Phase I Study of a Novel Taxane BMS-188797 in Adult Patients with Solid Malignancies

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Abstract

Purpose: Preclinical studies show that BMS-188797 has a broad spectrum of antitumor activity in *in vitro* cytotoxicity assays and tumor xenograft models. We did a phase I trial designed to determine the maximum tolerated dose and the pharmacokinetics of BMS-188797 when administered i.v.

Materials and Methods: BMS-188797 was administered i.v. over 60 minutes once every 21 days to 51 patients. The initial dose cohort of 3.75 mg/m^2 was set at approximately one third the lethal dose in dogs. Doses were subsequently escalated in cohorts according to a modified Fibonacci design.

Results: Fifty-one patients received a total of 160 cycles of therapy. The dose-limiting toxicity of febrile neutropenia occurred in two patients at the 200 mg/m^2 cohort. Moderate to severe sensory neuropathy occurred in 12 patients (24%). Four radiographic partial responses based on the Response Evaluation Criteria in Solid Tumors occurred: two in subjects with breast cancer, one in a subject with non – small cell lung cancer, and one in a subject with renal cell carcinoma. The duration of the partial responses observed were 24.1 months (renal cell carcinoma), 5.7 and 4.3 months (breast cancer), and 4.5 months (non – small cell lung cancer). Pharmacokinetics appear linear at doses through 110 mg/m^2 but not at higher doses.

Conclusion: The dose-limiting toxicity in this single-agent study of BMS-188797 was febrile neutropenia. The recommended phase II dose of BMS-188797 as a single agent is 175 mg/m^2 i.v. for 1 hour administered every 3 weeks.

Taxane molecules are cytotoxic agents; their mechanism of action involves their ability to stabilize the assembly of tubulin into microtubules. Microtubules are the cellular structures that form mitotic spindles and are required for chromosomal segregation (1). Paclitaxel (BMS-181339, Taxol, Bristol-Myers Squibb, Philadelphia, PA) was the first taxane approved for cancer therapy in December 1992 (2). In the presence of paclitaxel, cells accumulate in the mitotic phase of the cell cycle and undergo apoptosis as they attempt to divide (3). Paclitaxel has proven clinical activity in non – small cell lung cancer (4), head and neck cancer (5), breast cancer (6), and ovarian cancer (7). Despite its activity in these solid malignancies, the development of resistance while on treatment is common. In addition, a larger number of solid tumors show primary resistance to paclitaxel. There are different mechanisms of paclitaxel resistance, including overexpression of P-glycoprotein and mutations of the tubulin-binding site. Potential novel antitubule taxane-based drugs, with a broader spectrum of antitumor activity when compared with paclitaxel, would have an important clinical role in the treatment of solid malignancies. BMS-188797 is a member of the taxane family of agents and is a chemical derivative of paclitaxel (8). It possesses a single structural modification from paclitaxel in which the C4 carbon is modified to form the 4-desacetyl-4-methylcarbonate analogue of paclitaxel (see Fig. 1). Similar to paclitaxel, BMS-188797 has a very low aqueous solubility. BMS-188797 has the molecular formula $C_{47}H_{51}NO_{15}$ and a molecular weight of 869.9 g/mol. BMS-188797 has the same formulation as paclitaxel, with a nonaqueous solution of Cremaphor EL and dehydrated alcohol (50:50 based on volume).

Cytotoxicity assays done to evaluate the potential clinical activity of this compound show that BMS-188797 compares favorably to paclitaxel. In its ability to polymerize tubulin using previously described *in vitro* assays (9, 10), BMS-188797 proved to be twice as potent as paclitaxel. Preclinical toxicity of BMS-188797 is qualitatively similar to paclitaxel.

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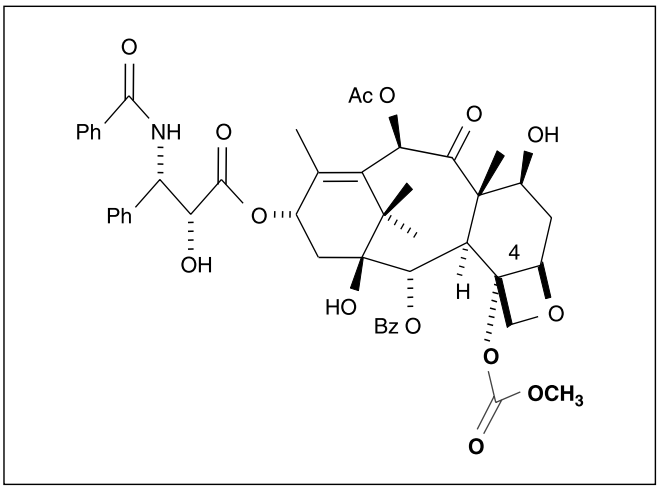

Fig. 1. The chemical structure of BMS-188797.

