Supplement to
Clinical Cancer Research

An Official Journal of the American Association for Cancer Research

11th NCI-EORTC-AACR symposium on new drugs in cancer therapy

November 7-10, 2000
Amsterdam

EORTC European Organization for Research and Treatment of Cancer

AACR American Association for Cancer Research

November 2000 • Volume 6 • Supplement

limiting in animals, but the CNS toxicity could be avoided by slowly infusing the compound, thereby avoiding peak plasma levels. The current clinical study investigates the feasibility of a weekly 3 hour infusional schedule. The starting dose of 110 mg/m^2 was determined from an ongoing q 3 week study. Sixteen patients with the following characteristics (range) have been treated at dose levels of 110, 220, 330, 385 and 440 mg/m^2: 10 males, 6 females, median age 61 (30 – 83), median number of prior chemotherapeutic regimens 2 (2 –12). One patient treated with a hepatocellular carcinoma (HCC) at 110 mg/m^2 who had progressed through prior doxorubicin, gemcitabine + 5FU, and an experimental pyrimidine antimetabolite, had a durable (9+ months) PR concomitant with symptomatic improvement. At 440 mg/m^2, 2 patients had DLTs: a neutrophil count that failed to return to 1000/mm^3 on the day of planned dosing resulting in a dose omission and CTC grade 3 reversible ataxia. The recommended phase II dose is being defined in two groups of patients: HCC and non-HCC. Treatment in HCC patients has been limited by mild reversible thrombocytopenia and the current dose is 220 mg/m^2. In the non-HCC group, at doses below 440 mg/m^2, no acute CNS toxicity has been seen and the current dose level is 385 mg/m^2. Toxicities include neutropenia, diarrhea, fatigue and peripheral neuropathy. Pharmacokinetics are linear up to 330 mg/m^2. Data are available for 16 patients to date (±SD): clearance = 1.11 (0.26) L/h/kg, Vdss = 0.39 (0.17) L/kg, apparent terminal half-life = 0.52 (0.24) h. Patients with HCC have a trend towards lower clearance, but this is not statistically significant. Conclusion: the weekly schedule of T138067 has been well tolerated, with evidence of activity, and is therefore recommended for evaluation in phase II.

565 Phase I and pharmacokinetic study of T138067, a synthetic microtubule depolymerizing agent, administered as a 3-hour infusion daily x 5 every 3 weeks. Schwartz G, Rowinsky EK, O'Dwyer P, Olivo N, Wright M, Walling J, Stevenson J. *Brooke Army Medical Center, Cancer Therapy and Research Center, San Antonio TX, University of Pennsylvania, PA and Tularik Inc., South San Francisco, CA.*

T138067 (2-fluoro-1-methoxy-4-[pentafluorophenylsuphonamide]benzene) is a novel microtubule inhibitor which covalently binds to β tubulin, inducing depolymerization and apoptosis of cells. Preclinical studies have demonstrated that T138067 has activity superior to paclitaxel in MDR overexpressing cell lines and xenografts. The compound undergoes rapid elimination via hepatic metabolism. In dogs myelosuppression and stomatitis were dose limiting, and in mice dose limiting acute CNS toxicity was related to C max. A daily x 5 schedule was chosen for clinical evaluation given the short plasma half life and the short half life of the T138067 adduct bound to tubulin (10 to 24 hours). To date 8 patients (pts): 5 males and 3 females, median age 61 years (range 44 to 77), colorectal 4 pts, hepatocellular carcinoma 1 pt, renal cell carcinoma 1 pt, gastric stromal 1pt, have been treated at 3 dose levels (44 mg/m^2 5 cycles; 88 mg/m^2, 6 cycles; 175 mg/m^2 3 cycles). Treatment has been well tolerated (1 pt with CTC grade [G] 1 leukopenia, 1 pt with G2 anemia and 1 pt with G1 thrombocytopenia). Pharmacokinetic data are available for 6 patients treated at the 44 and 88 mg/m^2 dose levels (SD): clearance = 49.3 (13.5) L/h/m^2, Vdss = 15.4 (4.6) L/m^2, apparent terminal half life = 0.3 (0.03) h. No accumulation of T138067 has been observed and exposure remains consistent over the 5 days of treatment. Accrual of patients in this study continues.

