Abstract

Purpose: To evaluate the safety and biological activity of three different doses of marimastat given for 6 months to patients with biochemically relapsed prostate cancer. 

Experimental Design: Patients with a biochemical relapse within 2 years of primary therapy, a prostate-specific antigen (PSA) increase of at least 50% within 6 months of study entry, and no prior systemic therapy were eligible. Patients were randomized to receive marimastat at total daily doses of 5, 20, or 40 mg for 6 months unless dose-limiting toxicity or new evidence of disease occurred.

Results: Thirty-nine patients were treated. Grade 3-4 reversible musculoskeletal toxicity was the only dose-limiting toxicity. Increasing dose was associated with increased probability of experiencing dose-limiting toxicity (5.9%, 42.9%, and 88.9% for the 5, 20, and 40 mg groups, respectively; \( P = 0.03 \)). Accrual was discontinued early on the two higher dose levels due to toxicity. A significant decrease in PSA slope was shown in the 20 mg group when compared with the 5 mg group (0.117 and \(-0.0046\), respectively; \( P = 0.03 \)) The 40 mg group (versus the 5 mg group) showed a similar change (0.109) with a trend towards significance (\( P = 0.07 \)). An increased serum matrix metalloproteinase 2 level at month 3 compared with the baseline correlated with a decrease in PSA slopes (Slope, 0.001; 95% confidence interval, 0.0002–0.0018; \( P = 0.02 \)).

Conclusion: These data suggest that marimastat has a biological effect and may effectively delay progression in patients with biochemical relapsed prostate cancer, as shown by the change in PSA slope; however, dose-limiting toxicity at active doses is significant. Confirmatory studies with less toxic matrix metalloproteinase inhibitors employing more conventional end points are indicated. This design is feasible and potentially efficient for screening antimetastatic agents.

Prostate cancer remains the most common malignant neoplasm diagnosed in adult males in the United States (1). During the past 15 years, widespread clinical use of the prostate-specific antigen (PSA) test has resulted in a significant increase in the proportion of patients presenting initially with early stages of disease. Currently, \( \sim 80\% \) of newly diagnosed patients present with no clinical evidence of metastatic disease (1). Most of these patients are treated either with radical prostatectomy, external beam radiation, or brachytherapy. Data from uncontrolled studies suggest that 30% to 50% of patients treated with local modalities of treatment will show evidence of biochemical (PSA) relapse during a 10-year follow-up period (2–5). The natural history of patients with biochemical relapse disease is currently a focus of intensive study. Various clinical variables have been shown to predict for the development of bone metastasis in these patients. Among the significant factors are the pathologic Gleason score, time of PSA relapse, and the PSA doubling time (6, 7). Recent reports suggest that the rate of increase of PSA is the most powerful predictor for the development of distant relapse in patients with biochemical relapse disease is currently a focus of intensive study. Various clinical variables have been shown to predict for the development of bone metastasis in these patients. Among the significant factors are the pathologic Gleason score, time of PSA relapse, and the PSA doubling time (6, 7). Emerging new antiprogression approaches, targeted at various known stages of the metastasis cascade, have the potential of altering the natural history of early prostate cancer and benefit patients at high risk for distant relapses by postponing or preventing progression. Whereas it is logical to focus the development of such approaches in the adjuvant setting or in patients with low disease burden (e.g., patients with PSA relapse only), clinical trials in this patient population pose a significant methodologic challenge primarily because of the lack of clinically validated, short-term, study end points (9).
Marimastat (BB-2516) is an inhibitor of a family of enzymes known as matrix metalloproteinases (MMP) which are zinc-dependent proteinases that collectively degrade and remodel the extracellular matrix (10–13). MMPs are overexpressed in malignant tissues and in the blood of patients with a variety of tumor types (14–17). A direct correlation between MMP expression and outcome has been suggested in some malignancies (18–21). Marimastat is a MMP inhibitor (MMPI) that mimics the structure of collagen and chelates the zinc atom reversibly in the MMP's active site. It is the first orally available MMPI and is an inhibitor of the major MMPs (e.g., collagenase, gelatinase A and B, etc.). It was shown to reduce the size and number of metastases in preclinical models of breast and lung cancer (22). Polyarthritus was the dose-limiting toxicity reported in the initial phase I/II studies with twice daily (bid) oral doses ranging from 2 to 100 mg (23). A phase I trial in 88 patients with hormone-refractory prostate cancer indicated that doses of ≥10 mg bid accomplished through plasma concentration above 40 ng/mL (24) which corresponds to the in vitro IC_{50} of MMPs (22). Overall, there was modest toxicity reported with few grade 3 to 4 musculoskeletal events. A preliminary trial in advanced gastric cancer suggested some activity mostly in a subset of these patients (25), whereas no improvement in survival was reported in advanced pancreatic and breast cancer (26, 27).

