Introduction

The initial responses of prostate cancers to therapies that deplete or block androgen action are among the most dramatic in clinical oncology. These responses are not durable and over time, virtually all tumors progress to a castration-resistant state that is manifested by a range of clinical phenotypes, but at a molecular level show evidence of reactivation and continued dependence on androgen receptor (AR) signaling for growth (1). Consequently, the AR remains an important therapeutic target. BMS-641988 is a novel AR antagonist that has a 20-fold higher binding affinity to AR, and between 3- and 7-fold greater potency as an antagonist of AR-mediated transcription in cell-based reporter assays, compared with the most widely used anti-androgen, bicalutamide (2).

In preclinical studies, BMS-641988 inhibits the growth of CWR-22-BMSLD1 human prostate xenografts, which have a mutant AR (3). These tumors are sensitive to castration but are only marginally sensitive to bicalutamide. BMS-641988 also stabilizes tumors that are progressing on bicalutamide (P < 0.05), although the tumors regrow upon discontinuation of treatment, which is consistent with a cytostatic as opposed to cytocidal effect (2). Both BMS-641988 and bicalutamide are active against LuCaP 23.1 prostate cancer xenografts, which possess amplified expression of wild-type AR (4), although BMS-641988 is more potent (2). The downstream effects on transcriptional and proteomic profiles

Purpose: BMS-641988 is an androgen receptor antagonist with increased potency relative to bicalutamide in both in vitro and in vivo prostate cancer models. A first-in-man phase I study was conducted to define the safety and tolerability of oral BMS-641988 in patients with castration-resistant prostate cancer (CRPC).

Experimental Design: Doses were escalated from 5 to 150 mg based on discrete pharmacokinetic parameters in cohorts of three to six subjects. After establishing safety with 20 mg of BMS-641988 in the United States, a companion study was opened in Japan to assess differences in drug metabolism between populations.

Results: Sixty-one men with CRPC were treated with daily BMS-641988. The pharmacokinetics (PK) of BMS-641988 and its active metabolites were proportional to dose. One patient experienced an epileptic seizure at a dose of 60 mg administered twice. Despite achieving target drug exposures, antitumor activity was limited to one partial response. Seventeen of 23 evaluable patients (74%) exhibited stable disease on imaging (median 15 weeks; range 8–32), and 10 of 61 patients (16%) achieved a ≥30% decline in levels of prostate-specific antigen (PSA). Partial agonism was seen within the context of this study upon removal of the drug as evidenced by a decrease in PSA.

Conclusions: Although the clinical outcomes of predominantly stable disease and partial agonism were similar to what was observed in the preclinical evaluation of the compound, the limited antitumor activity of BMS-641988 at therapeutic dose levels coupled with an episode of seizure activity led to study closure.

Clin Cancer Res; 17(4): 880–7. ©2010 AACR.
Translational Relevance

Despite acquired resistance to androgen deprivation with or without an antiandrogen therapy with bicalutamide, prostate cancers continue to depend on androgen receptor (AR) signaling for growth, suggesting that AR inhibitors of increased potency may have efficacy in castration-resistant prostate cancer (CRPC). BMS-641988 is a novel AR antagonist that has a 20-fold higher binding affinity to AR, and between three- and seven-fold greater potency as an antagonist of AR-mediated transcription in cell-based reporter assays, compared with bicalutamide. As a result of promising preclinical activity, BMS-641988 was evaluated in this multi-institutional phase I study for men with CRPC. In the setting of an episode of seizure attributable to the study drug and limited antitumor activity in part due to counteragonism, further development of BMS-641988 was stopped in favor of exploring second-generation antiandrogens, which focus on preventing translocation of AR into the nucleus and retain antagonism in the setting of increased AR.

are indicative of a blockade of androgen-driven signaling, more similar to castration than bicalutamide treatment.

In vitro experiments show that the enzyme cytochrome P450 3A4 (CYP3A4) converts BMS-641988 to BMS-570511, which is in turn reduced to BMS-501949 by cytosolic reductases. All three compounds antagonize AR-dependent transcription, function as AR antagonists in rats, and show equipotent growth-inhibitory effects against CWR-22 xeno-grafts (data not shown). Notably, in the most sensitive dog species, seizures were observed with BMS-501949 at doses of 25 mg/kg corresponding to exposures of 1,010 μmol/L h as defined by the area under the concentration–time curve from 0 to 24 hours (AUC0–24). No seizures were observed with the parent compound BMS-641988.