566 Phase I and pharmacokinetic study of BMS-188797, a new taxane analog, given every three weeks in patients with advanced malignancies. Sullivan DM,[1] Rago R[1], Ruckdeschel JC[1], Dellaportas AM[1], Mahany JJ[1], Lush RM[1], Dalton WS[1], Bulanhagui C,[2] Gupta E,[2] Tarby C,[2] Sonnichsen D,[2] Gustafson N,[2] Gallant G.[2] *[1]H. Lee Moffitt Cancer Center, Tampa FL, USA. [2]Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton NJ and Wallingford CT, USA.*

BMS-188797 is one of several new taxane analogs being evaluated in phase I studies with superior activity in a experimental tumor models compared to paclitaxel. The main objective of this study was to establish the maximum tolerated dose and the dose-limiting toxicities (DLTs) of BMS-188797 given every 3 weeks by a 1-hour infusion. Patients (pts) were not premedicated. Fifty-one pts (13 renal cell, 11 NSCLC, 4 colon, 4 breast, and 19 other) - 35 males and 17 females - with a median age of 58 years (range: 20–77) were treated. Data is available for 41 pts with an ECOG performance status of 0 (21 pts), 1 (16 pts) or 2 (4 pts) having received from 0 to 5 prior chemotherapy regimens. Eleven pts had received prior taxane and 23 had received prior radiotherapy. The following dose levels were explored (# pts): 3.75 (6), 7.5 (3), 15 (3), 30 (3), 60 (6), 80 (3), 110 (3), 150 (6), 175 (5), 200 mg/m^2 (3). At 200 mg/m^2, DLT consisting of febrile neutropenia. Drug-related toxicities included neutropenia, nausea, vomiting, diarrhea, sensory neuropathy, arthralgia/myalgia and skin toxicity. No hypersensitivity reactions were reported. Partial responses were confirmed in 4 pts (2-breast, 1-renal cell, 1-NSCLC). The terminal half-life was approximately 28.3 hours and the average volume of distribution was approximately 164 L/m^2. The C_{MAX} and AUC (24h) values increased in a dose-related manner up to the 110 mg/m^2 dose level, beyond this level there were disproportional increases in these parameters. BMS-188797 is a new taxane that can be safely administered in pts with advanced malignancies. Encouraging antitu-

567 Phase I study of BMS-188797, a new taxane analog, given weekly in patients with advanced malignancies. Goldstein L,[1] Vaders L, Rogatko A, Bulanhagui C,[2] Gupta E,[2] Tarby C,[2] Sonnichsen D,[2] Gustafson N,[2] Gallant G.[2] *[1]Fox Chase Cancer Center, Philadelphia (PA), USA. [2]Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton (NJ) and Wallingford (CT), USA.*

BMS-188797 is a new taxane analog with superior activity in a number of experimental tumor models compared to paclitaxel. The main objective of this study was to establish the maximum tolerated dose (MTD) and the dose-limiting toxicities (DLTs) of BMS-188797 given weekly on day (d) 1, 8 and 15 every 21 days (1-hour infusion) in patients (pts) with advanced malignancies. Initially, no premedication was given. An accelerated Phase I design using rapid dose escalation was used. When pre-defined toxicity was observed, an escalation with overdose control (EWOC) scheme was to be used. Eleven pts (3 breast, 2 renal cell, 1 NSCLC, 1 sarcoma, 1 cervix, 1 endometrial, 1 adrenocortical and 1 head & neck) - 7 females and 4 males - with a median age of 47 years (range: 38–67) and an ECOG performance status 0 (9 pts) or 1 (2 pts) were enrolled. All pts had received prior chemotherapy (range: 1–5 regimens) and 7 had received prior radiotherapy. Data is summarized for 11 pts having received a median of 2 courses (crs) (range: 1–7):