In *in vitro* cytoxicity assays, the IC_{50} of BMS-188797 was comparable with paclitaxel in the human colon cancer cell line HCT-116 and the human ovarian cell line A2780 (11). In the *in vivo* human xenograft tumor models utilizing the M109 murine lung carcinoma, HCT/pk MDR human colon carcinoma, and the L2987 human lung carcinoma, BMS-188797 was superior to paclitaxel based on log cell kill and cure rate differences. In addition, BMS-188797 did better in the HOC79 ovarian cell line, a tumor derived from a patient clinically unresponsive to paclitaxel. In all of the *in vivo* studies done, BMS-188797 was never found to be inferior to paclitaxel.

In summary, BMS-188797 displayed superior efficacy to paclitaxel in four *in vivo* tumor models. Two of the cell lines used for the human xenografts were derived from human carcinomas that had shown paclitaxel resistance clinically. These data led to clinical trials to determine the maximum tolerated dose (MTD) and recommended phase II dose of BMS-188797 in adult patients with advanced, incurable malignancies.

Patients and Methods

Study design. A phase I study design, involving adult patients with measurable or evaluable solid malignancies, who were refractory to known effective therapy, or for whom no proven effective antitumor therapy existed, was used. This was an open, nonrandomized and dose-escalating study. The study compound, BMS-188797, was administered i.v. for 1 hour every 21 days. A standard phase I design with a dose-escalation scheme utilizing a modified Fibonacci design was utilized. Subjects gave verbal and written informed consent before study entry. The study followed the ethical principles of Good Clinical Practice in accordance with the Declaration of Helsinki. The study was approved by the H. Lee Moffitt Cancer Center Scientific Review Committee and by the University of South Florida Institutional Review Board.

Patient selection. Patients with a tissue diagnosis of malignancy, which was deemed incurable and not suitable for or had exhausted standard forms of therapy, were considered for enrollment. Standard phase I eligibility criteria were used. All subjects were treated at the H. Lee Moffitt Comprehensive Cancer Center and Research Institute on the Phase I Clinical Research Unit. All patients gave written informed consent according to institutional and federal guidelines before study enrollment and treatment with study drug.

Handling and dispensing of the study drug. BMS-188797 was supplied by Bristol-Myers Squibb Pharmaceuticals Research Institute and packaged in 12 mL type 1 glass vials. The drug was diluted before infusion with 0.9% sodium chloride USP or 5% dextrose USP to yield a final concentration of 0.3 to 1.2 mg/mL. Diluted BMS-188797 was stored in plastic bags (polypropylene or polyolefin) and administered through polypropylene-lined administration sets to avoid patient exposure to the plasticizer di-(2-ethylhexyl)phthalate, which may be leached out of polyethylene-lined administration sets. The investigational drug supply was kept in a secure area, stored at room temperature, and protected from the light.

BMS-188797 was infused continuously for 1 hour by means of a regulated infusion pump. The patient's blood pressure and heart rate were monitored every 15 minutes during the infusion, and a physician was present in the Clinical Research Unit during the infusion of study drug.

Prophylactic premedication was not routinely used, unless a hypersensitivity reaction occurred. Patients experiencing a grade 2 hypersensitivity reaction were subsequently premedicated on all future cycles of therapy with an antihistamine. Patients who experienced a grade 3 hypersensitivity reaction were premedicated with p.o. H_1 and H_2 antagonists and i.v. corticosteroids 0.5 hour before future therapy with study drug. The majority of courses (154 of 160, or 96%) did not require prophylaxis for hypersensitivity reaction. Growth factors were not allowed on study.

Treatment and dose escalation. The starting dose was 3.75 mg/m^2 and was determined as slightly higher than one third the minimal toxic dose in dogs. Three patients were treated at each dose level. No allowance was made for intrapatient dose escalation. Provided no patient in a cohort experienced a dose-limiting toxicity (DLT), enrollment to the next escalated dose was undertaken. Initially, doses were escalated in successive patient cohorts by increments of 100% (i.e., doubling of the dose), until the first occurrence of DLT or the first occurrence of any other grade 2 therapy-related toxicity (except for grade 2 nausea or vomiting, alopecia, fatigue, anorexia, anemia, alkaline phosphatase elevation, fever, or local injection site reactions). Once such a toxicity was identified, doses in subsequent cohorts were escalated based on a modified Fibonacci design (see Table 1). Patients were observed for 7 days before starting any other patients at that dose level. Subsequent cohorts were not opened until two patients at the current dose level had been observed for at least 21 days after drug infusion and a third patient had reached at least day 7 of course 1.

If one DLT was observed in a cohort, a total of six patients were enrolled at that dose level. The DLT cohort was defined as the dose level where two or more DLTs occurred. The MTD was defined as one dose level below the dose level where ≥33% of patients experienced DLTs during the first course. A maximum of 15 patients was planned to be treated at the MTD. Toxicities were defined according to the National Cancer Institute Common Toxicity Criteria version 2.0.[3]

For the purposes of this study, a DLT was defined as any of the following events occurring during the first cycle of therapy: a grade 4 neutropenia [i.e., absolute neutrophil count (ANC) <500 cell/mm^3 for ≥5 consecutive days] or febrile neutropenia (i.e., fever >38.0°C with an ANC <500 cell/mm^3); grade 4 thrombocytopenia or a bleeding episode requiring platelet transfusion; grade 3 or greater nausea and/or emesis despite the use of maximal medical intervention; grade 2 or greater cardiovascular toxicity; grade 3 or greater nonhematologic toxicity; and delayed recovery (≥2 weeks) after scheduled retreatment from a toxicity related to treatment with BMS-18879.