To evaluate the pharmacokinetics (PK), safety, and activity of BMS-641988 in humans, a first-in-man phase I dose-escalation study was initiated in the United States through the Prostate Cancer Clinical Trials Consortium (Study ID CA185-002). The starting dose was 5 mg/d, which was estimated by allometric scaling to be equivalent to one-tenth of a dosage in dogs that caused no clinical toxicity at 1 month. The minimum efficacious exposure of the compound of 12.7 μmol/L h (AUC0–24) was projected to occur in humans in the range of 60–80 mg/d (Fig. 1). Because of regulatory requirements and historical differences in drug exposure and safety profiles, a companion study (CA185-005) was subsequently implemented to learn about PK, safety, and activity in a native Japanese population. The starting dose for the Japanese cohort was 20 mg, based on results from the US reporting no dose-limiting toxicities (DLTs) at this level.

Materials and Methods

This was a first-in-man phase I dose-escalation study of BMS-641988 in CRPC. The US study (CA185-002) was conducted at Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center (MSKCC), New York; University of Wisconsin Carbone Cancer Center, Madison, Wisconsin; and Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland. Seventy-seven patients were enrolled in the United States, of whom 54 were treated from February 6, 2006 through March 31, 2009. The companion study,
CA185-005, was conducted across multiple institutions in Japan and enrolled a total of 8 patients, with seven receiving treatment. The study was approved by the institutional review board at each site. All patients signed an institutional review board and approved written informed consent before the conduct of any study procedures and after a full explanation of the study.

Eligible patients had histologically confirmed prostate cancer and progressive castration-resistant disease, defined by the combination of castrate levels of testosterone (<50 ng/mL) and a rising prostate-specific antigen (PSA) level, with or without detectable metastases. The criteria for rising PSA required a minimum of three measurements obtained more than 1 week apart, with the last value 5 ng/mL or greater (5).

The pre-study evaluation included a history and physical examination, complete blood and platelet count, chemistry panel, PSA level, and electrocardiogram (ECG). Imaging for metastatic disease included a radionuclide bone scan and either computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, chest, abdomen, and pelvis. Patients with a history of significant cardiac disease or a seizure disorder were excluded.

BMS-641988 was administered orally under fasting conditions. The starting dose in the US study was 5 mg/d, and subsequent dosages were 10, 20, 40, 60, 100, and 150 mg/d. In the companion Japanese study, the starting dose was 20 mg. Beginning with the 40 mg cohort, the first 2 patients of each group in the United States were randomized in a 1:1 ratio and in a double-blinded fashion to receive a single dose of BMS-641988 or placebo on cycle 1, day 1 (cycles defined as 28 days) to evaluate single-dose PK and the QTc interval. Assuming acceptable safety results, both patients subsequently received BMS-641988 continuously on a daily schedule starting on cycle 1, day 8, and 4 additional patients were enrolled at the same dosage. These additional patients were not randomized but had single-dose PK sampling and a 7-day washout before continuous daily dosing. All patients were observed for 28 days to insure safety before the next higher dose level was opened for enrollment. At least 3–6 patients were treated at each dose level, provided no DLTs occurred; and for the purposes of acquiring additional safety and efficacy data, an additional number of participants could have been enrolled at any dose level that had no DLT.

**Patient evaluation**

Patients were examined and assessed for adverse events at a minimum of monthly intervals, and toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 3.0). Routine clinical and laboratory assessments were conducted weekly during the first 8 weeks of treatment and every 2 weeks in subsequent cycles. Twelve-lead ECGs were obtained in triplicate on day 1 of each cycle and more frequently in patients who were randomized to receive a single day 1 dose followed by continuous dosing 7 days later. The ECGs were analyzed by a central laboratory and evaluated for changes in QTcF and QTcB from baseline. PSA measurements were done for every cycle or more frequently if indicated. Bone scans and CT and/or MRI were repeated at 3-month intervals.