Dose Level	No. of pts	No. of crs	DLTs
5 mg/m^2	1	1	—
20 mg/m^2	3	10	—
40 mg/m^2	2	8	—
80 mg/m^2	2	3	—
120 mg/m^2	2	2	Delay for neutropenia (Grade 3) - 1 pt
123 mg/m^2	1	3	—

At 120 mg/m^2, 1 pt developed a DLT (dose delay for neutropenia). EWOC escalation was then initiated. Other drug-related toxicities reported include: nausea, vomiting, diarrhea, sensory neuropathy, and myalgia. One grade 2 hypersensitivity reaction was reported. Patients are now being premedicated. One breast cancer patient treated at a weekly dose of 20 mg/m^2 reported a complete response. Plasma and urine pharmacokinetic data were obtained for all patients and will be presented. MTD has not been reached and the study is enrolling patients at 141 mg/m^2.

568 Phase I and pharmacokinetic study of RPR116258A, a novel taxane derivative, administered intravenously over 1 hour every 3 weeks. LJ Denis[1], EK Rowinsky[1], L Ochoa[1], D Hao[1], K Molpus[1], E Hooker[2], D Semiond[2], C Garay[2], M Besenval[2] and AW Tolcher[1]. *[1]Cancer Therapy and Research Center, San Antonio, USA and [2]Aventis Pharma USA/France.*

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 antiemetics or treatment to prevent hypersensitivity reactions were permitted at cycle 1. Prior taxanes use was also permitted.

Eleven pts (7 males/4 females; median age 66 yrs [32–80]; median PS 0 [0–2]) have been enrolled and 39 treatment courses were evaluable at dose levels of 10 (3 pts), 15 (6 pts) and 20 mg/m^2 (2 pts). The main toxicity was diarrhea Gr 3 in 2 patients at 15mg/m^2 that was controlled by loperamide. Minor Gr 1 or Gr 2 toxicities included diarrhea (3 pts), fatigue (3 pts), nausea (3 pts), vomiting (2 pts), neutropenia (3 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 cycle 1 and 2 and showed a three-phasic elimination profile. Preliminary mean (± SD) PK parameters indicated a high total body clearance (CL) of 33 (±11) L/h/m^2, a large volume of distribution (V_{ss}) of 1260 (±720) L/m^2 and a long terminal half-life of 44 (± 25) hours. Intrapatient variability of CL over 2 cycles was low (16%). One minor tumor response has been reported in one prostate cancer patient treated at 15 mg/m^2.

In conclusion, RPR116258A, a new taxane, is well tolerated at the studied dose levels. MTD is not yet reached. Preliminary PK results indicate a long terminal half-life justifying the intermittent dosing schedule every 3 weeks.

569 Phase I and pharmacokinetics (PK) study of RPR 116258A given as 1-hour infusion in patients (pts) with advanced solid tumors. A Lortholary[1], JY Pierga[2], R Delva[1], V Girre[2], E Gamelin[1], A Terpereau[2], G Crespel[1], P Pouillart[2], H Fontaine[3], D Semiond[3], D Pérard[3], M Besenval[3], V Diéras[2]. *[1]CPP, Angers, [2]Institut Curie, Paris, [3]Aventis Antony, France.*

RPR 116258A is a new taxoid with a broad spectrum of activity: activity on mdr-1 expressing tumor cells *in vitro* and against B16/TXT resistant melanoma and ability to cross blood brain barrier. This new compound was tested in phase I study using Simon's design 4B. The drug was administered as 1-hour infusion

