Phase I Study of the Taxane BMS-188797 in Combination with Carboplatin Administered Every 3 Weeks in Patients with Solid Malignancies

Mayer N. Fishman,1 Christopher R. Garrett,1 George R. Simon,1 Alberto A. Chiappori,1 Richard M. Lush,1 William R. Dinwoodie,1 J. Joseph Mahany,1 Anne M. Dellaportas,1 Alan Cantor,2 Ashwin Gollerki,3 Marvin B. Cohen,3 and Daniel M. Sullivan1

Abstract

Rationale: BMS-188797 is one of several novel taxanes in ongoing clinical development. It has superior activity in experimental tumor models when compared with paclitaxel. BMS-188797 has a single C-4 modification, a 4-desacetyl-4-methylcarbonate, compared with paclitaxel.

Methods: We did a phase I study, in which a fixed dose of carboplatin was combined with a dose escalation schedule of BMS-188797, both administered once every 3 weeks, in patients with advanced solid malignancies.

Results: Thirty patients were treated, 11 at the proposed recommended phase II dose. The dose-limiting toxicity was myelosuppression. There was a linear relationship between administered dose of BMS-188797 and the measured area under the curve (AUC). There was significant interpatient variability of BMS-188797 AUC at the maximum tolerated dose. Two radiographic partial responses were observed: one patient with duodenal adenocarcinoma and one patient with esophageal adenocarcinoma (time on study, 19 and 30 weeks, respectively).

Conclusion: The recommended phase II dose for BMS-188797 and carboplatin administered on a once-every-3-week schedule is carboplatin AUC = 5 mg min/mL and BMS-188797 at a dose of 135 mg/m².

Taxane-based therapies are indicated in the therapy for cancers, including non–small cell lung (1), breast (2), ovarian (3), prostate (4), and head and neck (5). Clinical application of the commercially available taxanes (paclitaxel and docetaxel) is associated with myelotoxicity, peripheral neuropathy, and hypersensitivity reactions. The major mechanism of action is through stabilization of microtubule polymerization, blocking cells at the mitotic phase of the cell cycle and inducing detectable DNA fragmentation, apoptosis, and tumor regression (6). Additional biochemical effects may include more subtle proapoptotic effects, such as up-regulation of p53 (7–9).

Resistance to taxane therapy is a frequent clinical event. Mechanisms of resistance include mutations of the binding site on \( \text{h-tubulin} \). Although the relevance of this in human cancer is not established (10). Another taxane resistance mechanism is up-regulation of ATP-binding cassette transporter proteins, including P-glycoprotein (11, 12). Finally, an effect on taxane sensitivity may result from the differential expression of \( \text{h-tubulin} \) isotypes, which may be modulated by other receptor activation or gene expression (13).

In view of these limitations intrinsic to the available taxanes, there is preclinical and clinical development of novel taxanes ongoing. BMS-188797 is a synthetic analogue of paclitaxel. It differs in that the C4 carbon is modified to form the 4-desacetyl-4-methylcarbonate. The side chain of \( \text{h-tubulin} \) Phe272 is a point of contact with the C4 methyl group of paclitaxel (14).

In vitro, BMS-188797 is twice as potent as paclitaxel in a tubulin polymerization assay (15, 16); the solubility is comparable for the two compounds. This superior per mole potency has been considered promising as less Cremophor/ethanol vehicle would need to be administered per dose, possibly obviating the need for premedication. BMS-188797 was superior in four in vivo tumor models and was more active than paclitaxel-resistant cell lines (17). In vitro studies comparing BMS-188797 with paclitaxel show that BMS-188797 to be equal to, or superior, in terms of efficacy. In in vitro cytotoxicity assays, the IC50 of BMS-188797 was comparable with paclitaxel in the human colon cancer cell line HCT-116 and the human ovarian cell line A2780 (18). In in vitro human xenograft models using the M109 murine lung carcinoma, the 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. BMS-188797 was superior to paclitaxel when evaluated using HOC709 human ovarian cancer cell line, derived from a subject whose tumor was clinically resistant to paclitaxel. In no in vitro study has BMS-188797 been shown to be inferior to paclitaxel.