Hypersensitivity reactions were not considered DLTs for the purposes of this study. If a subject encountered a DLT, the treatment was withheld until recovery of the toxicity to grade 1 or less. The subject was subsequently treated at one dose level below where the DLT occurred.

[3] The Revised Common Toxicity Criteria: Version 2.0. http://ctep.cancer.gov/reporting/ctc.html.

Table 1. Dose levels and number of patients enrolled

Dose level (mg/m^2)	Number of patients	Number of treatments
1 (3.75)	6	14
2 (7.5)	3	11
3 (15)	3	10
4 (30)	3	14
5 (60)	6	15
6 (80)	3	14
7 (110)	3	7
8 (150)	6	21
9 (175)	15	49
10 (200)	3	5
Total	51	160

The maximum administered dose was defined as the dose level where a DLT was observed in a minimum of two patients (greater than or equal to two DLTs out of six patients treated).

Treatment assessment. Before initiation of therapy, a complete medical history and physical examination were done. A complete blood count, chemistry group, electrolyte panel, 12-lead electrocardiogram, urinalysis, and chest roentgenogram were also done. Every 3 weeks, a history, toxicity assessment, and physical examination was done while a subject was on study, in addition to a complete blood count and differential, electrolyte, and chemistry panel. Tumor assessment, including serum tumor markers and radiologic assessment of all sites of known evaluable or measurable disease, was done before initiation of therapy and at 6-week intervals. The Response Evaluation Criteria in Solid Tumors criteria (12) were used to assess radiographic response. Subjects were withdrawn from study for the following: radiographic evidence of disease progression, patient withdrew consent, excessive treatment toxicity, or at the treating physician's discretion.

Sample collection and drug analysis. Five milliliters of blood were collected for pharmacokinetic analysis using Becton-Dickinson vacutainers that contained K_3EDTA as the anticoagulant (Becton-Dickinson, Franklin Lakes, NJ). Pharmacokinetic analyses were done in all patients during cycle 1. Repeat plasma pharmacokinetic sampling was optional for cycle 2. Serial blood samples were drawn at time 0 (pretreatment), 30 minutes after the start of the infusion, and at 60 minutes (drawn before the end of the infusion). Postinfusion samples were collected at 15, 30, 60, and 90 minutes and at 2, 3, 4, 5, 7, 23, 47, and 71 hours after the end of the BMS-188797 infusion. Within 1 hour of collection, the plasma was separated by centrifugation at 1,000 rpm for 15 minutes at 4°C. Plasma was stored at or below 20°C until analysis. Plasma samples were analyzed for BMS-188797 concentrations by high-performance liquid chromatography. After the addition of internal standard, BMS-183061, to 1.0 mL plasma, the sample was loaded onto a CN-U solid-phase extraction column. The compounds were eluted with 0.1% formic acid in methanol, the eluate evaporated to dryness, and the residue reconstituted. Chromatographic separation of the compounds was achieved on a YMC-ODS-AQ, 4.6 × 150 mm, 3 μm column using a mobile phase containing 30% water in acetonitrile. Detection was by UV absorbance at 228 nm. The standard curve range was 2.5 to 1,000 nmol/L.

Pharmacokinetic and pharmacodynamic analysis. Estimates of pharmacokinetic parameters for BMS-188797 were derived from individual concentration-time data sets by noncompartmental analyses (13). The values of the maximum plasma concentration (C_{max}) were directly recorded from experimental observations. The area under the plasma concentration versus time curve from time 0 to the time of the last measurable concentration T ($AUC_{0\text{-}T}$) was calculated using a combination of linear and log trapezoidal summations. The first-order rate constant of decline of BMS-188797 concentrations in the terminal phase of the plasma concentration-time data set, λ, was estimated by log-linear regression, using no weighting factor, of at least three data points yielding a minimum mean square error. The absolute value of λ was used to estimate the apparent terminal elimination half-life, $t_{1/2}$. The last measurable concentration and the rate constant, λ, were used to extrapolate the $AUC_{0\text{-}T}$ to estimate $AUC_{0\text{-}\infty}$ (the area under the curve from time 0 to infinity). The total body clearance (Cl) was calculated by dividing the dose by $AUC_{0\text{-}\infty}$. The volume of distribution at steady state (V_{SS}) was calculated using standard noncompartmental methods.