To further evaluate the safety and clinical activity of marimastat in prostate cancer, we evaluated patients with biochemical evidence of disease recurrence after primary treatment. The biological properties of MMPs, which are primarily antimetastatic effects, would suggest that the most appropriate setting to evaluate these compounds is before the establishment of clinically evident metastases.

The main goals of this study were to determine the safety and tolerance of long-term (at least 6 months) administration of marimastat in patients with biochemically relapsed prostate cancer and to evaluate a dose-dependent effect on the slope of PSA during treatment with three different doses of marimastat in a prospective randomized, double-blind, phase I/II trial. The results of this trial are reported herein.

### Patients and Methods

This investigator-initiated, single-center, randomized, double-blind phase I/II study evaluated the safety and efficacy of three different doses of oral marimastat in patients with biochemically relapsed prostate cancer. Study drug and placebo were provided by British Biotech. All data were managed and controlled at the Johns Hopkins Hospital.

**Eligibility.** Patients with a histologically confirmed diagnosis of prostate cancer with evidence of biochemical relapse within 2 years after primary therapy (radical prostatectomy or radiotherapy) were eligible. The PSA eligibility criteria was defined as a ≥50% increase within 6 months of study entry. Patients treated initially with radical prostatectomy alone had to show two PSA increases above the nadir with baseline PSA >0.2 but <50 ng/mL and at least one of the following conditions: Gleason score of ≥7, microscopic evidence of non–organ-confined disease (i.e., seminal vesicle involvement or established capsule penetration or positive surgical margins or microscopic pelvic node involvement-N1 disease) or a PSA that never became undetectable post operatively. Patients treated primarily with radiotherapy had to show three consecutive PSA increases, a baseline PSA >1.0 but <50 ng/mL and at least one of the following conditions: Gleason score of ≥7, pretreatment PSA of ≥20 ng/mL, or a clinical stage of T2N2M0 or greater. Patients who received postoperative radiotherapy were also eligible as long as they satisfied the other criteria for surgical patients.

Eligible patients could not have had prior hormonal therapy, except for neoadjuvant hormonal therapy and ≤6 months adjuvant hormonal therapy, all discontinued ≥6 months before study entry (and a pretreatment serum testosterone within the reference range), prior chemotherapy or other MMPI or more than one prior biological response modifier or vaccine therapy.

All patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of ≥6 months, adequate hematologic (WBC of ≥3,500/mm^3 and/or ANC of >1,500/mm^3 and PLT of ≥100,000), renal function (BUN of ≤30, serum creatinine of ≤2.0 mg/dl, or an estimated CrCl of at least 50 ml/min), and hepatic function (total bilirubin ≤ institutional upper limit of normal, aspartate aminotransferase and/or alanine aminotransferase ≤2.5 times institutional upper limits of normal), serum testosterone within the institutional normal levels, no uncontrolled medical illness (neurologic, cardiovascular or other illnesses considered as unwarranted high risk), no history of malignancy (except for nonmelanomatous skin cancer or controlled superficial bladder cancer), or treatment for any cancer over the past 5 years. Patients with palpable or radiological evidence of local recurrence (excluding prostascint scan) or patients with any site of metastases were not eligible.

All patients signed an institutionally approved informed consent.

**Study design.** Eligible patients were stratified according to their primary modality of treatment (one group had radical prostatectomy alone or radical prostatectomy followed by post-operative adjuvant or salvage radiotherapy, and the second group had radiotherapy alone) and by their baseline PSA (≤4 and >4 ng/mL). Patients were randomized to one of three treatment arms: arm A, marimastat 5 mg/d (5 mg + identical placebo AM and two placebo PM); arm B, 20 mg/d (10 mg + identical placebo AM and 10 mg + identical placebo PM); and arm C, 40 mg/d (two 10 mg AM and two 10 mg PM) for 6 months or until meeting criteria for trial withdrawal. After 6 months, treatment was continued until progression or as otherwise specified (including toxicity) for patients who did not show evidence of progression during the initial 6-month study period. Patients were randomized at the Johns Hopkins Hospital. Both patients and investigators were blinded.