Platinum analogues are in wide contemporary use for treatment of advanced solid cancers. The molecular basis for taxane and platinum analogue synergy is a schedule-dependent effect in which taxane exposure results in higher accumulation of the platinum analogue (19).

BMS-188797, administered as monotherapy in patients with advanced malignancies, has undergone phase I evaluation administered on a weekly (20) and a once-every-3-week schedule (21). The respective recommended phase II doses were 50 and 175 mg/m², respectively, with the dose-limiting toxicities (DLT) in both studies being prolonged neutropenia and diarrhea in the former study and febrile neutropenia in the latter study. The most frequently observed serious (grade ≥3) toxicities observed in both of these phase I studies was myelosuppression. We report here a phase I dose escalation trial of BMS-188797 in combination with carboplatin: BMS-188797 was administered as a 1-hour infusion immediately followed by carboplatin as a 1-hour infusion on day 1 of each 21-day cycle.

Patients and Methods

Inclusion and exclusion criteria. Subjects with nonhematologic malignancies, which had progressed on standard therapy, or for whom no life-prolonging treatment was known, were eligible for enrollment. Additional requirements for entry included histologic or cytolgic confirmed diagnosis of cancer, Eastern Cooperative Oncology Group performance status of 0 or 1, age >18, and adequate bone marrow, hepatic, and renal function defined by lab results on the treatment day showing neutrophils >1,500/mm³, platelets >100,000/mm³, aspartate aminotransferase and alanine aminotransferase <2.5 × ULN (unless clearly related to liver metastasis), total bilirubin <1.5 mg/dL, and creatinine <1.5 × ULN (unless clearly related to liver metastasis). Subjects were not eligible if they had been recently treated for their cancer (2 weeks after last hormonal therapy, except megestrol acetate for anorexia or cachexia; at least 4 weeks after last chemotherapy, immunotherapy, radiotherapy, or major surgery; and at least 6 weeks after nitrosoureas or mitomycin C). Toxicities from previous therapies must have had recovered to baseline or to grade ≤1. Either measurable or nonmeasurable disease was allowed.

Subjects were not eligible if they had received more than two prior regimens for metastatic disease, prior therapy with platinum and/or taxane analogues, or were currently receiving therapy with corticosteroids. Patients were also not eligible if they had known brain metastases, a serious uncontrolled medical disorder or active infection, had experienced a prior hypersensitivity reaction to Cremophor EL, or had a psychiatric disorder or dementia that would impair rendering informed consent or compliance with treatment or follow-up. Women of childbearing potential were also excluded if they were pregnant, breast-feeding, or unwilling to use an effective method of birth control. Patient characteristics are shown in Table 1. Informed consent was obtained before any protocol-related procedures, including the use of an informed consent document approved by the University of South Florida Institutional Review Board. This consent process and the trial conduct were consistent with the declaration of Helsinki and Good Clinical Practice guidelines. Subjects were not eligible if they had been recently treated for their cancer (<2 weeks after last hormonal therapy, except megestrol acetate for the treatment of anorexia or cachexia; <4 weeks after last chemotherapy, immunotherapy, radiotherapy, or major surgery; <6 weeks after nitrosoureas or mitomycin C). Toxicities from previous therapies must have had recovered to baseline or to grade ≤1.

Treatment was administered every 21 days. Treatment was discontinued for the following reasons: disease progression, intolerable or unresolved toxicity, withdrawal of a subject’s consent, noncompliance with the protocol, life-threatening toxicity, grade ≥3 vestibular toxicity, loss of auditory acuity, requirement for corticosteroid medication (except as required for hypersensitivity reaction or as used for antinausea treatment), or at the investigator’s discretion.

Drug preparation and administration. Both carboplatin (Paraplatin) and BMS-188797 were supplied by Bristol-Myers Squibb (Princeton, NJ). Carboplatin was reconstituted to 10 mg/mL. This solution was administered on a weekly (20) and a once-every-3-week schedule (21). The respective recommended phase II doses were 50 and 175 mg/m², respectively, with the dose-limiting toxicities (DLT) in both studies being prolonged neutropenia and diarrhea in the former study and febrile neutropenia in the latter study. The most frequently observed serious (grade ≥3) toxicities observed in both of these phase I studies was myelosuppression. We report here a phase I dose escalation trial of BMS-188797 in combination with carboplatin: BMS-188797 was administered as a 1-hour infusion immediately followed by carboplatin as a 1-hour infusion on day 1 of each 21-day cycle.