The relationship between BMS-188797 systemic exposure and toxicity as indicated by the percent decrease in the ANC was explored. The percent decrease in ANC was calculated as: %decrease in ANC = (100% × [pretreatment count − nadir count]) / pretreatment count. The relationship between $AUC_{0-\infty}$ and decreased ANC was described with a sigmoid E_{max} model of drug action $E = E_0 + E_{max} \times AUC^{\gamma} / (AUC^{\gamma} + AUC_{50}{}^{\gamma})$. The input values were the observed percent change in ANC (E) and the AUC for each subject. The minimal effect (E_0) was fixed at 0%. These values were fit to the sigmoid E_{max} model using Kinetica 4.0.2 (InnaPhase Corporation, Philadelphia, PA). The output values were the maximal effect (E_{max}), the AUC at which the effect is 50% of the maximal effect (AUC_{50}), and a constant that describes the sigmoid nature of the curve (the exponent γ). Discrimination between pharmacodynamic models was guided by minimization of the weighted sum of squares and SEs for the pharmacodynamic parameters, examination of the dispersion of the residuals, and use of the objective function, Akaike criteria, and Schwartz criteria.

Results

General. A total of 51 patients were enrolled on study from September 29, 1998, until April 11, 2000 (patient characteristics are shown in Table 2). Fifty-one patients were evaluable for toxicity and response. Almost half of the subjects were asymptomatic at the time of enrollment and more than two

Table 2. Patient characteristics

Patient characteristics	Number of patients
Subjects entered	51
Subjects assessable	51
Age (y)	
<65	35 (69%)
≥65	16 (31%)
Sex	
Male	34 (67%)
Female	17 (33%)
Eastern Cooperative Oncology Group performance status	
0	25 (49%)
1	19 (37%)
2	7 (14%)
Previous treatment	
No prior therapy	16 (31%)
Prior chemotherapy (no. of regimens)	35 (69%)
One	11 (22%)
Two	8 (16%)
Three	10 (20%)
Four	1 (2%)
Five	5 (10%)
Prior radiation therapy	29 (57%)

thirds had received prior chemotherapy. Seventeen (49%) received prior paclitaxel therapy and 3 (9%) received prior therapy with docetaxel. The majority had received prior radiation therapy. Non–small cell lung cancers and renal cell carcinomas were the most common tumor types enrolled on study (the distribution of tumor types is shown in Table 3). Four radiographic partial responses based on the Response Evaluation Criteria in Solid Tumors occurred; two in subjects with breast cancer, one subject with non–small cell lung cancer, and one subject with renal cell carcinoma. The duration of the partial responses observed were 24.1 months (renal cell carcinoma), 5.7 and 4.3 months (breast cancer), and 4.5 months (non–small cell lung cancer). The subject with lung cancer and the two subjects with breast cancer had received prior paclitaxel therapy, and were considered taxane resistant; the subject with renal cancer did not receive prior therapy.

The first dose cohort (3.75 mg/m^2; Table 3) was expanded to six owing to the presence of a grade 3 cardiovascular toxicity (syncope) that developed in the third patient enrolled, which was felt to be possibly related to study drug by the treating physician. However, no additional grade 3 or greater toxicity was observed in the next three patients treated at that dose level, and it was felt to be safe to dose escalate to the 7.5 mg/m^2 level.

The next nine successive patients treated at dose levels 2 to 4 tolerated therapy without a DLT. The second patient at the 60 mg/m^2 dose level developed a culture negative grade 4 neutropenia lasting >5 consecutive days following the first cycle of therapy. Of note, this patient was heavily pretreated with chemotherapy because of a stage IV rectal cancer initially treated with neoadjuvant chemoradiation therapy, followed by surgery and intraoperative radiation therapy. Three years before his diagnosis of rectal cancer, he received neoadjuvant chemoradiation therapy followed by surgery for a localized malignant fibrous histiocytoma of the thigh, which was not to relapse. Upon hepatic relapse of his rectal cancer, he was treated with single-agent irinotecan until progression, followed by single-agent capecitabine. This patient's significant prior chemotherapy and irradiation may explain his diminished bone marrow tolerance to the BMS-188797. He was treated with two further cycles of study drug at the 30 mg/m^2 level with good tolerance. Due to the DLT observed at this dose cohort (60 mg/m^2), four additional patients were enrolled and no DLT was observed in these subjects.

DLTs were not encountered at the 80 and 110 mg/m^2 cohorts (dose levels 6 and 7). The third patient treated at the 150 mg/m^2 cohort (level 8) experienced grade 4 neutropenia, with a central venous catheter–associated *Staphylococcus aureus* bacteremia and catheter-associated upper extremity deep venous thrombosis. This prompted three additional subjects to be enrolled onto this dose cohort; no further DLT was observed in these patients. The first three patients enrolled at dose level 9 (175 mg/m^2) did not have a DLT; thus, subjects were enrolled on dose level 10 (200 mg/m^2).

The first patient enrolled on the 200 mg/m^2 level tolerated the first cycle of therapy well, with only grade 2 neutropenia being the most severe toxicity observed. His second cycle was complicated on day 11 by hospitalization for a grade 4 febrile neutropenia (culture negative febrile neutropenia requiring hospitalization) and grade 4 anemia. The second patient on the 200 mg/m^2 cohort developed grade 4 neutropenia (not requiring hospitalization) and grade 2 peripheral neuropathy following the second cycle of therapy. The third patient in the 200 mg/m^2 cohort developed a grade 4 febrile neutropenia (culture negative febrile neutropenia requiring hospitalization) following the first cycle of therapy. With the second DLT in this cohort of three patients, 200 mg/m^2 was determined to be the maximum administered dose and 12 additional patients were enrolled in the 175 mg/m^2 cohort. Of note, all of the DLTs experienced were hematologic, with the exception of the grade 3 cardiovascular event in the first cohort, which was most likely not related to study drug.

