Phase I and Pharmacokinetic Study of BMS-188797, a New Taxane Analog, Administered on a Weekly Schedule in Patients with Advanced Malignancies

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ABSTRACT

Purpose: The purpose of this study was to establish the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), and preliminary activity of BMS-188797 administered weekly.

Experimental Design: Patients with advanced malignancies were treated with escalating doses of BMS-188797 on a weekly schedule as a 1-h i.v. infusion. Plasma sampling was performed to characterize the pharmacokinetics of BMS-188797.

Results: Eighteen patients with advanced malignancies were enrolled at three dose levels ranging from 35 to 65 mg/m². The number of patients evaluated at each dose level was as follows: 35 mg/m² (n = 3); 50 mg/m² (n = 9); and 65 mg/m² (n = 6). At 65 mg/m², three of six patients had a DLT (one had grade 4 neutropenia lasting >7 days, and two had grade 3 diarrhea). Expansion of the 50-mg/m² dose cohort to nine patients established this dose as the MTD, with one patient experiencing a DLT (grade 4 neutropenia with fever). Two partial responses were observed (lung cancer, 7+ months; ovarian cancer, 6+ months durations), as well as two minor responses (esophageal cancer, 5 months; ovarian cancer, 5 months). Both patients with partial responses had been clinically resistant to paclitaxel. Plasma pharmacokinetic mean values of maximum concentration (Cmax) and area under the curve (AUC0–48) increased in a dose-dependent manner within the range of doses used in this study, and in three of four patients, the DLTs correlated with AUC.

Conclusions: The MTD and the recommended Phase II dose of weekly BMS-188797 is 50 mg/m². The drug demonstrates antitumor activity in taxane-refractory solid tumors and is now being evaluated in combination with carboplatin.

INTRODUCTION

Paclitaxel is the first member of a novel class of cytotoxics that stabilize microtubules, causing cells to accumulate in the mitotic (M) phase of the cell cycle and undergo apoptosis (1, 2). Both paclitaxel and docetaxel display antitumor activity in experimental tumor models and are active clinically in a broad range of cancers (3). The clinical utility of these agents is limited by drug resistance and toxicities that include myelosuppression and peripheral neuropathy.

Many analogues of paclitaxel have been synthesized, with the goals of achieving a broader spectrum of antitumor activity and a more favorable toxicity profile (4). BMS-188797 is the 4-desacetyl-4 methyl carbonate analogue of paclitaxel. Like paclitaxel, BMS-188797 inhibits cell cycle progression by blocking cells at the mitotic phase of the cell cycle. BMS-188797 demonstrated equivalent or superior antitumor activity compared with paclitaxel and docetaxel in all in vivo models that were tested, including the HCT/pk human colon carcinoma with multidrug resistance expression (5). In the tubulin polymerization assay, BMS-188797 was approximately twice as potent as paclitaxel (5). In vitro studies suggest a reduced cross-resistance with paclitaxel in P-gp2 mediated multidrug resistance cell lines. The other human tumor models in which a therapeutic advantage was observed include the ovarian carcinoma line A2780, L2987 lung carcinoma, and HOC79, a clinically derived ovarian carcinoma xenograft partially resistant to paclitaxel (5).

Weekly paclitaxel administration has been developed in attempts to increase dose intensity, decrease toxicity, and increase efficacy (6–10). The primary aims of this Phase I trial were to determine the MTD of weekly BMS-188797, establish the recommended Phase II dose based on the MTD, and assess the DLTs and safety of the drug when administered by a 1-h i.v. infusion. Secondary objectives were to determine the plasma pharmacokinetics of weekly BMS-188797 and describe any evidence of antitumor activity.
MATERIALS AND METHODS

This was an open-label, single-arm Phase I dose-escalation study of weekly BMS-188797 in patients with nonhematological malignancies, performed at Stanford University Medical Center.