Table 1. Patient characteristics

| No. patients | 30 |
| Gender (M/F) | 17:13 |
| Age median (range) | 61 (37-83) |
| Performance status 0:1 | 16:14 |
| Measurable disease | 30/30 |
| No. prior chemotherapy regimens | |
| None | 14 |
| 1 | 3 |
| 2 | 7 |
| 3 | 5 |
| 6 | 1 |
| Prior radiation therapy | 8/30 |
| Prior hormonal or immunotherapy | 7/30 |

Diagnoses
- Colorectal cancer: 7
- Kidney cancer: 7
- Non-small cell lung cancer: 5
- Mesothelioma: 2
- Adenoid cystic carcinoma: 2
- Other*: 9

*One each of adenocarcinoma of unknown primary, duodenal, esophageal, gastric, gastrointestinal stromal tumor, melanoma, and mucoepidermoid carcinoma.

Chemical structure of BMS-188797. Fig. 1.
further diluted in 250 mL of 0.9% NaCl and delivered i.v. over 30 minutes. The carboplatin dose was calculated using the modified Calvert formula (22), with the serum creatinine obtained on the day of administration. BMS-188797 was packaged as 50 mg/8.3 mL (6 mg/mL) injection concentrate with 50% Cremophor EL/50% dehydrated alcohol USP, in 12-mL type 1 flint glass vials, labeled with batch number and stored at 15°C to 25°C protected from light. For administration, BMS-188797 was diluted in 0.9% NaCl injection, USP, to a final concentration of 0.3 to 1.2 mg/mL in nondi(2-ethylhexyl)phthalate infusion containers (Vitalmix, PDI Medical Products, San Diego, CA). Carboplatin was administered by a 30-minute infusion using a Baxter Flowguards pump and was immediately followed by a 60-minute infusion of BMS-188797.

Due to a hypersensitivity reaction which had been observed in the phase I single-agent study (19), premedication with i.v. diphenhydramine (50 mg), ranitidine (50 mg), and dexamethasone (20 mg), 30 minutes before the start of BMS-188797 infusion was administered. The use of serotonin receptor antagonists was allowed but not required. If a subject developed a hypersensitivity reaction, the infusion was stopped, and the subject was treated with appropriate therapy as specified within the protocol. If the reaction was grade ≤2, the investigator could, at their discretion, rechallenge the subject with study drug.

Pharmacokinetics, specimen collection, and analysis. To characterize the plasma pharmacokinetics after the initial BMS-188797 1-hour infusion, plasma specimens were collected for determination of maximum plasma concentration (C_max), time of C_max (T_max), mean residence time, plasma elimination time (t_1/2), BMS-188797 area under the curve (AUC), steady-state volume of distribution (Vss), and total body clearance. Pharmacokinetic variables of BMS-188797 were calculated by noncompartmental methods as previously described elsewhere (21).

Plasma specimens for the pharmacokinetic measurements were collected using a separate line from the infusion, with the following time points: pre-BMS-188797 and then 30 and 60 minutes into the infusion. Additional samples were obtained 15, 30, 60, and 90 minutes and 2, 3, 4, 5, 7, 24, 48, and 72 hours after the infusion. Samples were collected in tubes containing EDTA, placed on ice, and then centrifuged at −1,500 relative centrifugal force for 15 minutes to separate plasma. Unless otherwise noted, all materials used in the sample processing were obtained by Sigma-Aldrich (St. Louis, MO). Within 1 hour of collection, the plasma was transferred to a screw-cap polypropylene tube and stored frozen at less than or equal to −20°C. Plasma samples were analyzed for BMS-188797 concentrations by high-performance liquid chromatography. After the addition of internal standard, BMS-183061, 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 an YMC-ODS-AQ, 4.6 × 150 mm, 3 μm column (YMC Europe, Schermbeck, Germany) 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.