**Definition of progression.** Criteria for disease progression at 6 months (termination of treatment) were defined as any evidence of metastatic disease or local recurrent disease or an increase in PSA at 6 months >50% over PSA value at baseline.

Treatment was discontinued before 6 months if there was any evidence of local progression (development of local symptoms as pain, bleeding or obstruction due to local prostate cancer progression, radiologically, or as evident by digital rectal examination), development of metastatic disease, or dose-limiting toxicity.

**Definition of dose-limiting toxicity.** Dose-limiting toxicity was defined as the occurrence of grade 4 toxicity or any recurrent grade 3 toxicity as defined by the National Cancer Institute Common Toxicity Criteria (version 2.0). If grade 3 toxicity was observed, treatment was stopped until recovery to grade 1. Patients whose toxicities did not recover to grade 1 within 3 weeks were removed from study. If any patient developed evidence of dose-limiting toxicity, the study pharmacist was informed, his treatment was unblinded, and the Data Safety Monitoring Board was informed. If three dose-limiting toxicities occurred at the same dose level, the Data Safety Monitoring Board would recommend permanent closure of that arm to the principal investigator and the study proceeded with the remaining two arms.

**Rationale for dose selection.** The selection of doses was based on plasma marimastat concentrations observed in patients with metastatic prostate cancer treated in our initial phase I trial (24) and the known in vitro IC_{50} data available for the different MMPs (22). On our previous phase I trial, the targeted marimastat plasma concentration of 40 to 200 ng/mL at 2 months (defined as steady state, which corresponds to the IC_{50} concentration in vitro) were observed in all patients with the 20 mg bid dose of marimastat. Patients treated with the 10 mg bid dose had
lower plasma concentrations with a mean around 40 ng/mL. Patients receiving 5 mg/d dose had plasma concentrations well below 40 ng/mL. Marimastat is 95% protein bound with this fraction being the inactive form. The targeted plasma concentrations specified above have been corrected for this property.

**Baseline and follow-up evaluation.** Baseline evaluation included history and physical exam, hematologic, renal and hepatic functions, testosterone level and a free and total PSA, bone scan, a chest X-ray, and a computerized tomography of the abdomen and pelvis. During study, treatment patients had a monthly toxicity notation, a DRE, a physical examination if clinically indicated, a hepatic panel, and blood was drawn for free/total PSA levels. (PSA samples were frozen and processed after 6 months of treatment or sooner if clinically indicated. The PSA data was therefore not available to investigators or patients for the first 6 months). In addition, patients had a physical examination and renal function tests every 3 months. Imaging studies were repeated every 6 months or sooner if clinically indicated. (All patients had their monthly serum and plasma stored in −80°C allowing evaluation of other potential biomarkers).

**Statistical methods.** The major statistical end point of this study was the change in PSA slope. A regression of the log PSA on the time of PSA measurements for each patient was calculated for the pretreatment PSA values and for the on-treatment values. The slope observed during treatment was deducted from the pretreatment slope and a positive response for each individual patient was declared when the slope during treatment was lower than the pretreatment slope. The mean changes in PSA slope were calculated for the three treatment arms and compared with an ANOVA.

The relationship between the change in PSA slope (pretreatment minus on-treatment) and the change in fibroblast growth factor and vascular endothelial growth factor quantities (3-month value minus pretreatment), was also evaluated by linear regression analysis.

Time to progression was defined as the time to evidence of metastases, time to initiation of hormonal therapy, or the time to 50% increase in PSA compared with the baseline. Event time distributions for this end point were estimated with the method of Kaplan and Meier and compared using the log-rank statistic or the proportional hazards regression model. The simultaneous effect of two or more factors was studied using the multivariate proportional hazards model.

The association of dose group with two binary end points, toxicity and a 50% increase in PSA on trial, were evaluated based on cross-tabulations and logistic regression modeling.