Because of the preclinical toxicity studies, all investigators and research participants were counseled about the potential risk of seizures, and neurological monitoring with examinations and active precautions, including driving restrictions, were implemented prophylactically.

**Pharmacokinetic analysis**

Blood samples starting from cycle 1, day 1 were collected over a 144-hour period for PK assessment. Blood samples for PK evaluation were also collected over 24 hours on cycle 1, day 15 and cycle 2, day 8. Trough plasma drug concentrations were measured before dosing on day 1 of every cycle beginning with cycle 3. Plasma samples from all patients were assayed for BMS-641988, BMS-501949, and BMS-570511 concentrations using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) assay.

The plasma concentration–time data for BMS-641988, BMS-501949, and BMS-570511 were analyzed by the non-compartmental method using Kinetica version 4.4.1 (Thermo Electron Corporation). The PK parameters assessed included maximum observed concentration (Cmax), time of maximum observed concentration (Tmax), area under the plasma concentration–time curve during a dosing interval (AUC0–τ), and terminal phase half-life (T1/2).

The Cmax and Tmax were obtained from experimental observations. Using no weighting factor, the terminal log-linear phase of the concentration–time curve was identified by least-square linear regression of at least three data points that yielded a maximum G-criterion, which is also referred to as adjusted R2. The T1/2 was calculated as Ln 2/Kd, where Kd was the absolute value of the slope of the terminal log-linear phase. The AUC0–τ was calculated using the mixed log-linear trapezoidal algorithm in Kinetica.

Because BMS-570511 is rapidly converted to BMS-501949 in all animal species tested, no preclinical assessment of its toxicity could be made before using in humans. As a result, 1/10 of the no observable adverse effect level (NOAEL) for BMS-501949 corresponding to an AUC0–τ of 101.0 μmol/L h was used as a threshold guide for dose escalations, along with projected exposures of parent and all active metabolites before the decision to escalate to the next dose level.

**Antitumor effects**

Antitumor effects were assessed using the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria (6). Specifically, PSA changes were reported using waterfall plots and osseous disease on radionuclide bone scan was recorded as improved, progressed, or no change. Soft-tissue disease was evaluated based on CT imaging by modified response evaluation criteria in solid tumors (RECIST; ref. 7). Every effort was made to keep patients...
on BMS-641988 therapy until the time of radiological progression.

Results

Patients
Fifty-four participants were treated with BMS-641988 in the United States and 7 in Japan. Twenty-three enrolled patients were not treated due to screen failures. Baseline demographics and characteristics are listed in Table 1. Most patients (65%) had received three or more prior treatment regimens, including 16 (26%) who had also received chemotherapy with docetaxel.

Dosages of BMS-641988 in the United States ranged from 5 to 150 mg/d. No patients remained on treatment. Forty-two patients (78%) discontinued treatment because of disease progression as judged by the treating clinician. The remaining patients discontinued the study due to drug toxicity (2%), pain (2%), rising PSA (4%), or were removed due to study closure after the report of a seizure in Japan (15%).

Safety and tolerability
Adverse events regardless of causality are shown in Table 2. Overall, the most frequent adverse events were fatigue (25%) and gastrointestinal events (31%), all of which were grade 1 or 2. Most notable was a grade 3 epilepsy event that occurred in a patient receiving 60 mg BMS-641988 in Japan. After two daily doses of BMS-641988, the patient lost consciousness with "loud sneezing,“ drooling, and hypertension. These symptoms were witnessed by medical personnel and resolved within 30 minutes without intervention. A neurologist who assessed the patient 5 minutes after recovery reported that the clinical findings were unclear but that the electroencephalogram findings were partially abnormal. No acute findings were detected by MRI with contrast. The study drug was discontinued due to the event and subsequently a decision was made to end the trial. PK analysis for this patient is not available.

Pharmacokinetics
The plasma concentrations of BMS-641988 and its active metabolites, BMS-570511 and BMS-501949, were proportional to dose in the dosage range of 5 to 100 mg (Fig. 1). At all dose levels, concentrations of BMS-641988, BMS-570511, and BMS-501949 remained well below the BMS-501949 NOAEL associated with seizures in preclinical dog models. At doses of 60 mg and higher, the sum of the active metabolites BMS-501949 and BMS-501949 crossed the 1/10 of BMS-501949 seizure threshold, the significance of which is unknown.