Patient Selection. Patients were eligible if they had pathological confirmation of a malignancy that was unresponsive to ≤3 standard therapies or for which there was no known effective treatment. Treatment with a prior taxane (paclitaxel or docetaxel) was permitted. Patients were required to have measurable disease, an Eastern Cooperative Oncology Group performance status of 0–2, and anticipated survival of >3 months. No chemotherapy, immunotherapy, wide-field radiotherapy (≥30% of the bone marrow), or major surgery for 4 weeks before study entry was permitted. In addition, patients must have recovered to ≤grade 1 from toxicities of previous therapies. Laboratory parameters for inclusion were serum creatinine < 1.5 mg/dl, bilirubin < 1 mg/dl, aspartate aminotransferase < 3 × upper limit of normal, WBC count > 3,500/mm³, and platelet count > 100,000/mm³. Appropriate imaging performed <4 weeks before study entry were accepted for baseline tumor measurements. Exclusion criteria included active central nervous system metastasis, prior history of hypersensitivity to Cremophor EL, or pre-existing neurotoxicity. Female patients were required to be nonpregnant and nonlactating. The protocol was approved by the Stanford Committee for the Protection of Human Subjects and performed in accord with an assurance filed with and approved by the United States Department of Health and Human Services, and all patients signed an informed consent form.

Drug Administration and Dose Escalation. The starting dose of BMS-188797 was 35 mg/m² weekly, which was one-third the dose that had been safely administered in an every 3 week Phase I study with BMS-188797 (11). Three dose levels were evaluated: 35; 50; and 65 mg/m². BMS-188797 was administered by a 1-h i.v. infusion on day 1, 8, and 15 of each 21-day cycle. BMS-188797 was supplied in 50-mg vials containing 50% Cremophor EL and dehydrated ethanol in a volume of 8.3 ml. The drug was diluted before infusion with either 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP, to a final concentration of 0.3–1.2 mg/ml and administered through polyethylene-lined administration sets.

Patients were treated for at least two cycles unless progression or unacceptable toxicity occurred. Cohorts of three patients were treated at each dose level. If a DLT was observed in one patient, the cohort was expanded to six patients. If no further DLT was observed, the next dose level was opened. If two DLTs were observed, then the MTD would be defined as the next lower dose level. Escalation to a higher dose level occurred only after three patients at a given dose level had been observed for 21 days. If, after dose escalation to a new level, a DLT occurred during the second course of a patient at a prior dose level, current accrual at the new (higher) dose level was suspended until the prior cohort had been expanded to six patients. When the MTD for weekly BMS-188797 was reached, that dose level was expanded to nine patients to determine its suitability as the recommended dose for Phase II single-agent studies. Patients requiring more than two dose reductions were taken off study, except for patients with objectively responding disease. Responding patients could continue treatment on study if a third dose reduction was required after consultation and approval by the sponsor.

Treatment was scheduled to be administered on days 1, 8, and 15 every 21 days. To be retreated, patients had to continue to satisfy eligibility requirements of performance status, hematological parameters, and hepatic and renal function criteria. In addition, before retreatment, all toxicities must have recovered to baseline or ≤grade 1. All patients were followed for a minimum of 4 weeks after the last dose of BMS-188797 or until toxicities resolved.

DLTs. Adverse events and other symptoms were graded according to the National Cancer Institute Common Toxicity Criteria Version 2.0. DLTs were defined as any of the following occurring in the first or second course and considered related to BMS-188797: ANC < 500 cells/mm³ for ≥7 consecutive days or febrile neutropenia [i.e., fever of ≥38.5°C (nonaxillary)] with ANC < 1,000 cells/mm³; thrombocytopenia < 10,000 cells/mm³ or bleeding episode requiring platelet transfusion; any grade 3 or greater nonhematological toxicity except fatigue/asthenia, transient arthralgia/myalgia (unless unresponsive to medical intervention), aspartate aminotransferase and alanine aminotransferase elevations that resolve to baseline within 21 days, or nausea and/or vomiting (unless unresponsive to medical intervention). In addition, DLT included continuing toxicity that delayed retreatment for ≥21 days, and more than one dose omission within one treatment course of three weekly doses. A patient experiencing a DLT could receive subsequent therapy at the next lower dose level, provided the patient had recovered from all toxicities to baseline or grade 1.