All statistical computations were done using the SAS PC package or EGRET. All P values are two sided and all confidence intervals (CI) are at the 95% level.

The planned study size was based on the assumption that without effective treatment at least 80% of the patients would continue to show an increase in PSA at the same rate at the end of 6 months. Because in study arm A we employed a very low dose of marimastat, it was assumed that at least 80% of the patients in this arm would show no change in the rate of increase of PSA with treatment. A sample size of 30 patients in each treatment group provided 90% power to detect a decrease in the PSA progression rate for arms B and C from 80% to 40% (50% of the projections for arm A) using a two-sided $\chi^2$ test with a significance level of 0.05.

**Results**

From June 1999 to May 2001, 41 patients were registered. One patient had evidence of histologically confirmed local recurrence detected at the time of the baseline physical exam and one patient withdrew consent before initiating treatment. Thirty-nine patients were eligible and randomized. Of the thirty-nine patients that entered on this trial, 17 were given 5 mg of marimastat a day, 13 were given 20 mg (10 mg bid), and 9 received 40 mg (20 mg bid). The patients were well balanced between the trial arms with regard to time to PSA progression and their pretreatment PSA slope. The pretreatment patient characteristics of the three groups are summarized in Table 1.

**Toxicity.** The toxicity data is described on Table 2. Three patients on each of the two higher dose arms (20 and 10 mg bid) developed dose-limiting musculoskeletal toxicity which resulted in early discontinuation of treatment arms B at 13 patients and C at nine patients. Accrual to arm A was discontinued thereafter in view of the low likelihood that this will be associated with any therapeutic benefit.

The only grade 3 to 4 toxic side effect of marimastat was the appearance of a reversible, dose-limiting, inflammatory poly-arthritis (clinically manifested as arthralgia, erythema, and joint swelling with severe limitation of function). There was strong correlation between dose and dose-limiting toxicity. Compared with the 5 mg dose, patients given 20 mg/d were 13.7 times (95% CI, 1.38-136.13; $P = 0.03$) more likely to have dose-limiting toxicity, and the 40 mg/d group was 128.0 times (95% CI, 7.05-1,000; $P = 0.001$) more likely to experience severe toxicity. Similarly, the median time to development of dose-limiting toxicity was inversely correlated with marimastat dose (5 months for 40 mg/d, 6 months for 20 mg/d, and 18 months for 5 mg/d; see Table 2).

**Prostate-specific antigen changes.** The mean number of pretreatment and on-treatment PSA measurements per patient was 7 (range, 4-11) and 6.3 (range, 4-12), respectively. Mean (95% CI) pretreatment PSA slopes were 0.14 (0.11-0.16), 0.19 (0.12-0.27), and 0.19 (0.11-0.28) in the 5, 20, and 40 mg dose groups. These means were not significantly different across the arms ($P = 0.25$). The mean (95% CI) changes in slope (pretreatment minus on treatment) in the three groups were as follows (Table 2): arm A (5 mg/d) $-0.0046$ (−0.07 to 0.06; which essentially reflects no change in the slope), arm B (20 mg/d) 0.117 (0.03-0.2), and arm C (40 mg/d) 0.109 (−0.03 to 0.25), respectively (Fig. 1). The 20 mg group had a significant change in slope with treatment when compared with the 5 mg group ($P = 0.03$). Despite small numbers, the change in slope of the 40 mg group versus the 5 mg group still showed a trend towards significance ($P = 0.07$). The 20 and 40 mg group comparison is not significant ($P = 0.89$).

The proportion of patients in each group that had a PSA progression of >50% at the end of treatment was evaluated in each arm. When compared with the 5 mg group, the odds ratio for a 50% increase of the PSA at the end of treatment in the 10 mg bid group was 0.18 (95% CI, 0.04-0.96; $P = 0.05$). The odds ratio for the 20 mg bid group was 0.27 (95% CI, 0.04-1.64; $P = 0.15$); however, the limited sample size in that group precludes any definitive conclusions.

A total of five patients experienced a PSA decline of >50% with an overall median duration of 5 months (range, 3.5-16 months). Two of the five were on the 5 mg dose. One was the only patient on that arm experiencing dose-limiting toxicity and the other had blood levels of 35.5 ng/mL (higher than the median of the 20 mg arm). One patient was on the 20 mg dose and the remaining two were on the 40 mg dose.

