A Phase I Study of Oral BMS-275291, a Novel Nonhydroxamate Sheddase-Sparing Matrix Metalloproteinase Inhibitor, in Patients with Advanced or Metastatic Cancer

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ABSTRACT

Purpose: BMS-275291 is a novel broad-spectrum inhibitor of matrix metalloproteinase (MMPs) rationally designed to spare a class of closely related metalloproteinases known as sheddases. Inadvertent sheddase inhibition is hypothesized to play a role in the dose-limiting joint toxicities occurring with hydroxamate-based MMP inhibitors. This trial was conducted to establish the recommended phase II dose; determine safety, toxicity, and pharmacokinetics of BMS-275291; and to assess potential markers of sheddase activity (tumor necrosis factor-α (TNFα) release and TNFα-RII shedding).

Experimental Design: This was an open label, single arm, phase I study conducted at two centers. Patients with advanced or metastatic cancer were treated with once-daily oral BMS-275291 at doses escalating from 600 to 2400 mg/day. Six to eight patients/dose level were to be studied with the recommended phase II dose level expanded to a total of 15 patients. Pharmacokinetic sampling was performed on days 1, 15, and 29 at 0, 0.5, 1, 2, 4, 6, 8, and 24 h after dosing. Radiological tumor assessment was performed every 8 weeks.

Results: Forty-four evaluable patients were enrolled in this study with the most frequent tumor types being colorectal cancer and non-small cell lung cancer. Dose limiting toxicities were observed at 600 mg/day (one of eight patients with grade 3 transaminitis) and at 1200 mg/day (1 of 15 patients with grade 3 rash and grade 4 shortness of breath), both in the context of predisposing conditions. No dose-limiting toxicities occurred at 900, 1800, or 2400 mg/day. The most frequent adverse events considered possibly, probably, or definitely drug-related were joint toxicity (myalgia/arthritis), rash, fatigue, headache, nausea, and taste change, all of which were mild, grade 1, grade 2, and not dose-limiting. No objective tumor responses were observed. Twelve of forty-four patients received treatment for 4+ months, six for 8+ months, three for >1 year. Desired trough levels of parent BMS-275291 were maintained with once daily dosing. The mean plasma concentration of parent BMS-275291 at trough exceeded the calculated in vitro IC50 value for MMP-2 and IC90 value for MMP-9 at the recommended phase II dose of 1200 mg/day. No major changes in serum concentrations of sheddase enzymatic products, TNFα or TNFα-RII, were observed.

Conclusions: BMS-275291 is a nonhydroxamate MMP inhibitor with a novel mercaptoacetyl zinc-binding group. In this study, plasma concentrations of BMS-275291 continuously exceeded in vitro MMP IC50 values without dose-limiting joint toxicity. In this refractory patient population, a suggestion of disease stabilization was observed in 12 patients. On the basis of preclinical, clinical, and pharmacokinetic data, the recommended phase II dose for future study is 1200 mg/day.

INTRODUCTION

Matrix metalloproteinases (MMPs) are involved in normal wound healing, ovulation, and embryogenesis (1, 2) as well as in tumor growth, tumor metastasis, and tumor angiogenesis (3–5). MMPs are proteolytic enzymes that are thought to facilitate growth and angio genesis of tumors at primary and metastatic sites (2). There are >20 enzymes classified as MMPs, and MMP-2 and MMP-9 have been shown to be consistently overexpressed in human cancer; however, the precise pattern of overexpressed MMPs varies by tumor type. Elevated expression of various MMPs in serum or biopsy samples has been correlated with increased local invasiveness or shorter survival in several malignancies including non-small cell lung cancer (6–9), colorectal cancer (10, 11), and others (11–15).