Pharmacokinetic Analyses. Serial blood samples were collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 h after the start of the 1-h infusion. Within 1 h of collection, the plasma was separated by centrifugation at 1000 rpm for 15 min 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 of 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 was evaporated to dryness, and the residue was 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 2.2–870 ng/ml.

Estimates of pharmacokinetic parameters for BMS-188797 were derived from individual concentration-time data by non-compartmental analyses (12). Maximum plasma concentrations (Cmax) were recorded directly from experimental observations. The area under the plasma concentration-versus time curve from time 0 to the time of the last measurable concentration, T (AUC0–T), was calculated using a combination of linear and log trapezoidal summations. The first-order rate constant of decline of plasma BMS-188797, λ, was estimated by log-linear regression of at least three data points. The absolute value of λ was used to estimate the terminal elimination half-life, T1/2. The last measurable concentration and the rate constant, λ, were used to
extrapolate the AUC_{0-T} to estimate AUC_{0-\infty} (the area under the curve from time 0 to infinity). Total body clearance (Cl) was calculated by dividing the dose by AUC_{0-\infty}. Volume of distribution at steady-state (V_{SS}) was calculated using standard non-compartmental methods.

The relationship between BMS-188797 systemic exposure and toxicity as indicated by the percentage decrease in the ANC was explored. The percentage decrease in ANC was calculated as follows: % decrease in ANC = (100% × [pretreatment count – nadir count]/pretreatment count. The relationship between AUC_{0-\infty} and decreased ANC was described with a sigmoid $E_{\text{max}}$ model of drug action $E = E_0 + E_{\text{max}} \times \text{AUC}^{\gamma}/(\text{AUC}^{\gamma} + \text{AUC}_{50}^{\gamma})$. The input values were the observed percentage 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 $E_{\text{max}}$ model using Kinetica 4.0.2 (InnaPhase Corp., Philadelphia, PA). The output values were the maximal effect ($E_{\text{max}}$), 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 $\gamma$).

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.

**Statistical Methods.** Descriptive statistics were used in the analysis of safety. For each of the pharmacokinetic parameters, summary statistics were tabulated by dose of BMS-188797. Scatter plots $versus$ dose were examined for relationships to dose.

**Efficacy Analyses.** The primary efficacy parameters were response rate and time to progression. PR was defined as a 50% reduction in the sum of products of the two largest perpendicular diameters of all measurable lesions for at least 4 weeks and with no new lesion or progression of assessable disease. MR was defined as partial regression of disease of at least 4 weeks and with no new lesion or progression of assessable disease. The time to progression was measured from tumor size measured as the bidimensional product of perpendicular diameters.

**RESULTS**

Between April and November 2000, 18 patients were enrolled, with characteristics shown in Table 1. Thirteen of 18 patients had received prior paclitaxel-containing regimen. None of the patients had received prior docetaxel therapy. A total of 78 cycles (234 doses) were administered over the three dose levels administered (Table 2). Dose omissions in the first two cycles occurred in 12 patients (6 patients at dose level 50 mg/m$^2$ and 6 patients at dose level 65 mg/m$^2$).

Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Gender</th>
<th>Age</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Median</td>
<td>Ovary</td>
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<tr>
<td></td>
<td>Female</td>
<td>Range</td>
<td>Lung</td>
</tr>
<tr>
<td>18</td>
<td>5</td>
<td>62</td>
<td>Colon</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>33–74</td>
<td>GI$^b$ stromal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Others$^b$</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

$^a$ GI, gastrointestinal.  
$^b$ One each of mesothelioma, breast, esophagus, ampulla of Vater, and peritoneal.

Initially, premedication for possible hypersensitivity was not required. However, the occurrence of a grade 3 hypersensitivity reaction in one patient in the first cohort resulted in a protocol amendment requiring premedication for all patients receiving BMS-188797. The premedication regimen consisted of dexamethasone, an antihistamine such as diphenhydramine, and an H$_2$-receptor blocking agent such as cimetidine or ranitidine.