Most of BMS-641988 was converted. Upon administration of 40 mg of BMS-641988, the steady-state proportions were 55.1% (AUCTAU = 59.5 μmol/L h) for BMS-570511, 37.1% (AUCTAU = 40.0 μmol/L h) for BMS-501949, and 7.8% (AUCTAU = 8.37 μmol/L h) for BMS-641988 (Table 3). PK results were similar for the Japanese patients based on a smaller patient cohort (Table 4).

Antitumor effects
Prostate-specific antigen. A waterfall plot of the maximum percentage change in PSA levels from baseline of the 61 assessable patients is presented in Figure 2. Overall, 10 of 61 patients (16%) had a ≥30% decline in PSA and all were chemotherapy naive. None of the 16 patients with prior exposure to chemotherapy had a PSA decline of 30% or greater.

Several patients experienced a decrease in serum concentrations of PSA after discontinuation of BMS-641988. This response was predicted by the preclinical observation that both BMS-641988 and BMS-570511 caused proliferation of LNCaP cells, a cell line that expresses mutant AR2, which suggests that, similar to other antiandrogens such as bicalutamide, BMS-641988 can develop partial agonist properties in a clinical setting.

Table 1. Baseline demographics and characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>United States</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled</td>
<td>77 (94)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Patients treated</td>
<td>54 (69)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Age, y</td>
<td>69 (56–85)</td>
<td>73 (63–80)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>51 (94)</td>
<td>0</td>
</tr>
<tr>
<td>Black</td>
<td>3 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Japanese</td>
<td>0</td>
<td>7 (100)</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
<td>25 (5.3–959.7)</td>
<td>57 (8.38–616.9)</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>39 (72)</td>
<td>0</td>
</tr>
<tr>
<td>Prior radiation</td>
<td>37 (69)</td>
<td>1 (14)</td>
</tr>
</tbody>
</table>

NOTE: Percentages reflect the percentage of participants treated with study drug.
Abbreviations: PSA, prostate-specific antigen; CTC, circulating tumor cell.
Table 2. Number of participants with adverse events regardless of causality by worst grade

<table>
<thead>
<tr>
<th></th>
<th>United States (CA185-002, ( n = 54 ))</th>
<th>Japan (CA185-005, ( n = 7 ))</th>
<th>Total (( n = 61 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Total AEs</td>
<td>58</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Total patients with AEs</td>
<td>25 (46)</td>
<td>7 (13)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

**General disorders and administration site conditions**

- Fatigue: 11 (20), 4 (7), 0, 0, 0, 0 (15 (25))
- Edema: 2 (4), 0, 0, 0, 0, 0 (2 (3))
- Mucosal inflammation: 1 (2), 0, 0, 0, 0, 0 (1 (2))

**Gastrointestinal disorders**

- Constipation: 5 (9), 1 (2), 0, 0, 0, 0 (6 (10))
- Nausea: 4 (7), 0, 0, 0, 0, 0 (4 (7))
- Diarrhea: 3 (6), 0, 0, 0, 0, 0 (3 (5))
- Flatulence: 2 (4), 0, 0, 0, 0, 0 (2 (3))
- Dry mouth: 1 (2), 0, 0, 0, 0, 0 (1 (2))
- Dyspepsia: 1 (2), 0, 0, 0, 0, 0 (1 (2))
- Eruption: 1 (2), 0, 0, 0, 0, 0 (1 (2))
- Vomiting: 1 (2), 0, 0, 0, 0, 0 (1 (2))

**Metabolic and nutritional disorders**

- Anorexia: 5 (9), 0, 0, 0, 0, 0 (5 (8))
- Decreased appetite: 2 (4), 0, 0, 0, 0, 0 (2 (3))