The 15 patients treated at the 175 mg/m^2 cohort tolerated therapy well without significant toxicity. Two patients developed grade 2 rash, which was manifest as a fine, maculopapular rash distributed over the trunk and abdomen, which was felt to be likely drug related.

Hematologic toxicity. Myelosuppression was the principal toxicity encountered and was the DLT. The myelosuppression observed was mainly neutropenia (see Table 4), and was generally of short duration, resolving before the date of retreatment. The DLT was two episodes of prolonged grade 4 neutropenia at the 200 mg/m^2 dose. However, of the 15 patients treated at the 175 mg/m^2 dose, the incidence of neutropenia was tolerable, with 1 patient experiencing grade 3 neutropenia and 5 patients experiencing fever (three grade 1 and two grade 2) out of 13 patients experiencing some degree of neutropenia. The mean nadir absolute neutrophil count at the 175 mg/m^2 dose cohort was 1,690/mm^3. Thrombocytopenia and anemia toxicity was modest and tolerable.

Nonhematologic toxicity. The most common nonhematologic toxicities experienced were neurologic and musculoskeletal, with neuropathy, myalgias, and arthralgias being the most common. Although two thirds of the patients at the recommended phase II dose (175 mg/m^2) developed neuropathy, it was grade 1 in all instances. The neuropathy was manifest as parasthesias in the extremities and developed during the first cycle of therapy in the majority of cases; it resolved in all cases

Table 3. Tumor pathology of patients enrolled

Tumor pathology	Number of patients	Percentage (%)
Lung	15	29
Non – small cell	10	20
Small cell	1	2
Mesothelioma	4	8
Kidney	14	27
Colorectal	5	10
Colon	3	6
Rectal	2	4
Sarcoma	4	8
Gastrointestinal stromal tumor	3	6
Malignant fibrous histiocytoma	1	2
Melanoma	3	6
Breast	3	6
Testes	2	4
Other*	5	10

*Other represents one of each of the following: esophagus, cholangiocarcinoma, gall bladder, medullary carcinoma of the thyroid, and mucoepidermoid carcinoma of the parotid.

Table 4. Toxicity (worst grade, per course, by dose level for all treatment courses)

Hematologic toxicity

				Worst grade, per course, by dose level					
		Nadir neutrophils		Neutropenia		Anemia		Thrombocytopenia	
Dose level (mg/m^2)	No. of patients/ courses	Mean	Median (±SD)	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
1 (3.75)	6/14	8.83	3.96 (0.94)						
2 (7.5)	3/11	6.41	6.66 (3.00)						
3 (15)	3/10	2.63	2.61 (0.10)			1			
4 (30)	3/14	3.04	3.11 (0.27)			3			
5 (60)	6/15	1.46	1.09 (1.47)	1	3				
6 (80)	3/14	2.15	1.74 (0.99)	3				2	
7 (110)	3/7	1.00	0.72 (0.56)	2	1		1		
8 (150)	6/21	0.72	0.57 (0.69)	7	6	2			
9 (175)	15/49	1.69	0.82 (3.02)	15	9	2		6	
10 (200)	3/5	0.25	0.14 (0.29)	2	3	2			1
All	51/160	2.11	1.60 (2.34)	30	19	10	1	8	1

Nonhematologic toxicity

		Neuropathy					Myalgia			Gastrointestinal			
		Sensory			Motor					Nausea		Vomiting	
Dose level (mg/m^2)	No. of patients/ courses	Grade 1	Grade 2	Grade 3	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 2	Grade 3	Grade 2	Grade 3
1 (3.75)	6/14	3					1	3		1			
2 (7.5)	3/11	6								1			
3 (15)	3/10	2							1				
4 (30)	3/14	4											
5 (60)	6/15	4										1	
6 (80)	3/14	2											
7 (110)	3/7	1						7	1				
8 (150)	6/21	8	3	2		1		4	2	1	1	1	1
9 (175)	15/49	33	9	3	1					2	3	2	2
10 (200)	3/5	1	2	2						1			
All	51/160	75	14	7	1	1		14	4	6	4	4	3

upon discontinuation of the drug. Gastrointestinal toxicities were uncommon and the routine use of antiemetic therapy was not required. The frequencies of the most common nonhematologic toxicities are represented in Table 4.

Pharmacokinetic and pharmacodynamic evaluations. Plasma samples were obtained from 49 patients during the first cycle of treatment. One patient each at the 3.75 and 15 mg/m^2 dose levels were excluded from pharmacokinetic evaluation because of insufficient sample collection and collection from the infusion port. Plasma concentrations were generally quantifiable through 24 to 48 hours in patients administered 3.75 or 7.5 mg/m^2 of BMS-188797. Only C_{max} and AUC (0-24 hours) are reported for these dose levels. Plasma concentrations were quantifiable in all patients through 72 hours in all patients administered 15 mg/m^2 or greater of BMS-188797.