**Determination of MTD.** There were no DLTs observed at the 35 mg/m$^2$ dose. One patient developed a hypersensitivity reaction despite premedications and was removed from the study. The next cohort was treated at 50 mg/m$^2$, and none of the three patients experienced a DLT. At the third dose level of 65 mg/m$^2$, three of six patients developed a DLT (two developed grade 3 diarrhea, and one developed grade 4 neutropenia), and the MTD was thus determined to be 50 mg/m$^2$. Subsequently, six additional patients were treated at the MTD dose level for a total of nine assessable patients, and this dose was well tolerated, with only one of the nine patients experiencing a DLT (grade 4 neutropenia). The DLTs experienced at each dose level are shown in Table 2.

**Nonhematological Toxicity.** Of the 18 patients enrolled, all were assessable for toxicity. No grade 4 nonhematological toxicity was noted (Table 2). Grade 3 diarrhea was observed in two patients in the first cycle at a dose of 65 mg/m$^2$. This resolved with the use of standard doses of loperamide, and treatment at a lower dose level was well tolerated.

Other nonhematological toxicities were all mild (grade 1–2). Nail discoloration and increased brittleness were observed in nine patients after the fourth treatment and appeared to be progressive with increasing duration of treatment. One of nine patients developed a grade 2 peripheral neuropathy at 50 mg/m$^2$. Subsequent cycles administered at a lower dose level were well tolerated, with improvement of symptoms. Ocular tearing and nasal congestion were also reported in eight patients and appeared to be unrelated to the number of cycles administered.
This symptom resolved spontaneously. Treatment with artificial tears or other ocular moisturizers ameliorated symptoms in some patients. Fluid retention, i.e., peripheral edema (grade 1–2), developed in six patients (two patients at 35 mg/m$^2$ and four patients at 50 mg/m$^2$). Diuretics had little effect on this edema. Fatigue was mild and did not result in dose delays or dose reduction, except in one patient at the 50 mg/m$^2$ dose level, who experienced grade 3 fatigue during the sixth cycle of treatment.

One patient at the first dose level experienced a hypersensitivity reaction consisting of cough and dyspnea, which began within 30 min of the administration of BMS-188797. The patient’s symptoms resolved after the i.v. infusion rate was decreased and treatment with an antihistamine and steroids was given. Despite adequate premedication with an antihistamine and steroids for the subsequent dose of BMS-188797, the patient had a recurrence of symptoms and was removed from the study. This patient had bronchioalveolar carcinoma and had experienced a similar episode during a prior paclitaxel treatment. She was a heavy smoker with emphysema. Subsequent patients were premedicated without further hypersensitivity episodes.

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### Table 2 Dose levels, number of treatment cycles, and DLTs

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of patients</th>
<th>No. of cycles administered</th>
<th>DLTs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 mg/m$^2$</td>
<td>3</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>50 mg/m$^2$</td>
<td>9</td>
<td>50</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>65 mg/m$^2$</td>
<td>6</td>
<td>11</td>
<td>1 (17%)</td>
</tr>
</tbody>
</table>

* Patients were evaluated for DLT during the first or second cycle of therapy only.

### Table 3 Hematological toxicities by dose level of weekly BMS-188797a

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Grade 4 neutropenia</th>
<th>Grade 4 neutropenia with fever</th>
<th>Grade 3 neutropenia</th>
<th>Grade 1–4 thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 mg/m$^2$</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50 mg/m$^2$</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>65 mg/m$^2$</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* These toxicities are the highest grade recorded during the first two cycles.

### Hematological Toxicity

Hematological toxicity was mild, with seven patients developing grade 3 neutropenia, and five patients developing grade 4 neutropenia (Table 3). Of the five patients who developed grade 4 neutropenia, two patients each were treated at the 35 and 50 mg/m$^2$ dose levels, and one was treated at the 65 mg/m$^2$ dose level. The patient who received 65 mg/m$^2$ had experienced problems with hematological tolerance during prior chemotherapy with doxorubicin, ifosfamide, and dacarbazine. In this patient, grade 4 neutropenia developed 2 weeks after BMS-188797 administration and persisted for 2 weeks, necessitating removal from the study.