lected during the first 48 or 72 hours at cycle 1 and 2. 16 patients (10 males, 6 females, median age: 52) were included, 15 treated in the dose escalation phase at 10 mg/m^2 (3 pts), 20 mg/m^2 (7 pts), 30 mg/m^2 (5 pts) and 1 pt at 25 mg/m^2 to define the recommended dose (RD), with a total of 35 cycles (1–4). The maximum tolerated dose was reached at 30 mg/m^2 at which 3 DLTs out of 5 pts were observed : neutropenia Gr 4 > 5 days (2 pts)/ febrile neutropenia (1 pt). At the highest dose levels (20/30), the main other toxicities were: diarrhea (7 pts) of short duration (4 days) and controlled by loperamide. No cortical neurotoxicity was observed except 1 confusion Gr 2 resolved after interruption of concomitant treatment (antalgics, anxiolytics and omeprazole). One toxic death (septic shock with neutropenia Gr 4 despite prophylactic G-CSF) was observed after 3 cycles at 30 mg/m^2 in NSCLC pt. PK analysis showed a three-phasic elimination profile. Up to 25 mg/m^2, the drug had a high total body clearance (33–56 L/h/m^2), a very large volume of distribution (500–2000 L/m^2) and a long terminal half life (30–45h). One minor response (NSCLC) and 3 stable diseases (colon) were reported. Additional pts will be treated at 25 mg/m^2 in order to establish the RD.

570 Phase I study of Taxoprexin DHA-paclitaxel (TXP), a novel taxane with unique preclinical activity, toxicity profile, and pharmacology. AC Wolff[1], SD Baker[1], MK Bowling[1], MA Carducci[1], MO Bradley[2], FH Anthony[2], CS Swindell[2], PA Witman[2], NL Webb[2], and RC Donehower[1]. *The Johns Hopkins Oncology Center[1], Baltimore, MD and Protarga, Inc[2], Conshohocken, PA.*

TXP is a novel taxane consisting of docosahexaenoic acid (DHA), a natural fatty acid, covalently conjugated via an ester linkage to the 2'-OH position of paclitaxel (PAC). TXP lacks *in vitro* microtubule assembly activity, but arrests cells at the G_2/M phase, presumably by intracellular conversion to PAC. TXP (at equimolar dose to the PAC maximum tolerated dose - MTD) showed activity equivalent to PAC against M109 lung carcinoma in syngeneic mice, but TXP MTD was 4.4 times higher than PAC MTD (molar basis) and more active than PAC at their MTDs. Increased TXP activity relative to PAC may be due to higher sustained PAC concentration following TXP administration. Phase I study objectives are to determine MTD, toxicity, PK profile of TXP administered as a 2-hr infusion every 21 days. To date, 18 pts (median age 62; 8 women) received 54 cycles of TXP at 200 (4 cycles), 400 (10 cycles), 660 (18 cycles), 880 (11 cycles), and 1100 (11 cycles) mg/m^2. In 6 patients treated at 1100 mg/m^2 (equivalent to PAC dose of 803 mg/m^2), grade 3 and 4 neutropenia occurred in 2 of 11 (all cycle 1) and 6 of 11 (two in cycle 1) cycles, respectively. One grade 1 neurotoxicity was seen, but no alopecia. TXP plasma PK analysis during cycle 1 revealed linear behavior and following mean (SD) parameters: $t_{1/2}$ = 27 (14) hrs, V_{ss} = 2.2 (0.98) L, Cl = 1.4 (1.2) mL/min. TXP at 880 mg/m^2 showed following mean (range) PAC exposures, which are less than 1% of TXP exposure: C_{max} = 0.17 (0.040) μM; AUC = 3.2 (2.0) μM*hr; time > 0.05 μM = 21 (6–48) hrs. PAC exposure correlated with the degree of neutropenia. TXP may have more favorable PK and toxicity profile than PAC. MTD has yet to be determined.