Presafety evaluation within 2 weeks of starting included a history and physical examination, performance status, vital signs, toxicity assessment using the National Cancer Institute Common Toxicity Criteria version 2.0, complete blood count with differential, lactate dehydrogenase, comprehensive metabolic panel, magnesium, phosphorus, electrolycardiogram, and urinalysis. Presafety evaluations required within 4 weeks of start of drug included chest roentgenogram and baseline radiographic assessment of measurable or evaluable disease. A pregnancy test, as applicable, was required within 72 hours of starting drug and every other cycle thereafter.

Dose level assignment and escalation. The dose level of 100 mg/m² BMS-188797 in combination with carboplatin AUC = 6 mg min/mL was chosen for the initial cohort with subsequent dose levels of BMS-188797 of 100, 125, 150, and 175 mg/m² initially chosen. The following were to be considered as DLT events occurring in the first cycle: absolute neutrophil count < 500 cells/mm³ for ≥7 consecutive days, febrile neutropenia (temperature ≥38.5°C, with absolute neutrophil count < 1,000 cells/mm³), platelets < 10,000 or bleeding requiring platelet transfusion, any grade ≥3 nonhematologic toxicity [except fatigue/asthenia, transient arthralgia or myalgia, nausea, or vomiting (except nonresponsive to optimal medical management)], and aspartate aminotransferase or alanine aminotransferase elevations that resolve to baseline within 3 weeks], and a delay of recovery from toxicity causing a delay of >3 weeks. Events occurring after the first 21 days were recorded as a toxicity but not defined as a DLT. Intrapatient dose escalation was allowed for those subjects who completed two courses without toxicity worse than the Common Toxicity Criteria version 2.0 grade 1 during the previous two cycles, providing two subjects had completed a full treatment course at that dose level without experiencing a DLT. If subjects experienced a DLT, subsequent cycles were administered at one lower dose level of BMS-188797 and a carboplatin at an AUC of 1 mg min/mL lower. The only exception was isolated severe thrombocytopenia, after which only the carboplatin target AUC was reduced. Subjects were permitted only two dose reductions. If a subject continued to experience DLT after two dose reductions, they were removed from study. Use of colony-stimulating factors was restricted to the case of secondary prophylaxis, at the discretion of the investigator. Prophylactic use of erythropeoitin was not restricted.

Additional cycles of chemotherapy were administered to subjects in the absence of disease progression or prohibitive toxicity. The modified WHO Criteria was used for radiographic evaluation of disease response.

Statistical analysis and sample size. This was a phase I trial to determine the maximum tolerated dose (MTD) for this combination schedule. At each dose level without a DLT, it was planned to treat at least three patients. If no DLT events were observed, the dose level was

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**Table 2. Dose escalation scheme**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>BMS-188797 (mg/m²)</th>
<th>Carboplatin AUC (mg min/mL)</th>
<th>No. treated</th>
<th>DLT (febrile neutropenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
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<td>2</td>
<td>125</td>
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<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>135</td>
<td>5</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Fig. 2.** Worst grade of neutropenia, per dose level, in cycle 1.
considered tolerable, and the next higher cohort was opened to accrual. If two or more DLT events were observed, the dose level was considered not tolerated. If a single DLT were observed among the first three patients, up to three additional patients (total of six) at that dose level were to be enrolled, unless a second DLT was observed. Expansion of the MTD cohort to at least nine subjects so as to better characterize the pattern of toxicity and confirm the proposed phase II dose was planned.

Results

Patient characteristics. Between April 2000 and December 2001, 31 subjects were enrolled; one died before receiving protocol therapy (excluded from patient characteristics). One subject had a grade 2 hypersensitivity reaction during the BMS-188797 (Fig. 1) infusion. Demographic and prior therapies data for the 30 subjects treated are shown in Table 1.

Treatment results. A total of 84 cycles were administered to 30 subjects. Of the 54 cycles administered after cycle one, 16 were administered at a reduced dose due to previous toxicity. Despite premedication with dexamethasone, ranitidine, and diphenhydramine, one subject had an immediate allergic reaction during the first infusion of BMS-188797 and was withdrawn from the study. Of the 27 subjects that were evaluable for response that had received at least one full cycle of chemotherapy, two subjects experienced a partial response (esophageal and duodenal adenocarcinomas; time on study, 133 and 212 days, respectively).