Peptidic and nonpeptidic inhibitors have been rationally designed and selected based on the molecular structure of MMPs determined by X-ray crystallographic studies (16). Matrix metalloproteinase inhibitors (MMPIs) have been designed to inhibit a broad range of MMPs or to target specific MMPs selectively. Initial clinical trials with marimastat showed that this agent caused musculoskeletal toxicity that was dose limiting (17, 18). The mechanism of this toxicity has not been com-
BMS-275291, Sheddase-Sparing, MMPI

MATERIALS AND METHODS

Patient Selection. The protocol was approved by George-town and Duke University Institutional Review Boards. Inclusion criteria included the following: (a) histologically confirmed advanced cancer having failed standard therapy; (b) 18 years of age or older; (c) Karnofsky performance status ≥70%; (d) adequate hematological function (neutrophil count ≥1500/mm³, platelet count ≥100,000/mm³, hemoglobin ≥8 g/dl), hepatic function [aspartate aminotransferase, alanine aminotransferase <2 times upper limit of normal, total bilirubin <1.5 times upper limit of normal, alkaline phosphatase <2 times upper limit of normal], and renal function (serum creatinine <1.5 times upper limit of normal; and (e) if applicable, negative pregnancy test and effective means of contraception. Exclusion criteria included the following: (a) chemotherapy, immunotherapy, or radiotherapy within 4 weeks of the study; (b) investigational drug or major surgery within 2 weeks of the study; (c) known brain metastases (in the absence of neurological symptoms, baseline CNS imaging was not required for study entry); (d) prior history of inflammatory arthritis treated with systemic steroids or inflammatory arthritis within 6 months of the study; and (e) any condition that did not permit compliance with the protocol. All patients provided signed informed consent.

Treatment Plan. This study was a dose escalation phase I study of oral BMS-275291 in patients with advanced cancer. Drug was supplied as 150 mg of gelatin capsules and as 300 mg of tablets. Patients received a single oral daily dose and were assessed weekly for the first 4 weeks and every 2 weeks thereafter. Patients underwent radiographic disease assessment at week 9 of treatment and then every 8 weeks thereafter. In the absence of progressive disease, patients were allowed to continue on treatment. Five dose levels were evaluated (600, 900, 1200, 1800, and 2400 mg). In-patient dose escalation was not
permitted. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria. Six to eight patients were enrolled to each dose level, and if dose-limiting toxicity (DLT) was observed in ≤1 patient, the dose was escalated to the next dose level. Escalation to the next dose level occurred only after the last patient on the previous dose level was observed for 4 weeks, and <1 patient experienced a DLT at that dose level. Further dose level escalation would be discontinued if DLT was observed in ≥two of six patients. A recommended phase II dose was chosen based on clinical, pharmacokinetic, and surrogate marker data rather than based on maximum-tolerated dose; this dose level would be expanded to 15 patients according to the protocol to further characterize the recommended phase II dose level. Complete blood counts and chemistry (creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase/aspartate aminotransferase) were performed weekly for 4 weeks and every 2 weeks thereafter; prothrombin time and partial thromboplastin time were performed every 2 weeks, and platelet aggregation studies were performed on day 29. Chest radiograph or chest computed tomography scan and electrocardiogram were performed at baseline. Imaging studies to evaluate possible tumor response were performed every 8 weeks.

Twenty patients had pretreatment and on-study punch biopsies of skin from the fore arm as part of a study of the effect of BMS-275291 on wound angiogenesis. This was an ancillary study conducted only at Duke University and is reported separately (25).

Sample Collection and Analysis. Blood samples for pharmacokinetics were obtained on days 1, 15, and 29 at predose and at 0.5, 1, 2, 4, 6, 8, and 24 h after dosing, as well as predose on days 8 and 22. BMS-275291 contains a free sulfhydryl group and forms disulfide dimers with other sulfhydryl-containing molecules in vivo. Therefore, analytical methods were developed to quantitate both BMS-275291 and “total” BMS-275291 (BMS-275291 plus any BMS-275291 recovered from reducible disulfides containing BMS-275291). Because a free sulfhydryl group is required for activity, disulfides of BMS-275291 are inactive. To quantitate monomeric BMS-275291, blood samples were collected into tubes containing methyl acrylate to react with free sulfhydryl groups of monomeric BMS-275291. The resulting BMS-275291-methyl acrylate derivative was quantitated to provide monomeric BMS-275291 concentrations. For the quantitation of total BMS-275291, blood samples were treated with tris 2-carboxyethyl phosphine to reduce disulfide linkages before quantitation of BMS-275291.