**Investigations**

- Electrocardiogram QT prolonged: 1 (2), 1 (2), 1 (2), 0, 1 (14), 0 (4 (7))
- Hemoglobin decreased: 0, 1 (2), 0, 0, 1 (14), 0 (2 (3))
- Neutrophil count decreased: 0, 1 (2), 0, 0, 0, 0 (1 (2))
- Weight decreased: 1 (2), 0, 0, 0, 0, 0 (1 (2))

**Nervous system disorders**

- Dizziness: 3 (6), 0, 0, 0, 0, 0 (3 (5))
- Peripheral sensory neuropathy: 1 (2), 0, 0, 0, 0, 0 (1 (2))
- Epilepsy: 0, 0, 0, 0, 0, 1 (14) (1 (2))

**Vascular disorders**

- Hot flush: 4 (7), 0, 0, 0, 0, 0 (4 (7))
- Hypertension: 0, 0, 0, 0, 1 (14), 0 (1 (2))

**Skin and subcutaneous tissue disorders**

- Hyperhidrosis: 1 (2), 1 (2), 0, 0, 0, 0 (2 (3))
- Rash: 1 (2), 0, 0, 0, 0, 0 (1 (2))

**Musculoskeletal and connective tissue disorders**

- Arthralgia: 1 (2), 0, 0, 0, 0, 0 (1 (2))
- Musculoskeletal stiffness: 1 (2), 0, 0, 0, 0, 0 (1 (2))
- Myalgia: 1 (2), 0, 0, 0, 0, 0 (1 (2))

**Blood and lymphatic system disorders**

- Thrombocytopenia: 1 (2), 0, 0, 0, 0, 0 (1 (2))

**Eye disorders**

- Vision blurred: 1 (2), 0, 0, 0, 0, 0 (1 (2))

**Respiratory, thoracic, and mediastinal disorders**

- Dry throat: 1 (2), 0, 0, 0, 0, 0 (1 (2))
- Pleural effusion: 0, 0, 0, 1 (14), 0, 0 (1 (2))

**Infection**

0, 0, 0, 1 (14), 0, 0 (1 (2))

NOTE: Data shown are number (%).
Abbreviations: \( n \), number of subjects; AE, adverse events.
CT and bone imaging. Measurable disease as defined by RECIST (6, 7) was noted in 23 of 61 patients (38%) receiving at least one dose of study medication. The best clinical response based on investigator assessment was a confirmed partial response in 1 patient (4%), stable disease in 17 patients (74%), and progressive disease in 5 patients (22%). No favorable changes on radionuclide bone scan were observed in the 45 patients (74%) with osseous metastases at baseline.

Table 3. Mean pharmacokinetic parameters of patients from study CA185-002 (United States) on cycle 2, day 8