571 Phase I study of cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel (ABI-007) in solid tumors. Nuhad K. Ibrahim[1], Julie A. Ellerhorst[1], Richard L. Theriault[1], Edgardo Rivera[1], Bita Esmaeli[1], Patrick Soon-Shiong[2], Robert S. Benjamin[1], Gabriel N. Hortobagyi[1]. *[1]The University of Texas M. D. Anderson Cancer Center, Houston TX USA; [2]American Pharmaceutical Partners Inc., Los Angeles, CA USA.*

The paclitaxel formulation utilizes a mixture of cremophor EL/ethanol, due to insolubility of paclitaxel. Cremophor has been associated with hypersensitivity reactions and may limit the maximum tolerated dose (MTD) of paclitaxel due to its own toxicity. The new cremophor-free ABI-007 might be used without premedication. To determine its MTD, a phase I study was conducted in patients (pts) with advanced solid tumors. Thirteen pts with metastatic breast cancer (MBC), and 6 pts with melanoma were treated with ABI-007 without premedication in a 30-minute infusion every 21 days. The starting dose was 135 mg/m^2, and the total number of courses was 93, with the median (M) number delivered 5 (range [R], 1–11). M age was 50 years (R, 33–83). M performance status was 1 (R, 0–2); M number of prior chemotherapy regimens for the pts with MBC was 4 (R, 2–7) and for the pts with melanoma, 2.5 (R, 1–4). The MTD was 300 mg/m^2. There was one case of neutropenic fever due to skin infection. G3–4 non-hematologic toxicities were rare and included peripheral neuropathy 5, perioral numbness 5, skin blisters 2, and polyuria/polydypsia 4. Reversible ocular toxicities included keratitis G3, 3 pts; blurred vision G 2, 2 pts; eye flashes G1, 1 pt; and dry-eye syndrome G1–2, 3 pts. No hypersensitivity reactions were seen. The dose-limiting toxicity was peripheral neuropathy and superficial keratitis. A phase II study of ABI-007 at 300 mg/m^2 Q 21 days for MBC is in progress.

572 Enhanced bioavailability of oral paclitaxel by valspodar (PSC 833), an inhibitor of small bowel P-glycoprotein and cytochrome P450. B. I. Sikic, R. Advani, G. A. Fisher, J. Halsey, P. Cohen, and B. L. Lum. *Division of Oncology, Stanford University, Stanford, California 94305; Novartis Pharmaceuticals, Inc., East Hanover, New Jersey 07936.*

Inhibiting small intestinal P-glcoprotein (P-gp) by cyclosporine or valspodar (PSC) significantly enhances the bioavailability of paclitaxel (Ptx) in mice. Oral administration of Ptx would benefit patients by reducing cost, premedications, weeks 2–6. PSC was administered on week 3 at 1 mg/kg and sequentially increased to 3, 5 and 5 mg/kg x 8 doses. Five patients in cohort 2 received 4 sequential weeks of treatment with increasing doses of PSC. 15 patients have been entered. Toxicities have been mild with Gr. 1 nausea, Gr. 2 ataxia, Gr. 1/2 arthralgias, and Gr. 1 diarrhea. In cohort 1, PSC increased the oral bioavailability of Ptx by 2- to 3-fold as measured by area-under-the-curve and durations of exposure to Ptx in plasma above 0.1 μM and 0.05 μM. Evidence of antitumor effects was seen in 4 patients. In cohort 2, bioavailability was not affected by increased PSC dosing. This may be due to Cremophor in the formulations of Ptx and PSC, leading to a rapid GI transit time. Mild diarrhea or loose stools were noted in several patients on the day of drug administration. The amount of Cremophor in cohort 2 ranged from 20 to 40 g (mL) per weekly dose. Future cohorts are assessing the effect of co-administration of loperamide 2 mg with Ptx and PSC to decrease bowel motility, as well as adding a second dose of Ptx and PSC 6 hours after the initial dose, to achieve similar durations of exposure to Ptx in plasma above 0.1 μM and 0.05 μM as for IV Ptx.