Dose escalation. At the first cohort (BMS-188797 100 mg/m² followed by carboplatin AUC = 6 mg min/mL), none of the three patients experienced a DLT (see Table 2). At the second dose level, BMS-188797 was escalated to 125 mg/m². Two of six subjects had cycle 1 DLT at the second dose level (125 mg/m² BMS-188797 followed by carboplatin AUC = 6 mg min/mL), consisting of febrile neutropenia, one of which was prolonged neutropenia (grade 3 for 35 days). Due to the toxicity encountered, the protocol was amended to allow for a third dose level with a reduced dose of carboplatin (AUC = 5 mg min/mL) in combination with 125 mg/m² BMS-188797.

At this dose level, none of the three subjects had a DLT. At the fourth dose level (150 mg/m² BMS-188797 followed by carboplatin AUC = 5 mg min/mL), two of three evaluable patients experienced a DLT, both febrile neutropenia. Three additional subjects were treated at the third dose level (125 mg/m² BMS-188797 followed by carboplatin AUC = 5 mg min/mL), and none experienced a DLT. An intermediate dose level (135 mg/m² BMS-188797 followed by carboplatin AUC = 5 mg min/mL) was tested, and none of the six subjects evaluated at this dose level experienced a DLT. This was determined to be the recommended phase II dose. An additional five subjects were enrolled at this dose level, and none experienced a DLT.

Description of the toxicity events. As in the phase I single-agent studies, the DLT events were predominantly hematologic; all of the DLT events were grade 3 or 4 neutropenia with fever. There were two additional patients with neutropenia in this study not documented to have resolved to absolute neutrophil count >500 (grade <4) until the 8th and 7th days, respectively; these were not DLT-defined events.

The worst grade of neutropenia in cycle 1 was frequently grade 4; the frequency and grade of neutropenia that developed in cycle 1 and in all cycles is shown in Fig. 2. Figure 3 shows nonhematologic toxicity events across all cycles. One patient discontinued treatment after 134 days due to grade 2 sensory neuropathy (cumulative dose, 745 mg/m² following six cycles) and another after 213 days for grade 2 motor neuropathy (cumulative dose, 780 mg/m² following six cycles). There were no deaths attributed to toxicity. Metabolic toxicities included grade 1 hypomagnesemia in 7.9% of all cycles. Grade 2 thrombocytopenia was seen in 3.6% of patients treated, and grade 3 was seen in 1.2% of patients. Grade 3 hyperbilirubinemia developed in one subject treated.

Pharmacokinetic results. Specimens for pharmacokinetics were collected and measured from 26 subjects, including eight at the MTD. Figure 4 shows mean plasma concentrations within each BMS-188797 dose level versus time. The AUC(0—∞) for BMS-188797 for each measured subject was computed by a trapezoidal approximation (see Table 3). The average (± SD) of the computed mean residence times in the present study was 10.8 ± 3.2 hours, slightly lower than 15.0 ± 6.9.
the MTD of 135 mg/m², or at the third highest dose
significant variability of the AUC when BMS-188797 is given from 4,911 to 19,939 mg min/mL, a 4-fold variation. There is
min/m², comparable with 147.4 receiving 110 to 200 mg/m² in the single-agent study (21). The mean steady-state volume of distribution was
min/m², not markedly different from paclitaxel- or docetaxel-refractory subjects will be needed to determine if this
novel compound meets the developmental objective of non–cross-resistance.

The pharmacokinetic studies revealed some consistent and some variable features in the clearance of the drug. The more consistent features are the relationship of $C_{\text{MAX}}$ to AUC, the shape of the curve in general, and the half-life for elimination and mean residence time. Metabolism and clearance of taxanes are complex. The more precise prediction of the individual determinants of clearance remains an area for development, for BMS-188797, as well as paclitaxel or docetaxel. The primary end point of the present trial was based on DLT frequency, independent of the measured blood levels. The relatively small structural difference between paclitaxel and BMS-188797 alters the aqueous solubility of the compound but does not alter the major mechanism of action, which is binding to tubulin. There is currently no available structure-activity relationship explanation for the superior preclinical activity of BMS-188797 when compared with paclitaxel. The toxicities encountered were similar to those described with the combination of paclitaxel and carboplatin. The low frequency of thrombocytopenia seen with this combination may possibly be attributable to the platelet-sparing effect observed when paclitaxel is combined with carboplatin (23).