An on-line extraction liquid chromatography-tandem mass spectrometry method was developed for the quantitation of unchanged BMS-275291. Chromatography was carried out using a Shimadzu LC-10AD VP pump and a Waters 2690 high-performance liquid chromatography system. Plasma samples containing methyl acrylate and internal standard (CH3921) were processed using an automated 96-well solid-phase extraction. Chromatographic separation was achieved isocratically on a YMC Basic, 2 50 mm, 5 μm column maintained at 35°C using an isocratic mobile phase containing water, acetonitrile, methanol, and ammonium acetate. Detection was by positive ion electrospray mass spectrometry in the selected ion-monitoring mode. The standard curve ranged from 20 to 5000 ng/ml and was linear. The intra-assay precision was within 8.5% relative standard deviation, and the inter-assay precision was within 9.7% relative standard deviation. The assay accuracy was within 5.6% of the nominal values.

A liquid chromatography mass spectrometry method was developed and validated for the quantitation of total BMS-275291. Plasma samples containing tris 2-carboxyethyl phosphine and internal standard (CH3921) were processed using an automated 96-well solid-phase extraction. Chromatographic separation was achieved isocratically on a YMC Basic, 2 50 mm, 5 μm column maintained at 35°C using an isocratic mobile phase containing water, acetonitrile, methanol, and ammonium acetate. Detection was by positive ion electrospray mass spectrometry in the selected ion-monitoring mode. The standard curve ranged from 20 to 5000 ng/ml, the intra-assay precision was within 6.1% relative standard deviation and the inter-assay precision was within 5.5% relative standard deviation. The assay accuracy was within 5.2% of the nominal values.

Pharmacokinetic Analysis. The plasma concentrations-time data for parent and total BMS-275291 were analyzed by noncompartmental methods using the program MENU/PK-MENU (SAS, Cary, NC). There was insufficient data (sampling only up to 24 h after dosing), for terminal elimination half-life determination for both parent and total BMS-275291. Compartmental analysis was performed using WinNonlin (v1.5, Pharsight Corp.).

Surrogate End Point Biomarker Studies and Analysis. Samples for quantitation of serum tumor necrosis factor-α (TNF-α) and soluble TNF receptor were collected immediately before dosing (predose) on days 1, 15, and 29. TNF-α and TNF-α receptor II extra cellular domain were assayed in patient plasma using commercially available ELISA kits (HSTA50 and DRT200, respectively; R&D Systems) using the manufacturer’s recommended method. ELISA plates were analyzed using a Molecular Devices V max Kinetic Microplate reader (Menlo Park, CA) at the recommended wavelengths.

RESULTS

Patient Characteristics. A total of 44 patients were treated with BMS-275291 at escalating dose levels of 600 to 2400 mg/day. Patient characteristics are shown in Table 1.
Table 2  Adverse events

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dose level</th>
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<tr>
<td></td>
<td>600 mg/day</td>
<td>900 mg/day</td>
<td>1200 mg/day</td>
<td>1800 mg/day</td>
<td>2400 mg/day</td>
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<td></td>
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<tr>
<td></td>
<td>(n = 8)</td>
<td>(n = 9)</td>
<td>(n = 15)</td>
<td>(n = 6)</td>
<td>(n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1  2  3  4</td>
<td>1  2  3  4</td>
<td>1  2  3  4</td>
<td>1  2  3  4</td>
<td>1  2  3  4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
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<td>4  2  3  4</td>
<td>2  3  4  2</td>
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<tr>
<td>Fatigue</td>
<td>4  5</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2  1</td>
<td>1  1</td>
<td>1  1</td>
<td>1  1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth/taste</td>
<td>1  2</td>
<td>3</td>
<td>1  1</td>
<td>1  1</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Nausea</td>
<td>2  2</td>
<td>3</td>
<td>1  1</td>
<td>1  1</td>
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<tr>
<td>Headache</td>
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<td>Anorexia</td>
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<tr>
<td>Flushing</td>
<td>3  3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1  1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Transaminitis</td>
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</table>