573 Preclinical pharmacology of the epothilone B analog BMS-247550—an epothilone analog possessing potent activity against paclitaxel sensitive and resistant human tumors. Lee, Francis Y.F., Vite, Gregory D., Borzilleri, Robert M., Arico, Michele A., Clark, John L., Fager, Krista L., Kan, David, Kennedy, Kelly A., Kim, Andres S-H., Smykla, Richard A., Wen, Mei-Li, Kramer, Robert A. *Oncology Drug Discovery, Bristol-Myers Squibb PRI, Princeton, NJ 08543.*

BMS-247550, a semi-synthetic analog of epothilone B, demonstrated significant improvement over paclitaxel in several critical aspects. BMS-247550 is active against human cancer models that are naturally insensitive to paclitaxel or have developed resistance to paclitaxel, both in cell culture systems *in vitro* and in human tumor xenografts grown in nude mice. BMS-247550 has the ability to overcome all major forms of paclitaxel resistance mechanisms including the 170 kD P-glycoprotein-mediated multidrug resistance and tubulin mutation. BMS-247550 exhibits a very broad spectrum of antitumor activity against paclitaxel-sensitive human tumor xenografts: A2780 (ovarian); HCT116 and LS174T (colorectal) as well as paclitaxel-resistant human tumors: HCT116/VM46 (MDR resistant, colorectal); A2780Tax (ovarian, tubulin mutation); Pat-7 (early passage xenograft from a patient who developed resistance to TAXOL®); Pat-21 (Breast, early passage xenograft from a patient who was refractory to TAXOL® + D-Verapamil combination therapy) and Panc-26 (early passage xenograft from a patient with metastatic pancreatic carcinoma). Pharmacokinetics-tumor response studies determined that the minimum effective plasma concentration in nude mice for antitumor activity was ≈ 30 nM. Surrogate biomarker studies in tumor-bearing rats showed a strong correlation between BMS-247550 antitumor efficacy and the degree of tubulin polymerization induced in peripheral blood mononuclear cells. These preclinical efficacy data suggest that BMS-247550 has the potential to demonstrate improved clinical efficacy in TAXOL®-insensitive and sensitive disease types.

574 Phase I and pharmacology study of the epothilone B analog BMS-247550 in patients with advanced cancer. D Spriggs*, M.D., S.Soignet*, M.D., B. Bienvenu*, M.D., S.. Letrent+, Ph.D and D. Lebwohl+, M.D. H.Burris#, M.D * *Memorial Sloan Kettering Cancer Center, New York, NY; #Sarah Cannon Cancer Center, Nashville, TN; and +Bristol-Myers Squibb, Wallingford, CT.*

The epothilones are a class of agents which induce tubulin polymerization and are cytotoxic for taxane refractory tumors in preclinical testing. BMS-247550 is an epothilone B analog with excellent preclinical activity. Sixteen patients with refractory cancers have enrolled in a clinical study which examined BMS-247550 administered once every three weeks as a 1 hour infusion. No premedications were initially administered. Plasma pharmacokinetics(PK) and tubulin polymerization in peripheral blood mononuclear cells (PBMCs) were assessed during Course 1 and 2. Plasma concentrations of BMS-247550 were determined by an LC/MS/MS assay and the degree of tubulin polymerization in PBMCs via Western blot. To date, patients have received doses of 7.4, 15, 30, 50, and 65 mg/m^2. At doses below 50 mg/m^2, the drug was extremely well tolerated and no limiting toxicity was observed. Following a grade 2 immediate hypersensitivity reaction, all patients treated at 30 mg/m^2 and above received diphenhydramine and cimetidine but corticosteroids were not required. At 65 mg/m^2, two patient experienced grade 4 neutropenia and one patient experienced transient Grade 3 neuropathy. Additional patients will be treated at 50 mg/m2. The mean CL_T, and V_{SS}, and $T_{1/2}$ values across each dose cohort ranged from 230–423 mL/min/m^2, 399-1157 L/m^2, and 23–50 h, respectively. PK parameters appeared to be similar across Course 1 and 2. Data from patients in the 50 mg/m^2 cohort indicate enhanced tubulin polymerization in PBMCs at 1 and 6 h post-dose. Antitumor activity has been observed at the 65 mg/m^2 dose level.

This clinical study has been supported by Bristol-Myers Squibb.