B. L. Lum, C. Tarby, S. Choe, C. A. Bulanhagui, G. Gallant, B. I. Sikic; Stanford University Medical Center, Stanford, CA; Bristol-Myers Squibb, Princeton, NJ*

BMS-188797 is a novel taxane with superior activity in experimental tumor models compared to paclitaxel. The main objective of this study was to establish the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of this agent given weekly on d. 1, 8, 15 every 21 d. as a 1 hr. infusion. Eighteen patients with advanced malignancies (median prior regimens 2.5) were enrolled between 4/00 and 11/00. Tumor types included: 4 ovarian, 3 lung, 2 colon, 2 GI stromal, 2 sarcoma and 5 others. Three dose levels were evaluated: 35 mg/m^2 (n=3), 50 mg/m^2 (n=9) and 65 mg/m^2 (n=6). At 65 mg/m^2, 3/6 patients had DLTs (1 gr.4 neutropenia 7d and 2 gr. 3 diarrhea); hence the dose level of 50 mg/m^2 was expanded to a cohort of 9 pts. This dose of 50 mg/m^2 is the MTD and was well tolerated with only 1/9 pts. experiencing a DLT (gr. 4 neutropenia with fever). Other transient gr. 2 side effects included nail changes (n=4), fatigue (n=3), edema (n=3), nausea (n=3), diarrhea (n=2) and neuropathy (n=1). 13 patients are evaluable for response: 2 PR (ovarian 6+ mo, lung 4 + mo), 2 MR (lung 4+ mo, esophageal 3 + mo) and 2 SD (ovarian 6 mo, rectal 3 mo). All the responders had previously received a paclitaxel containing regimen. Plasma and urine pharmacokinetic (PK) data are available for 11 pts at 35 mg/m^2 (n=3), 50 mg/m^2 (n=5) and 65 mg/m^2 (n=3). Mean values of CMAX and AUC (48 h) increased in a dose-related manner. Individual $T^1/2$ values ranged from 11.9 to 25.9 h and individual VSS values ranged from 84 to 192 L/m^2. Complete PK data will be presented. In conclusion, the MTD and the recommended phase II dose of single agent BMS-188797 is 50 mg/m^2. The drug demonstrates very encouraging antitumor activity, and is now being evaluated in combination with carboplatin.