The mean (SD) pharmacokinetic parameters for patients in the first cycle are shown in Table 5. The mean concentrations of plasma BMS-188797 plotted against time for the first cycle are shown in Fig. 2. The relationship of individual values of C_{max} and $AUC_{0-\infty}$ to dose are plotted in Fig. 3. Pharmacokinetics appears linear at doses through 110 mg/m^2 but not at higher doses. The C_{max} and AUC increased in relation to dose level through the 110 mg/m^2 dose level. There was a greater proportional increase in C_{max} and AUC compared with dose for the higher dose cohorts. At the 175 mg/m^2 dose level, the MTD, there was a 2.8-fold range of $AUC_{0-\infty}$ values among 13 patients. Across all dose levels, Cl values ranged from 75.6 to 301 $mL/min/m^2$, $t_{1/2}$ values ranged from 17.2 to 39.3 hours, and V_{SS} values ranged from 36.6 to 338 L/m^2. Lower Cl and V_{SS} values were observed at the higher dose levels.

The pharmacodynamic relationship between the percentage of decrease in ANC during cycle 1 and the BMS-188797 exposure as determined by the $AUC_{0-\infty}$ was well described by a sigmoid E_{max} model of drug action as shown in Fig. 4. Values for E_{max}, AUC_{50}, and were an 80.8% decrease in ANC, 2,256 nmol/L-hour, and 1.75, respectively.

Conclusion

Taxane compounds, including paclitaxel and docetaxel (Taxotere), currently play an important role in the clinical management of ovarian, breast, non–small cell lung cancer,

Table 5. Mean (SD) pharmacokinetic parameters for cycle 1 of BMS-188797

Dose (mg/m^2)	*N*	C_{max} (nmol/L)	AUC_{0-24} (nmol/L-h)	$AUC_{0-\infty}$ (nmol/L-h)	Cl (mL/min/m^2)	V_{SS} (L/m^2)	$t_{1/2}$ (h)
3.75	5	134 (29)	328 (61)	*	*	*	*
7.5	3	305 (48)	623 (182)	*	*	*	*
15	2	611 (309)	1,153 (661)	1,715 (1,081)	209 (129)	272 (93)	28 (11)
30	3	2,193 (499)	3,562 (1,077)	4,412 (1,863)	130 (37)	136 (31)	26 (1)
60	6	2,875 (745)	5,384 (1,635)	7,616 (2,649)	163 (43)	217 (72)	29 (4)
80	3	4,413 (567)	6,892 (258)	8,547 (769)	182 (16)	152 (27)	25 (6)
110	3	3,557 (637)	8,411 (3,230)	12,404 (5,485)	192 (77)	258 (78)	28 (4)
150	6	9,206 (2,582)	18,220 (3,933)	22,309 (5,539)	136 (34)	109 (32)	26 (3)
175	13	13,979 (2,782)	24,142 (6,295)	27,469 (8,250)	132 (39)	67 (13)	24 (7)
200	3	19,019 (5,840)	39,348 (4,473)	44,564 (5,031)	87 (10)	50 (12)	22 (1)

*Not calculated because of insufficient concentration versus time data.

esophagogastric, and head and neck cancers. Their main toxicities are myelosuppression, neuropathy, and, rarely, hypersensitivity reactions. Second-generation taxane-based compounds with the potential for superior efficacy and improved tolerability may make a significant impact on the survival and quality of life of patients with advanced cancer as well as on cure rates when utilized in the adjuvant setting. Such second-generation taxane compounds undergoing clinical evaluation include Epothilone B 906A (Novartis, Cambridge, MA), BMS-184476 (Bristol-Myers Squibb), and Epothilone B BMS-247550 (Bristol-Myers Squibb). These compounds have the same tubulin-binding site as paclitaxel and docetaxel, but seem to have a different activity profile when evaluated by preclinical cellular models as well as tumor xenograft models.

BMS-188797 is among a group of second-generation taxane-based compounds undergoing clinical evaluation. This phase I study showed that as a single agent, BMS-188797 can be administered safely in a population of heavily pretreated cancer patients. Encouraging single-agent activity was seen in four patients, including one patient with renal cell carcinoma, a disease where cytotoxic therapy has not made a significant impact. Future phase II studies will be required to determine

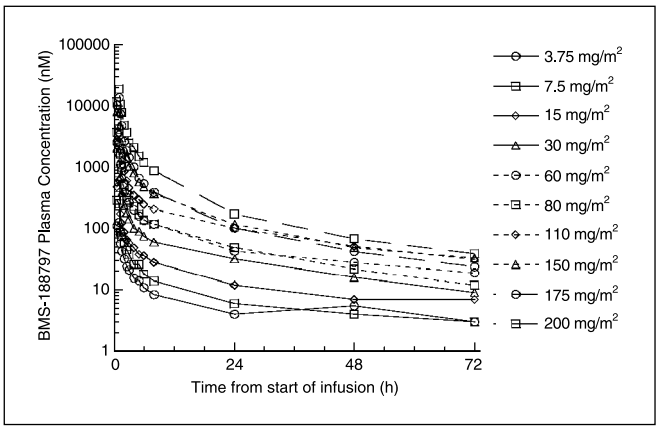

Fig. 2. Mean (SD) pharmacokinetic parameters for cycle 1 of BMS-188797.