One patient developed a grade 4 neutropenia with fever at a dose of 50 mg/m$^2$. Subsequent treatment at a dose of 35 mg/m$^2$...
was well tolerated. Grade 3 neutropenia occurred in three patients at a dose of 50 mg/m², resulting in an omission of the day 15 dose. One patient was able to receive four of six planned doses, whereas the other two patients were able to receive two of three planned doses. At the 65 mg/m² dose level, two patients developed grade 3 neutropenia resulting in the omission of the day 15 dose in cycle 1. Both of these patients were then treated at 50 mg/m² with good tolerance. No thrombocytopenia was noted at any dose level.

Pharmacokinetic and Pharmacodynamic Evaluation. Plasma samples were obtained from 18 patients during the first cycle of treatment. One patient at the 50 mg/m² dose level and one patient at the 65 mg/m² dose level were excluded from pharmacokinetic evaluation because of insufficient sample collection and collection from the infusion port. Plasma concentrations were quantifiable in all patients through 48 h.

Mean (SD) plasma concentration-time profiles are shown in Fig. 1, and mean BMS-188797 pharmacokinetic parameters are listed in Table 4. The mean values of $C_{\text{max}}$ and AUC$_{0-H11009}$ at each dose increased in a dose-related manner. At the 50 mg/m² dose level, the MTD, there was a 2.2-fold range of AUC$_{0-H11009}$ values. The relationship of individual values of $C_{\text{max}}$ and AUC$_{0-H11009}$ to dose is plotted in Fig. 2. There was overlap in $C_{\text{max}}$ and AUC$_{0-H11009}$ values among the doses. Overall dose levels Cl values ranged from 135 to 344 ml/min/m², $T_{1/2}$ values ranged from 11.9 to 136 h, and $V_{SS}$ values ranged from 84 to 1021 liters/m².

The pharmacodynamic relationship between the percentage of decrease in ANC during course 1 and the BMS-188797 exposure (AUC$_{0-H11009}$) was well described by a sigmoid $E_{\text{max}}$ model of drug action as shown in Fig. 3. Mean ± SD values of the $E_{\text{max}}$ model parameter estimates were as follows: $E_{\text{max}}$, 87.9 ± 7.6; AUC$_{50}$, 2381 ± 153; and $\gamma$, 5.7 ± 2.5.

Responses. PRs were observed in two patients, and MRs were observed in two patients. One of the patients with a PR was a 57-year-old woman with non-small cell lung cancer and extensive pleural-based disease who had received two prior chemotherapeutic regimens, including carboplatin and paclitaxel without remission. Her response is shown in Fig. 4. After 6 months of treatment, she developed a grade 2 peripheral neuropathy requiring a dose reduction to 35 mg/m². Because there was no improvement in the neuropathy after the dose reduction, she was removed from the study. The second patient with a PR was a 72-year-old woman with ovarian cancer who had received four prior chemotherapeutic regimens. Her disease had undergone remission with first-line therapy of carboplatin and pacli-
taxel but then failed to respond to this regimen at relapse. Her response is shown in Fig. 5. She tolerated the treatment well with grade 2 nail changes as the predominant toxicity. MRs were observed for 5 months each in a 69-year-old man with metastatic esophageal cancer previously treated with three prior chemotherapeutic regimens and a 53-year-old woman with ovarian cancer. All four patients who experienced tumor regressions with BMS-188797 had previously failed a paclitaxel-containing regimen. In addition to the responders, one patient with ovarian cancer had disease stabilization for 9 months.

DISCUSSION

Taxanes such as paclitaxel and docetaxel have demonstrated promising activity against several tumor types including ovarian, breast, esophageal, and non-small cell lung carcinomas (6, 13–15).

BMS-188797 is a chemical derivative of paclitaxel with potential advantages over paclitaxel. It possesses a single structural modification from paclitaxel (BMS-181339) in which the C4 carbon is modified to form the 4-desacetyl-4-methyl carbonate derivative of paclitaxel. In vitro assays suggest that BMS-188797 is approximately twice as potent as paclitaxel in the tubulin polymerization assay (5). At equimolar doses to paclitaxel, BMS-188797 has demonstrated equivalent or superior efficacy in a several preclinical tumor models (5).