Some patients received intermittent nonsteroidal anti-inflammatory drugs and acetaminophen for musculoskeletal symptoms. There was no evidence of a treatment effect on PSA with these compounds.
Marimastat pharmacokinetics/pharmacodynamics. Mean (95% CI) plasma concentrations of marimastat at 2 months in arms A, B, and C were 9.96 (5.37-14.55), 22.78 (15.38-30.18), and 70.84 (26.79-114.9), respectively (arm A versus B, \( P = 0.24 \); arm A versus C, \( P < 0.0001 \); and B versus C, \( P = 0.0005 \)).

A statistically significant correlation between marimastat plasma concentrations and the change in PSA slope was found (slope, 0.002; 95% CI, 0.0008-0.003; \( P = 0.02 \)). A decrease in the PSA slope correlated with increased marimastat blood level. This correlation however was based on one influential data point. This patient’s marimastat blood level (of 214 ng/mL) was repeated and confirmed. He had severe dose-limiting toxicity and was unable to complete 6 months of treatment. When this one very influential data point was removed from the analysis, this relationship did not remain significant (\( P = 0.85 \)).

Other biomarkers. Posttreatment changes of potential biomarkers (MMP-2, MMP-9, fibroblast growth factor, and vascular endothelial growth factor) were correlated with the change in PSA slope and PSA progression (as defined by the protocol; see Materials and Methods). Changes in growth factor levels and MMP-2 and MMP-9 (at month 3 compared with pretreatment levels) were compared across dose groups and were correlated with the change in PSA slope. Only MMP-2 significantly correlated with the change in PSA slope (Fig. 2; slope, 0.001; 95% CI, 0.0002-0.0018; \( P = 0.02 \)). Interestingly, an increase of MMP-2 levels at 3 months compared with the baseline significantly correlated with changes in PSA slope.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Marimastat (dose/d)</th>
<th>5 mg</th>
<th>20 mg</th>
<th>40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>58 (48-77)</td>
<td>59 (52-71)</td>
<td>63 (56-75)</td>
</tr>
<tr>
<td>No. patients</td>
<td>17</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Median Gleason (range)</td>
<td>7 (7-8)</td>
<td>8 (7-9)</td>
<td>8 (7-9)</td>
</tr>
<tr>
<td>PSA relapse, first year (%)</td>
<td>13/17 (76.5)</td>
<td>11/13 (84.6)</td>
<td>8/9 (88.9)</td>
</tr>
<tr>
<td>Prior local treatment (%)</td>
<td>RP 7 (41.2)</td>
<td>7 (53.8)</td>
<td>5 (55.6)</td>
</tr>
<tr>
<td>RT</td>
<td>1 (5.9)</td>
<td>2 (15.4)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Both</td>
<td>9 (52.9)</td>
<td>4 (30.8)</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td>Median prestudy PSA (range)</td>
<td>3.22 (0.69-26)</td>
<td>3.92 (0.68-9.23)</td>
<td>7.98 (1.21-36.5)</td>
</tr>
<tr>
<td>Stage (%)</td>
<td>T2 N0 2 (12.5)</td>
<td>1 (7.7)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>T3 N0</td>
<td>12 (75)</td>
<td>9 (69.2)</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td>T3 N1</td>
<td>2 (12.5)</td>
<td>3 (23.1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