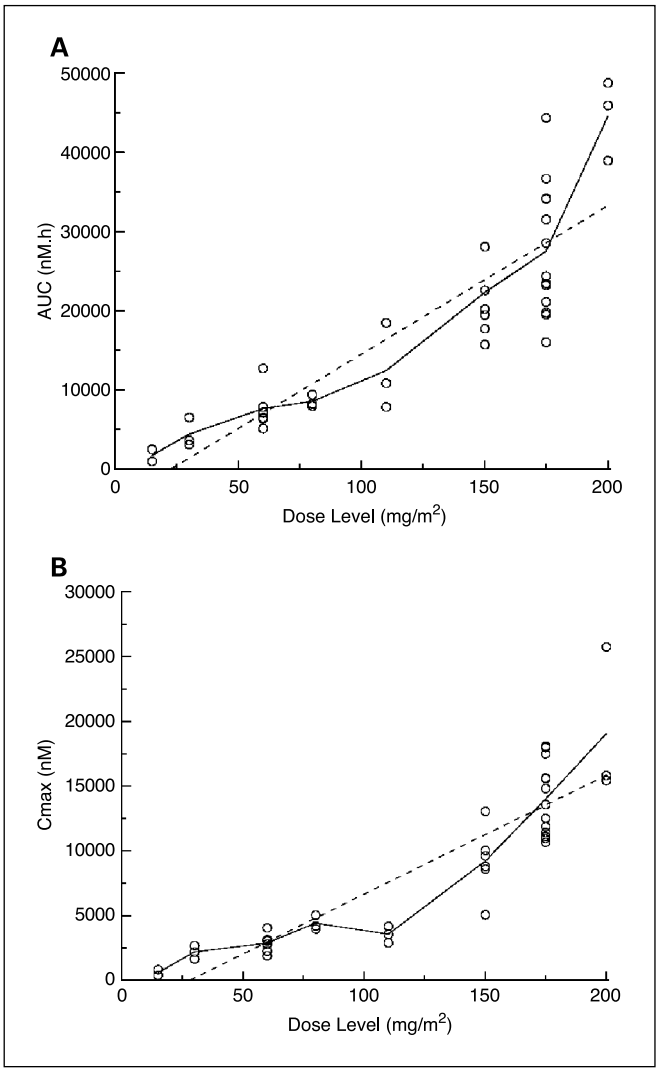

Fig. 3. *A,* individual BMS-188797 AUC values (○); fit of the data derived from linear least squares regression with an r^2 of 0.75 (*dashed line*); line plot of the mean AUC values (*solid line*). *B,* individual BMS-188797 C_{max} values (○); fit of the data derived from linear least squares regression with an r^2 of 0.78 (*dashed line*); line plot of the mean C_{max} values (*solid line*).

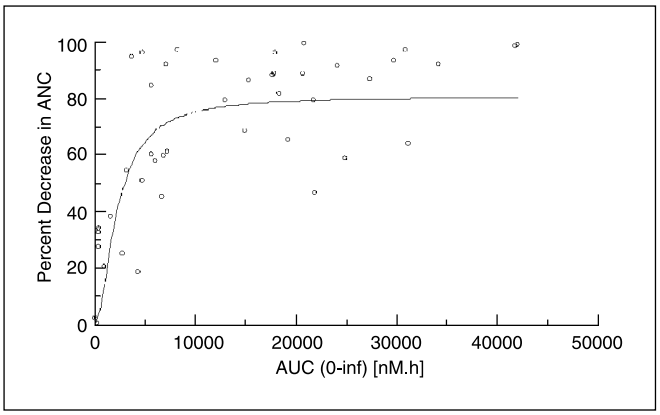

Fig. 4. Scatter plot showing the relationship between BMS-188797 $AUC_{0-\infty}$ and percentage decrease in ANC during cycle 1 (○). The solid line represents the fit of the sigmoid E_{max} model to the data.

whether BMS-188797 is a more effective taxane or whether it has a different spectrum of antitumor activity.

In a previous study of BMS-188797 administered on weekly schedule (14), linear pharmacokinetics was observed over the very limited dose range of 35 to 65 mg/m^2. In contrast, our phase I study of BMS-188797 administered every 3 weeks fully evaluated pharmacokinetics over the dose range of 15 to 200 mg/m^2 with a limited evaluation of 3.75 and 7.5 mg/m^2 doses. Whereas the pharmacokinetics appear linear through 110 mg/m^2, a range that includes that of the previous study, a decrease in clearance and volume of distribution, and a nonlinear increase in maximal concentration and AUC were noted at higher doses.

BMS-188797 is being evaluated as a weekly schedule in two ongoing phase I studies. Administered as a 1-hour infusion on days 1, 8, and 15 every 21 days, the MTD was determined to be 50 mg/m^2 (15). Encouraging activity was seen during this trial; two patients (ovarian and non–small cell lung cancer) achieved a partial response. The MTD had not been reached at the time of publication for a second phase I trial evaluating weekly administration of BMS-188797 (16).