The clinical experience described herein suggests that the carboplatin and BMS-188797 doublet may be suited for further clinical development in phase II trials in solid tumors for which previously there has been activity identified for other taxane/platinum combinations. Partial responses in duodenal and esophageal adenocarcinomas suggest that further phase II clinical trials that evaluate the treatment of paclitaxel- or docetaxel-refractory subjects will be needed to determine if this novel compound meets the developmental objective of non–cross-resistance.

Table 3. Mean pharmacokinetic data, per dose level

<table>
<thead>
<tr>
<th>Dose level (m²)</th>
<th>$C_{\text{MAX}}$ (mg/mL)</th>
<th>AUC$_{0}\rightarrow\infty$ (ng h/mL)</th>
<th>MRT (h)</th>
<th>$t_{1/2}$ (h)</th>
<th>CLT (mL/min/m²)</th>
<th>V$_{SS}$ (L/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/150/m² (3)</td>
<td>7.254 ± 1.679 (23%)</td>
<td>11.513 ± 3.39 (23%)</td>
<td>13.6 ± 2.6 (19%)</td>
<td>30.9 ± 6.2 (20%)</td>
<td>145 ± 4 (3%)</td>
<td>118 ± 26 (22%)</td>
</tr>
<tr>
<td>125/175/m² (12)</td>
<td>8.083 ± 1.307 (16%)</td>
<td>13.286 ± 2.181 (16%)</td>
<td>10.5 ± 3.1 (30%)</td>
<td>26.1 ± 5.6 (21%)</td>
<td>161 ± 27 (17%)</td>
<td>100 ± 28 (28%)</td>
</tr>
<tr>
<td>150/200/m² (8)</td>
<td>6.447 ± 1.501 (23%)</td>
<td>12.829 ± 4.908 (38%)</td>
<td>10.4 ± 3.9 (38%)</td>
<td>22.1 ± 7.9 (36%)</td>
<td>209 ± 109 (52%)</td>
<td>126 ± 71 (56%)</td>
</tr>
</tbody>
</table>

NOTE: Data represents mean ± standard deviation with coefficient of variation expressed as a percentage in parenthesis.
Abbreviations: MRT, mean residence time; CLT, total body clearance.

Cycle 1 dose-limiting events were hematologic toxicity, consistent with the prior published single-agent experience. Using an empirical study design relying on frequency of DLTs (independent of AUC measurements), the recommended phase II dose for administration without growth factor support is 135 mg/m². The range of AUC across the eight measured values in the 135 mg/m² cohort is from 4,911 to 19,939 mg min/mL, a 4-fold variation. There is significant variability of the AUC when BMS-188797 is given at the MTD of 135 mg/m², or at the third highest dose administered, 125 mg/m².

Discussion

observed in the single-agent study but more comparable with the 12.1 ± 6.0 computed from the samples from patients receiving 110 to 200 mg/m² in the monotherapy study (21). Similarly, the average half-life for elimination was 25.3 ± 6.5 hours, comparable with the 25.5 ± 5.3 result in the single-agent study. The mean rate of clearance was 126 ± 68 mL/min/m², comparable with 147.4 ± 51.5 in the single-agent study (21). The mean steady-state volume of distribution was larger than total body water, $10^7 ± 46$ L/m², nonsignificantly lower than the average from the single-agent study but essentially not different from the average from the samples of patients receiving 110 to 200 mg/m² in the single-agent study (21).

Variability within the MTD dose cohort. The range of AUC of BMS-188797 across the eight measured values in the 135 mg/m² cohort is from 4,911 to 19,939 mg min/mL, a 4-fold variation. There is significant variability of the AUC when BMS-188797 is given at the MTD of 135 mg/m², or at the third highest dose administered, 125 mg/m².

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References

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