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Dose, mg</th>
<th>n</th>
<th>$C_{\text{max}}$, $\mu$mol/L Geo. mean (CV%)</th>
<th>$T_{\text{max}}$, h median (min, max)</th>
<th>AUCTAU, $\mu$mol/L h Geo. mean (CV%)</th>
<th>$T_{1/2}$, h mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-641988</td>
<td>5</td>
<td>3</td>
<td>0.12 (50)</td>
<td>3 (1.5, 3)</td>
<td>1.76 (57)</td>
<td>17.4 (6)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3</td>
<td>0.25 (20)</td>
<td>3 (1.5, 3)</td>
<td>2.02 (36)</td>
<td>16.1 (5)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>10</td>
<td>0.42 (28)</td>
<td>1.75 (1, 3)</td>
<td>4.64 (24)</td>
<td>14.4 (3)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>5</td>
<td>0.71 (38)</td>
<td>2 (1.5, 3)</td>
<td>8.37 (68)</td>
<td>13.6 (4)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>17</td>
<td>0.94 (43)</td>
<td>2 (0.5, 4)</td>
<td>12.83 (35)</td>
<td>21.1 (7.6)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>5</td>
<td>1.99 (29)</td>
<td>4 (2.4)</td>
<td>28.16 (27)</td>
<td>26.0 (11.5)</td>
</tr>
<tr>
<td>BMS-570511a</td>
<td>5</td>
<td>3</td>
<td>0.36 (25)</td>
<td>24 (6, 24)</td>
<td>7.41 (25)</td>
<td>30.9 (2)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3</td>
<td>0.67 (19)</td>
<td>3 (3, 4)</td>
<td>14.57 (13)</td>
<td>30.4 (1)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>10</td>
<td>1.38 (13)</td>
<td>3 (1, 8)</td>
<td>27.19 (15)</td>
<td>28.0 (3)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>4</td>
<td>2.92 (26)</td>
<td>6 (2, 4)</td>
<td>59.52 (32)</td>
<td>24.8 (8)</td>
</tr>
<tr>
<td></td>
<td>60a</td>
<td>7</td>
<td>3.99 (23)</td>
<td>6 (0, 8)</td>
<td>86.03 (21)</td>
<td>30.0 (7)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>3</td>
<td>6.35 (21)</td>
<td>2 (1.5, 8)</td>
<td>136.18 (24)</td>
<td>35.0 (6)</td>
</tr>
<tr>
<td>BMS-501949</td>
<td>5</td>
<td>3</td>
<td>0.19 (14)</td>
<td>2 (2, 3)</td>
<td>3.94 (13)</td>
<td>55.6 (10)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3</td>
<td>0.44 (12)</td>
<td>2 (2, 3)</td>
<td>9.4 (9)</td>
<td>49.3 (16)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>10</td>
<td>0.93 (31)</td>
<td>1.5 (0.5, 24)</td>
<td>16.34 (27%)</td>
<td>54.8 (15)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>5</td>
<td>2.26 (29)</td>
<td>2.25 (0, 24)</td>
<td>39.96 (32)</td>
<td>34.5 (28)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>17</td>
<td>2.64 (46)</td>
<td>1 (0, 24)</td>
<td>53.12 (46)</td>
<td>47.4 (12)</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>5</td>
<td>4.92 (25)</td>
<td>3 (0, 8)</td>
<td>97.01 (23%)</td>
<td>42 (NA)</td>
</tr>
</tbody>
</table>

NOTE: Estimated from cycle 1, day 1 concentration–time profiles following single-dose administration of BMS-641988. Abbreviations: $n$, number of subjects; $C_{\text{max}}$, maximum observed concentration; $T_{\text{max}}$, time of maximum observed concentration; AUCTAU, area under the plasma concentration–time curve over a 24-hour dosing period; $T_{1/2}$, terminal phase half-life; CV%, coefficient of variation; SD, standard deviation; NA, not available.

aStarting from 60 mg, the bioanalytical assay for BMS-570511 is exploratory in nature.

Discussion

The results of molecular profiling studies and experimental prostate cancer models show that continued AR signaling is a consistent feature of CRPC, and that therapies directed at inhibiting AR signaling can produce significant antitumor effects in the clinic (8–11). In preclinical studies using human prostate cancer xenograft models, BMS-641988 showed enhanced AR binding and

Table 4. Mean pharmacokinetic parameters of patients from study CA185-005 (Japan) on cycle 2, day 1

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Dose, mg</th>
<th>n</th>
<th>$C_{\text{max}}$, $\mu$mol/L Geo. mean (CV%)</th>
<th>$T_{\text{max}}$, h median (min, max)</th>
<th>AUCTAU, $\mu$mol/L h Geo. mean (CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-641988</td>
<td>20</td>
<td>3</td>
<td>0.6 (26)</td>
<td>3 (3, 3)</td>
<td>9.39 (28)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>3</td>
<td>0.64 (41)</td>
<td>3 (3, 4)</td>
<td>10.38 (51)</td>
</tr>
<tr>
<td>BMS-570511</td>
<td>20</td>
<td>3</td>
<td>1.37 (12)</td>
<td>6 (4, 8)</td>
<td>30.42 (10)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>3</td>
<td>2.65 (16)</td>
<td>8 (4, 8)</td>
<td>50.88 (14)</td>
</tr>
<tr>
<td>BMS-501949</td>
<td>20</td>
<td>3</td>
<td>0.95 (41)</td>
<td>2 (0, 3)</td>
<td>19.35 (47)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>3</td>
<td>2.39 (46)</td>
<td>4 (1, 24)</td>
<td>52.81 (48)</td>
</tr>
</tbody>
</table>