Intriguing preclinical human lung cancer cell line and xenograft data have shown that the addition of BMS-188797 to radiation can enhance the effects of radiation (17). These preliminary studies support further clinical trials evaluating the efficacy of BMS-188797 in combination with radiation. Two different dose schedules combining BMS-188797 with carboplatin have been evaluated. The MTD of BMS-188797 followed by carboplatin i.v. given every 21 days has been determined to be carboplatin AUC 5 mg mL/min and BMS-188797 135 mg/m^2.[4,5] A weekly schedule of BMS-188797 in combination with carboplatin administered every 21 days is ongoing; the MTD had not been reached at the time of publication (18). A combination trial with BMS-188797 followed by cisplatin has determined the recommended phase II dose to be BMS-188797 110 mg/m^2 followed by cisplatin 75 mg/m^2 (19).

In summary, BMS-188797 is a taxane analogue that can be safely administered i.v. as a single agent at a dose of 175 mg/m^2 every 21 days. The main toxicity encountered was myelosuppression. Prophylaxis for hypersensitivity reactions was not necessary for the vast majority of patients. Four patients achieved partial radiographic responses on therapy. This encouraging activity shown in a phase I study suggest that further phase II studies of BMS-188797 are warranted, both as single-agent therapy and in combination with other cytotoxic agents.

[4] M.N. Fishman, et al. Phase I study of BMS-188797 in combination with carboplatin administered every three weeks in patients with solid malignancies, in preparation.
[5] D. Sullivan, personal communication.

References

1. Rowinsky EK, Cazenave LA, Donehower RC. Taxol: a novel investigational antimicrotubule agent. J Natl Cancer Inst 1990;82:1247–59.
2. Arbuck SG, Christian MC, Fisherman JS, et al. Clinical development of taxol. J Natl Cancer Inst Monogr 1993;15:11–24.
3. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). N Engl J Med 1995;332:1004–14.
4. Ettinger DS. Overview of paclitaxel (Taxol) in advanced lung cancer. Semin Oncol 1993;20:46–9.
5. Forastiere AA. Current and future trials of taxol (paclitaxel) in head and neck cancer. Ann Oncol 1994;5:1–4.
6. Holmes FA, Walters RS, Theriault RL, et al. Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. J Natl Cancer Inst 1991;18:1797–805.
7. Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barrett RJ. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. J Clin Oncol 1994;12:1748–53.
8. Kadlow JF, Chen S-H, Dextrazane P. Discovery of more efficacious analogs of paclitaxel for human clinical evaluation. Report from the 219th meeting of the American Chemical Society (ACS) 2000. Abstract no. 298.
9. Williams RC, Lee JC. Preparation of tubulin from brain. In: Cunningham LW, Frederiksen DW, editors. Methods in enzymology. New York: Academic Press, Inc.; 1982. p. 9376–85.
10. Swindell CS, Krauss NE, Horwitz SB, Ringel I. Biologically active taxol analogs with deleted A-ring side chain substitutes and variable C-2′ configurations. J Med Chem 1991;345:1176–84.
11. Rose WC, Fairchild C, Lee FYF. Preclinical antitumor activity of two novel taxanes. Cancer Chemother Pharmacol 2001;47:97–105.
12. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.
13. Gibaldi M, Perrier D. Noncompartmental analysis based on statistical moment theory. 2nd ed. In: Pharmacokinetics. New York: Marcel-Dekker; 1982. p. 409–17.
14. Advani R, Fisher GA, Lum BL, et al. Phase I and pharmacokinetic study of BMS-188797, a new taxane analog, administered on a weekly schedule in patients with advanced malignancies. Clin Cancer Res 2003;9:5187–94.
15. Advani R, Fisher GA, Jambalos C, et al. Phase I study of BMS-188797, a new taxane analog administered weekly in patients with advanced malignancies. American Society of Clinical Oncology Annual Meeting; 2001. Abstract no. 422.
16. Goldstein LJ, Vaders L, Rogatko A, et al. A phase I study of BMS-188797, a new taxane analog, given weekly in patients with advanced malignancies. American Society of Clinical Oncology Annual Meeting; 2001. Abstract no. 2093.
17. Kim JS, Amorino GP, Pyo H, et al. The novel taxane analog, BMS-184476 and BMS-188797, potentiate the effects of radiation therapy *in vitro* and *in vivo* against human lung cancer cell lines. Int J Radiat Oncol Biol Phys 2001;51:525–34.
18. Advani RH, Fisher GA, Cho CD, et al. Phase I study of weekly BMS-188797 in combination with carboplatin in patients with advanced malignancies. American Society of Clinical Oncology Annual Meeting; 2002. Abstract no. 402.
19. du Bois A, Frickhofen N, Loehr A, et al. A phase I dose escalating study of novel taxane BMS-188797 in combination with cisplatin in patients with advanced malignancies. American Society of Clinical Oncology Annual Meeting; 2002. Abstract no. 401.

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