In this study, the MTD of BMS-188797 was found to be 50 mg/m² administered weekly. This is the recommended Phase II dose when administered as a single agent. The main DLTs were neutropenia and diarrhea. At a dose level of 65 mg/m², the DLTs in three of six patients were grade 3 neutropenia in one patient and grade 3 diarrhea in two patients. At 50 mg/m², the
The drug was well tolerated, with only one patient experiencing a DLT (grade 4 neutropenia). Six of the nine patients at this dose level were able to receive their treatments as planned, suggesting that a weekly interval schedule is feasible at this dose.

Observation of dose-limiting diarrhea observed with BMS-188797 differs from the toxicities reported for paclitaxel ordocetaxel, where diarrhea is characteristically not dose-limiting. This might be due to higher mucosal concentrations of BMS-188797 in the gastrointestinal tract due to a decreased affinity for the P-gp multidrug transporter, which is constitutively expressed in the apical surfaces. Dose-limiting diarrhea has been observed with other taxane derivatives, such as RPR 109881A, which also demonstrates a lower affinity for the P-gp drug transport pump (16).

Other nonhematological toxicities were generally mild (≤grade 2). Only one patient developed grade 3 fatigue, and one other patient developed grade 3 vomiting. Peripheral neuropathy was mild and grade 1 in all patients but one at the 50 mg/m² dose, in whom it was grade 2. This improved with a dose reduction to 35 mg/m². Like paclitaxel, the neuropathy appeared to be related to the duration of treatment. Unlike docetaxel, only mild fluid retention was noted in six patients. Hypersensitivity reactions to paclitaxel due to Cremophor EL have led to the practice of routine administration of premedications (17–19). In this study, one patient developed a hypersensitivity reaction and was removed from the study. Because this occurred early on in the accrual, subsequent patients were all premedicated without any reactions, and it is recommended that standard premedications be used for BMS-188797 as for paclitaxel. Mild tearing was observed in eight patients, similar to reports of weekly docetaxel in which conjunctival or tearing problems have been reported in 19–29% of patients (20).

Pharmacodynamic analysis using a sigmoidal E_max model demonstrated that the BMS-188797 AUC correlated with DLTs in three of four patients. Future pharmacodynamic analyses could assess patient characteristics that lead to the variability in the AUC, and further define appropriate target concentrations to enhance the therapeutic index of the agent. In a previous study of BMS-188797 administered on an every-3-week schedule (11), a nonlinear increase in maximal concentration and AUC was noted at doses greater than 110 mg/m². In contrast, our Phase I study of weekly BMS-188797 displayed linear pharmacokinetics within the dose range delivered.

Debate continues on whether there is benefit from bazing the dose of oncology agents on BSA (21, 22). In this study, a linear regression of the absolute clearance in ml/min versus BSA in m² produced a positive slope of 431 ml/min/m² with a coefficient of determination (R²) of 0.27. The clearance values ranged from 213 to 633 ml/min, and the BSAs ranged from 1.52 to 2.07 m². The range in BSA does not appear to account for the extremes in clearance. The results of this study do not provide a clear answer as to whether there is benefit from bazing the dose of BMS-188797 on BSA. However, in our group of cancer patients of typical BSA range, BSA was only able to explain 27% of the variability in BMS-188797 clearance. Other factors, such as variations in cytochrome P-450 enzymatic activity and P-gp intestinal excretion of taxanes, are likely to play a major role in BMS-188797 pharmacokinetics, similarly to that described previously for paclitaxel (21).

In this Phase I study, encouraging antitumor responses were observed (two PRs and two MRs), supporting the preclinical profile of this agent (5). All of the responding patients had received paclitaxel as prior therapy, suggesting that this agent is at least partially non-cross-resistant with paclitaxel.

In summary, this Phase I study indicates that weekly BMS-188797 is well tolerated and is a promising novel taxane. The recommended dose for further testing is 50 mg/m² administered weekly. It merits further evaluation in Phase II studies and in combination therapy in paclitaxel-naïve and -refractory patients. A study combining this agent along with carboplatin is currently ongoing at our institution.

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REFERENCES


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