### Table 2. Treatment characteristics, toxicity, and response

<table>
<thead>
<tr>
<th>Marimastat (dose/d)</th>
<th>5 mg</th>
<th>20 mg</th>
<th>40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 Arthralgia (DLT) (^*) (%)</td>
<td>1/17 (5.9)</td>
<td>6/13 (42.9)</td>
<td>8/9 (88.9)</td>
</tr>
<tr>
<td>Mean time to DLT, mo (range)</td>
<td>18</td>
<td>6 (4-9)</td>
<td>5 (3-7)</td>
</tr>
<tr>
<td>Reason for stopping marimastat (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>4/17 (23.5)</td>
<td>5/13 (38.5)</td>
<td>7/9 (77.8)</td>
</tr>
<tr>
<td>PSA progression</td>
<td>12/17 (70.6)</td>
<td>8/13 (61.5)</td>
<td>2/9 (22.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1/17 (5.9) (^†)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mean (median) steady state (at 2 mos). Marimastat-plasma concentration (ng/mL) (^‡)</td>
<td>9.96 (9.2)</td>
<td>22.78 (20.1)</td>
<td>70.84 (54.6)</td>
</tr>
<tr>
<td>(\geq50%) PSA decrease (%)</td>
<td>2/17 (11.8)</td>
<td>1/13 (7.7)</td>
<td>2/9 (22.2)</td>
</tr>
<tr>
<td>Mean (\Delta) PSA slope (^*) (95% CI)</td>
<td>(-0.0046 (-0.07 to 0.06))</td>
<td>0.117 (0.03-0.2)</td>
<td>0.109 (0-0.25)</td>
</tr>
<tr>
<td>PSA progression (\geq50%) increase over the baseline after 6 mos of treatment (^\ddagger) (%)</td>
<td>14/17 (82.4)</td>
<td>6/13 (46.2)</td>
<td>5/9 (55.6)</td>
</tr>
</tbody>
</table>

Abbreviation: DLT, dose-limiting toxicity.

\(^*\)20 versus 5 mg, \( P = 0.03 \); 40 versus 5 mg, \( P = 0.001 \).

\(^†\)Patient and treating physician elected to discontinue treatment after one year. Patient did not demonstrate a PSA decline nor a clinical or biochemical progression or dose-limiting toxicity.

\(^‡\)20 versus 40 mg, \( P = 0.0005 \); 5 versus 40 mg, \( P < 0.0001 \); 20 versus 5 mg, \( P = 0.24 \).

\(^\ddagger\)20 versus 5 mg, \( P = 0.03 \); 40 versus 5 mg, \( P = 0.07 \).

\(^\ddagger\)20 versus 5 mg, \( P = 0.06 \); 40 versus 5 mg, \( P = 0.15 \).
which suggest that an increase in MMP-2 levels during treatment may be an independent predictor of a potential benefit with this MMPI). This association was not significantly different across dose groups, as an overall test for heterogeneity of slopes was not significant (\(P = 0.99\)).

**Time to progression.** Development of metastases or a 50% increase in PSA compared with the baseline in the three dose groups was not significantly different, however the numbers are small which preclude more definitive conclusions.

Univariate analysis using progression as the end point was done. Age, Gleason score, pathologic and clinical stage, marimastat levels, baseline and month 3 levels of PSA, free PSA, MMP-2, MMP-9, fibroblast growth factor, and vascular endothelial growth factor were not significantly associated with time to progression. The only significant predictor for time to progression was the pretreatment PSA slope. Patients with a pretreatment PSA slope of >0.15 had a significantly increased risk of progression (hazard ratio, 2.84; 95% CI, 1.17-6.92; \(P = 0.02\)).

**Discussion**

We tested marimastat in patients with biochemically relapsed, nonmetastatic prostate cancer. Eligible patients were stratified and randomized to receive three pharmacologically determined doses of marimastat given for 6 months. The study objectives were to assess the relationship between PSA changes over time and marimastat dose and the safety of these 3 doses given over a planned 6-month period. The doses of 10 and 20 mg bid were chosen based on pharmacokinetic information collected in our previous study in 88 patients with metastatic hormone-refractory disease (24). The plasma concentrations at the steady state with these doses corresponded to the in vitro IC\(_{50}\) range. The selection of a different dose in each arm allowed us to assess the relationship among dose, toxicity, and changes in the rate of PSA changes. Furthermore, because study arm A employed very low doses of marimastat, it may be assumed that this represents a control arm most likely devoid of significant biological and clinical activity. In fact, the rarity of toxicity and the virtually unchanged PSA slope observed in this arm would support this assumption.