Adverse Events. Toxocities thought to be related to the study drug observed are listed by Common Toxicity Criteria grade and dose level in Table 2. Two dose-limiting toxicities occurred. One patient treated at 600 mg/day had an asymptomatic grade 3 elevation in aspartate aminotransferase that resolved after 7 days off drug. This patient had grade 1 aspartate aminotransferase elevation, a history of alcoholism and fatty liver infiltration by CT scan at baseline. One patient at 1200 mg/day had a grade 3 rash and a grade 4 dose-limiting dyspnea that was possibly related to study drug. This patient had progressive non-small cell lung cancer and a history of rheumatoid arthritis, scleroderma, and drug allergy. No dose-limiting toxicities occurred at the 900 mg/day (n = 9), 1800 mg/day (n = 6), or 2400 mg/day (n = 6) dose levels. One patient, a 62-year-old woman with a 22-year history of prior hormonal therapy and chemotherapy for breast cancer was discovered after 7 months on study to have bilateral, posterior, subcapsular cataracts.

The most frequent adverse events reported were generalized myalgia and specific arthralgias. These adverse events were reported in 26 of 44 (59%) patients. They were mild in the majority of patients, with grade 1 toxicity observed in 17 of 44 and grade 2 toxicity observed in 9 of 44 patients. No patient experienced grade 3 or 4 arthralgia or myalgia, and no arthritis was reported for any patient. Grade 1/2 arthralgia was often unifocal and resolved during continued drug administration or after discontinuation of study drug. One patient experienced a slowly progressive grade 2 tenosynovitis of both hands (left > right) that was associated with a weakly positive antinuclear antibody after 7 months of therapy. The antinuclear antibody resolved, and the tenosynovitis gradually improved over several months after discontinuation of study drug.

Ten patients developed drug-related rash within the first three weeks of BMS-275291 administration. In nine patients, rash was grade 1 or 2 in severity and resolved despite continued BMS-275291 administration. Pruritis accompanied rash in three patients; arthralgias of knees or ankles accompanied rash in two patients. In four patients, the rash was characterized as "flushing" and occurred in the first week. One patient with non-small cell lung cancer, described previously, developed dose-limiting rash. This patient developed grade 2 rash, which did not resolve during a one-week drug holiday. The patient was rechallenged with rapid return of the rash, which worsened to grade 3 and was associated with fever and worsening shortness of breath. The rash was typically a patchy erythematous rash without elevation. It was not localized to one region of the body. There were no acneiform changes or skin desquamation observed. Other commonly reported adverse events considered possibly drug-related included the following: fatigue in 14 of 44 (32%) patients; dry mouth or taste alteration in 9 of 44 (20%) patients; nausea in 10 of 44 (23%) patients; and headache in 7 of 44 (16%) patients. For each of these adverse event categories, the severity of these events was grade 2 or less and frequently resolved during continued study drug administration. There was no relationship between dose level and the incidence or severity of adverse events. These toxicities were typically mild and were not clearly temporally related to study drug administration. These toxicities often presented and abated with ongoing dosing of BMS-275291 and did not appear to alter the patient’s activities of daily living.

The maximum tolerated dose was not reached in this study. Only 1 of 6 patients at 600 mg/day and 1 of 15 patients at 1200 mg/day experienced a DLT. None of 33 patients treated at dose levels of 900, 1800, or 2400 mg/day experienced DLT.

No alterations in hematology, chemistry, coagulation, or platelet aggregation studies were observed with BMS-275291 (data not shown).

Surrogate End Points. Given the premise that inhibition of sheddases (such as TNF-α converting enzyme) is at least partially responsible for joint toxicity (18) observed with hydroxamate-based MMPIs, patients were sampled at pretreatment baseline, days 15 and day 29 for TNFα and TNFα-RII by ELISA assay. In 44 patients sampled, no major alterations in TNFα and TNFα-RII levels were observed during study drug administration compared with pretreatment baseline, consistent with the sheddase-sparing design of BMS-275291. The shed TNF-α RII levels in patient plasma typically ranged between
200 and 500 pg/ml with little intrapatient variability. The TNF-α similarly had little intrapatient variability with plasma levels in the 1–10 ng/ml range (data not shown).