Abbreviations: $n$, number of subjects; $C_{\text{max}}$, maximum observed concentration; $T_{\text{max}}$, time of maximum observed concentration; AUCTAU, area under the plasma concentration–time curve over a 24-hour dosing period; CV%, coefficient of variation.
was more potent than bicalutamide. It stabilized growth of bicalutamide-resistant tumors and produced differential effects on AR-mediated transcription when compared with either castration or bicalutamide treatment. (2) Despite achieving drug exposures shown to be active preclinically, antitumor activity was limited to one partial response on imaging and PSA declines /C20 30% in only 10 of 61 patients, all of whom were chemotherapy naive. In the setting of an episode of seizure activity attributable to the study drug, and the failure to meet basic efficacy criteria in an increasingly crowded area of therapy, clinical development of BMS-641988 was discontinued and the trial was terminated. Notably, the NOAEL for seizure activity with the active metabolite BMS-501949 (AUC TAU of 1,010 μmol/L h) was well above what was achieved in the clinic, and, as such, was not predictive of the outcome of seizure observed in a single patient treated at the 60-mg dose. Although the sum of BMS-501949 and BMS-570511 at the 60-mg dose level crossed the 1/10 of NOAEL seizure threshold, the significance of this is unclear because it is unknown whether BMS-570511 causes seizures with the same potency as BMS-570949 and if the toxicity of these metabolites are additive. The two seizures observed in a separate study of the novel AR antagonist MDV3100 (11) suggest that antiandrogens as a class may lower seizure thresholds, and is concordant with a recent report demonstrating that several AR antagonists (including the active metabolite BMS-501949) are GABA-A antagonists and can cause convulsions in animals (Foster WR, submitted).

One explanation for the lack of efficacy observed in this study is that, similar to the standard antiandrogens bicalutamide and flutamide, BMS-641988 has partial agonist activity. A decrease in serum concentrations of PSA after discontinuation of BMS-641988 was observed within the context of this study, a phenomenon referred to as an antiandrogen withdrawal response, consistent with counteragonism (12). This suggests that BMS-641988 retains the potential to promote tumor growth in certain conditions and is consistent with the preclinical observation that both BMS-641988 and BMS-570511 cause proliferation of LNCaP cells, a cell line that expresses mutant AR (2). Although the BMS-641988 compound was more potent than bicalutamide in prostate cancer models, in retrospect much of what was seen in this study was predicted by the preclinical work, including the potential for seizure activity, a maximal response of cytostasis or stable disease, and partial agonism. Thus, a more effective strategy for generating antiandrogens is to develop compounds that cause degradation or prevent translocation of AR into the nucleus. In this regard, BMS-641988 and its metabolites, along with first-generation AR antagonists such as bicalutamide, do not efficiently prevent AR translocation. Alternatively, second-generation antiandrogens engineered to retain antagonism in the setting of increased AR expression (such as MDV-3100), as well as 17–20 lyase inhibitors (such as abiraterone acetate and TAK-700), which reduce androgen levels in the testis, adrenal glands, and tumor, have recently shown promise and are now in late-stage development for CRPC (11, 13, 14). Recognizing that overexpression of the AR is a critical step in CRPC, these
and other similar approaches for developing compounds that contribute to androgen blockade may lead to more efficacious treatments for prostate cancer.

Disclosure of Potential Conflicts of Interest

All Bristol-Myers Squibb authors for this study (N.K.E. Fung, S. Cheng, I. Gan, M. Gottardis, M.T. Obermeier, J. Reddy, S. Zhang, B.J. Vakkalagadda, and L. Alland) are employees and stockholders in the company. M. Eisenberger serves on the Data and Safety Monitoring Board for Ipilimumab. The other authors disclosed no potential conflicts of interest.

Grant Support

Support for this research came from Bristol-Myers Squibb DOD W81XWH-09-1-0149, NCI 5P30CA06973. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 5, 2010; accepted November 9, 2010; published OnlineFirst December 3, 2010.

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Phase I Dose-Escalation Study of the Novel Antiandrogen BMS-641988 in Patients with Castration-Resistant Prostate Cancer

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Clin Cancer Res  Published OnlineFirst December 3, 2010.

Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-10-2955

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