There was significant correlation among the dose of marimastat, marimastat plasma concentrations, and toxicity (Table 2). A substantial proportion of patients receiving 10 or 20 mg bid doses developed severe inflammatory polyarthritis (dose-limiting toxicity) during the treatment period of study (whereas the 5 mg/d arm was associated with only one dose-limiting toxicity in a patient who received marimastat for 18 months). These results indicate that continuous, long-term, administration of marimastat at these doses is not feasible based upon the severe toxicity observed in this study. Phase I studies of newer and potentially safer MMPI compounds should test alternate schedules such as intermittent schedule if long-term administration is planned. One schedule employing intermittent therapy with a novel MMPI (CP-471,358) in a phase I trial was also associated with significant myalgia/arthralgia (28). Nonpeptidic MMPIs associated with a more selective MMP inhibition and potentially less musculoskeletal side effects were developed. Among them are AG3340 (prinomastat) and BAY 12-9566 which resulted in disappointing efficacy and also showed common musculoskeletal events (29, 30). BMS-275291 is a novel nonhydroxamate MMPI which was designed to spare inhibition of the metalloproteinase-mediated release of the tumor necrosis factor receptor which is believed to be the cause of the musculoskeletal side effects of the nonpeptidic MMPIs (31). In a phase I study, myalgia and arthralgia were seen but were non–dose limiting (32). In a phase II trial in (which suggest that an increase in MMP-2 levels during treatment may be an independent predictor of a potential benefit with this MMPI). This association was not significantly different across dose groups, as an overall test for heterogeneity of slopes was not significant (\(P = 0.99\)).

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**Time to progression.** Development of metastases or a 50% increase in PSA compared with the baseline in the three dose groups was not significantly different, however the numbers are small which preclude more definitive conclusions.

Univariate analysis using progression as the end point was done. Age, Gleason score, pathologic and clinical stage, marimastat levels, baseline and month 3 levels of PSA, free PSA, MMP-2, MMP-9, fibroblast growth factor, and vascular endothelial growth factor were not significantly associated with time to progression. The only significant predictor for time to progression was the pretreatment PSA slope. Patients with a pretreatment PSA slope of >0.15 had a significantly increased risk of progression (hazard ratio, 2.84; 95% CI, 1.17-6.92; \(P = 0.02\)).

**Discussion**

We tested marimastat in patients with biochemically relapsed, nonmetastatic prostate cancer. Eligible patients were stratified and randomized to receive three pharmacologically determined doses of marimastat given for 6 months. The study objectives were to assess the relationship between PSA changes over time and marimastat dose and the safety of these 3 doses given over a planned 6-month period. The doses of 10 and 20 mg bid were chosen based on pharmacokinetic information collected in our previous study in 88 patients with metastatic hormone-refractory disease (24). The plasma concentrations at the steady state with these doses corresponded to the in vitro IC\(_{50}\) of MMPs. The 5 mg/d dose was identified as a dose that was unlikely to reach plasma concentrations at or above the in vitro IC\(_{50}\) range. The selection of a different dose in each arm allowed us to assess the relationship among dose, toxicity, and changes in the rate of PSA changes. Furthermore, because study arm A employed very low doses of marimastat, it may be assumed that this represents a control arm most likely devoid of significant biological and clinical activity. In fact, the rarity of toxicity and the virtually unchanged PSA slope observed in this arm would support this assumption.

There was significant correlation among the dose of marimastat, marimastat plasma concentrations, and toxicity (Table 2). A substantial proportion of patients receiving 10 or 20 mg bid doses developed severe inflammatory polyarthritis (dose-limiting toxicity) during the treatment period of study (whereas the 5 mg/d arm was associated with only one dose-limiting toxicity in a patient who received marimastat for 18 months). These results indicate that continuous, long-term, administration of marimastat at these doses is not feasible based upon the severe toxicity observed in this study. Phase I studies of newer and potentially safer MMPI compounds should test alternate schedules such as intermittent schedule if long-term administration is planned. One schedule employing intermittent therapy with a novel MMPI (CP-471,358) in a phase I trial was also associated with significant myalgia/arthralgia (28). Nonpeptidic MMPIs associated with a more selective MMP inhibition and potentially less musculoskeletal side effects were developed. Among them are AG3340 (prinomastat) and BAY 12-9566 which resulted in disappointing efficacy and also showed common musculoskeletal events (29, 30). BMS-275291 is a novel nonhydroxamate MMPI which was designed to spare inhibition of the metalloproteinase-mediated release of the tumor necrosis factor receptor which is believed to be the cause of the musculoskeletal side effects of the nonpeptidic MMPIs (31). In a phase I study, myalgia and arthralgia were seen but were non–dose limiting (32). In a phase II trial in
early stage breast cancer, grade ≥ 2 musculoskeletal side effects were shown in 36% of patients on this compound many of which discontinued treatment due to these adverse events (33). A current phase II trial is evaluating BMS-275291 with zolendronate for treatment of patients with metastatic hormone-refractory prostate cancer to the bone.