**Efficacy.**  Of 44 patients, 12 patients received treatment for 4+ months, 6 patients for 8+ months, and 3 patients for >1 year. The median number of days on study was 8 weeks. Of the three patients treated for >1 year, two patients were enrolled at the 1200 mg/day dose level, and one patient at the 2400 mg/day dose level. The patient at the 2400 mg/day dose level was dose-reduced twice for mild myalgias and tolerated treatment well at 1200 mg/day dose level. No partial or complete tumor responses were observed in this study. A 51 year-old male diagnosed with mucinous cystadenocarcinoma pseudomyxoma peritoneum had previously experienced three treatment failures and remained stable for 15 months of treatment with BMS-275291.

**Pharmacokinetics.**  At the phase II dose of 1200 mg/day, plasma concentrations of parent BMS-275291 peaked at about 0.5–4 h after dosing. The accumulation index was about 1 based on data from both days 15 and 29, suggesting that steady state had been achieved by day 15 (Table 3). At the 1200 mg/day dose level, the mean $C_{\text{min}}$ value was 158 ng/ml based on trough concentrations values obtained predose on days 15, 16, 22, 28, and 29. This value was greater than the calculated in vitro IC$_{80}$ value for MMP-2 and greater than the calculated in vitro IC$_{90}$ value for MMP-9 (Fig. 2). Assessment of individual plasma concentration versus time profiles indicated that trough concentrations of all patients exceeded the in vitro IC$_{50}$ values for MMP-2 and MMP. The IC values were determined in vitro under reduced conditions, using purified human MMP-2 and MMP-9 and quenched fluorescent peptide substrate (22, 26). On the basis of Akaike Information Criterion indicating superiority of a two-compartment model compared with a one- or three-compartment model, the mean plasma concentration versus time data were modeled using an extravascular two-compartment model with first-order input, no lag time, and an iterative re-weighting scheme of [calculated concentration]$^{-2}$ was used. Correlation coefficient exceeding 0.98 between the observed and predicted mean data (Fig. 3), and coefficients of variation of <30% (data not shown) for the parameter estimates indicated that a reasonable fit of the data was achieved. Thus steady state was predictable from single dose data.

![Fig. 2](image_url)

**Figure 2**  Individual and mean plasma concentration versus time profiles of parent BMS-275291, the physiologically active form, obtained at steady state (at 1200 mg daily; day 29, $n = 13$). MMP, matrix metalloproteinase.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>$C_{\text{max}}$ ng/ml Day 1</th>
<th>$T_{\text{max}}$ h</th>
<th>AUC (24h) ng · h/ml Day 15</th>
<th>$C_{\text{min}}$ ng/ml Day 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent BMS-275291</td>
<td>10671 (4262)</td>
<td>0.5 (0.5, 4.0)</td>
<td>29553 (11140)</td>
<td>158 (65)</td>
</tr>
<tr>
<td>Day 15</td>
<td>8192 (4439)</td>
<td>1.0 (0.5, 2.0)</td>
<td>24276 (10347)</td>
<td></td>
</tr>
<tr>
<td>Day 29</td>
<td>7412 (4582)</td>
<td>1.0 (0.5, 4.0)</td>
<td>24496 (12176)</td>
<td></td>
</tr>
<tr>
<td>Total BMS-275291</td>
<td>36983 (17099)</td>
<td>1.0 (0.5, 4.0)</td>
<td>172611 (75095)</td>
<td></td>
</tr>
<tr>
<td>Day 15</td>
<td>35862 (18428)</td>
<td>1.0 (0.5, 4.0)</td>
<td>330820 (142886)</td>
<td>8112 (3114)</td>
</tr>
<tr>
<td>Day 29</td>
<td>34440 (17197)</td>
<td>1.0 (0.5, 6.0)</td>
<td>357451 (163266)</td>
<td></td>
</tr>
</tbody>
</table>

*a* Observed $T_{\text{max}}$.