Our results suggest that marimastat may have biological activity in patients with biochemically relapsed prostate cancer. This is shown by the suggested correlation between dose of marimastat and changes in the slope of PSA (Table 2; Fig. 1). However, in view of the small numbers involved, these results should be interpreted with caution. The clinical significance of changes in the PSA slope during treatment and its use as an end point for clinical trials still requires appropriate validation (9, 34). However, evolving data in this patient population indicate that the PSA doubling time is a potent predictor of outcome (refs. 6–8; this study also showed that the pretreatment PSA slope was the only significant predictor of progression) and may represent a potential end point for therapeutic benefit in this patient population. It remains possible however that despite the apparent similarities in the distribution of elements of known prognostic value (for the development of distant metastasis), any imbalance in the distribution of other disease related factors related to the metastatic process (such as presence or absence of nodal metastasis: N0 versus N1) may affect the potential benefit of this anti-metastatic compound.

An interesting observation was the association between increased MMP-2 levels at 3 months compared with baseline and change in the PSA slope. MMP-2 and MMP-9, among all MMPs have been described as having the closest association with tumor aggressiveness, metastatic potential, and clinical outcome (23). Elevation of MMP-2 during the initial 3-month period of treatment with MMPIs could help in identifying patients who are more likely to benefit from MMPIs with similar properties. Other MMPIs which inhibit MMP production (in addition to blocking their enzymatic activity) would be expected to cause decrease of MMP levels. An example is COL-3 (metastat), a newer MMPI which is a tetracycline derivative and inhibits the production of the MMPs (23). Kaposi sarcoma patients responding to metastat had a significant decrease in their MMP-2 levels from baseline when compared with nonresponders (35). The reasons for the differences between MMP-2 and MMP-9 levels remain unclear; however, this may be explained by differences in tissue inhibitor of metalloproteinases (TIMP) response to treatment. The proteolytic activity of MMPs is inhibited by the TIMP which are a family of specific TIMPs produced by many types of cells. The TIMPs inhibit the activation of pro-MMPs. TIMP-1 inhibits preferentially the pro-MMP-9, whereas TIMP-2 and TIMP-4 have higher affinity for pro-MMP-2. TIMP-2 is expressed constitutively in cultured cells, whereas the expression of TIMP-1 is predominantly regulated by various growth factors at the level of transcription (23). A differential response of TIMP production with an increase of TIMP-1 inhibiting MMP-9 along with a relatively stable level of TIMP-2, not blocking the elevating MMP-2 may explain the difference between MMP-2 and MMP-9 observed in this study.

The pharmacokinetic data of this study differs significantly from the observations in our previous study in patients with metastatic hormone refractory prostate cancer (24). Plasma concentrations in the range of 40 to 200 ng/mL were observed only in patients receiving 40 mg/d of marimastat. By contrast, doses of 20 mg/d achieved this targeted range in patients with metastatic hormone refractory prostate cancer and other advanced stage tumors (24, 36, 37). Studies of adjuvant marimastat in early stage breast cancer yielded results similar to those reported here; doses of 10 mg bid gave mean plasma levels of 11.9 to 12.8 ng/mL (38), which is even below the levels observed in the group of patients receiving the same dose in our current study. The toxicity observed in the breast cancer patients was quite similar to our population. The inverse pharmacokinetic relationship between marimastat (and perhaps other MMPIs) and tumor burden requires further study. It is possible that these and perhaps other unidentified factors may be associated with differences in enzymatic substrate activity, which may be reflected in the pharmacokinetics and possibly clinical properties of MMPIs.

In summary, marimastat belongs to a novel class of compounds that have been extensively evaluated clinically over the past few years. A better understanding of the clinical application of these interesting compounds is clearly needed. The biological activity of marimastat shown in our study by a change in PSA slope indicates that further studies with newer and potentially less toxic drugs from this class of compounds in prostate cancer may be warranted.

This design, employing a dose/response assessment in a randomized fashion may be an efficient method for drug development in this patient population with these and their nontoxic compounds.

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References

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