*b* Based on an average of values obtained on days 2, 8, 15, 16, 22, 29, and 30.
BMS-275291, Sheddase-Sparing, MMPI

Comparison of plasma concentration versus time data of BMS-275291 and total BMS-275291 at 1200 mg/day indicated that BMS-275291 constituted about 25% of total BMS-275291 (e.g., BMS-275291 and BMS-275291 recoverable from reducible disulfides) in the plasma at $C_{\text{max}}$ and constituted $<10\%$ at $C_{\text{max}}$. The accumulation index of the total form was about 2.0 (Table 3).

Because PK samples at the other dose levels were not evaluable or not available, dose proportionality assessment could not be performed. This assessment will be conducted in other ongoing phase I studies.

CONCLUSIONS

MMPIs have been evaluated extensively in the clinic; however, they have shown little clinical benefit when used as monotherapy in patients with advanced disease (24). Studies with MMPIs such as marimastat may have shown modest clinical efficacy and dose-proportional benefit but have been limited by musculoskeletal side effects including joint pain and stiffness. Musculoskeletal toxicity limits both the dose delivered and the duration of therapy (27–30). This toxicity has limited dose escalation or maintenance type treatment approaches for most MMPIs, particularly marimastat. BMS-275291 is similar to marimastat; it is a broad spectrum, peptidomimetic MMP inhibitor. However, unlike marimastat, BMS-275291 has a novel zinc-binding group that was selected to spare sheddases using high-throughput screening of a rationally designed, combinatorial chemical library. Sheddases are enzymes containing zinc that mediate the shedding of proinflammatory cytokines and cytokine receptors (including TNFα, TNFα-RII, interleukin-1-RII, L-selectin, and interleukin-6R) from the cell surface.

The initial daily starting dose of BMS-275291 was 600 mg in this phase I dose escalation study. This dose was 33% less than a dose (900 mg or 350 mg/m²) that was safe and well tolerated when given daily for 14 days to healthy normal males (24). This dose was also well below a dose (900 mg/m²) tolerated daily for 3 months in marmosets without toxicity and is one-third the dose of 1200 mg/m² tolerated daily for 3 months in cynomolgous monkeys without clinically evident drug-related toxicity (23). The initial dose level (600 mg/day) was chosen as the starting dose for this study because this dose has the potential to inhibit MMP activity in vivo as inferred from a comparison of achievable plasma concentrations of BMS-275291 in normal subjects to the measured in vitro IC₅₀ values of MMP-2 and MMP-9. Therefore, six to eight patients were accrued to each dose level (rather than the traditional three patients per dose level) to better characterize safety and permit more precise calculation of pharmacokinetic parameters. A range of patients (6–8) to be accrued per dose level was stipulated to provide flexibility of enrollment for this multicenter trial. Five dose levels were evaluated (600, 900, 1200, 1800, and 2400 mg) in this study. Specific dose levels (rather than escalation to DLT) were tested to identify a dose that is well tolerated with effective MMP inhibition. On the basis of the preclinical and clinical data described above, it was expected that escalation beyond 2400 mg/day would not provide additional benefit but might lead to unnecessary and unacceptable toxicity particularly with long-term administration. A pattern of late-occurring study drug-related toxicities has been observed with other broad spectrum MMPIs in development, and given the potential application of BMS-275291 as a long-term daily treatment (31), a traditional dose-escalation until the maximum-tolerated dose has been exceeded study design was not used in this study.

BMS-275291 toxicity was mild overall. The most frequent adverse events considered possibly drug-related were grade 1 or 2 joint toxicity, fatigue, rash, taste change, nausea, and headache, all of which often resolved during and despite continued study drug administration. The forestated toxicities were not clearly attributable to study drug administration, and as mentioned these toxicities did not consistently occur when starting or restarting study drug and frequently abated when treatment was continued under close observation. The majority of these patients had been extensively pretreated as shown in Table 4, and it is likely that patients may have had residual or intermittent symptoms related to their advanced cancer or prior treatments. There was no relationship between dose and incidence or severity for any adverse event. This lack of a dose-toxicity relationship may reflect the preselection of high-dose levels, which were known to result in continuously high-plasma concentrations, based on previous studies in healthy subjects. In particular, arthralgia was mild or moderate, mostly transient, and not dose-limiting. Grade 3 and 4 joint toxicity did not occur with BMS-275291. No patients discontinued BMS-275291.
treatment because of joint toxicity. For patients that came off of study because of other reasons and had joint toxicity at the time of study drug discontinuation, these joint symptoms usually resolved rapidly, within 1–2 weeks. Rash or flushing occurred in several patients within the first three weeks of therapy. In 9 of 10 cases, rash resolved despite continued BMS-275291 administration. In one case, extensive rash, drug-fever, and shortness of breath (in the setting of advancing non-small cell lung cancer) resulted in discontinuation of the patient from the study for toxicity.

In a previous study evaluating the disposition of BMS-275291 and total BMS-275291 in healthy volunteers, the half-life of parent BMS-275291 after 14 days of administration ranged from 23 to 53 h, suggesting that steady state could be achieved by about 11 days of dosing. Although the lack of substantial accumulation of unchanged BMS-275291 is not in complete agreement with the long terminal elimination half-life values, mean effective terminal elimination half-life estimates, ranging from 4 to 16 h, support the attainment of steady state by day 7 accompanied by minimal accumulation over the 14-day dosing period. These findings were in agreement with the observations in this trial. The half-life of total BMS-275291 (representing predominantly inactive disulfides of the drug) in healthy volunteers was assessed to be >100 h with accumulation; these observations were also similar to observations made in this trial.

Ultrafiltration experiments were conducted to evaluate the overall binding of radioactivity in human serum samples added to \[^{14}C\]BMS-275291 (32). The extent of protein binding (inclusive of disulfide linkages) was moderate and concentration dependent (77.2% at 100 ng/ml to 46.0% at 20,000 ng/ml). Therefore, chronic administration of 1200 mg/day BMS-275291 may result in plasma concentrations of BMS-275291 sufficient to inhibit MMP-2 and MMP-9 in cancer patients (33).

The rationale for recommending a 1200 mg/day dose is based on a number of considerations. Because MMPs are implicated in embryogenesis, ovulation, wound healing, wound angiogenesis, and cancer, a biologically active dose of an MMPI may have few readily observable adverse effects in the adult human. Preclinically, there is a dose-efficacy relationship for in vitro MMP inhibition, in vivo antiangiogenesis, and in vivo efficacy in the preinitiation B16BL6 tumor model. In vitro MMP inhibition is maximal at the IC\textsubscript{90}, and concentrations above the IC\textsubscript{90} added very little to in vivo antitumor activity in preclinical models. This would suggest a therapeutic ceiling with dose escalation of MMPIs. Additionally, in long-term monkey toxicology studies, the chronic toxicity (drug-induced lupus) appeared to be dose related, and this was one of the factors in the decision to study an intermediate dose of 1200 mg/day for subsequent phase II studies. In the phase I study of doses ranging from 600 mg/day to 2400 mg/day there was no relationship between dose and incidence or severity of adverse event of any kind. The dose of 1200 mg/day was the lowest dose at which the steady-state mean C\textsubscript{min} exceeded the in vitro IC\textsubscript{90} of key MMPs, suggesting that this may be the lowest dose that maximizes MMP inhibition. At 1200 mg/day, the area under the curve and C\textsubscript{min} exceeded the area under the curve and C\textsubscript{min} seen at efficacious doses in mice. At 1200 mg/day, the C\textsubscript{max} was less than the IC\textsubscript{50} for inhibition of sheddases, TNFs levels were not perturbed, and no patients experienced arthritis.

As the role of MMPs in cancer becomes more established, rational design becomes an important factor in MMPI development. Positive and negative experiences with earlier-generation MMP inhibitors must be considered when designing agents to optimize clinical activity and therapeutic index. BMS-275291 represents a novel, rationally designed MMPI that may realize the full potential of MMPIs by targeting a broad range of MMPs, similar to marimastat, without dose-limiting arthritis such that biologically relevant doses can be delivered with continuous inhibition of MMPs over a long term basis. Further clinical testing is under way to evaluate this potential.

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A Phase I Study of Oral BMS-275291, a Novel Nonhydroxamate Sheddase-Sparing Matrix Metalloproteinase Inhibitor, in Patients with Advanced or Metastatic Cancer

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