Phase II Study of Abiraterone Acetate in Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer Displaying Bone Flare Discordant with Serologic Response

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Abstract

Purpose: Abiraterone is an oral inhibitor of CYP17, which is essential for androgen biosynthesis. This multicenter study assessed its efficacy in patients with castration-resistant prostate cancer (CRPC), without prior chemotherapy or CYP17-targeted therapy, and frequency of bone scans discordant with prostate-specific antigen (PSA) and clinical response.

Experimental Design: Thirty-three patients received abiraterone acetate 1,000 mg daily with prednisone 5 mg twice daily in continuous 28-day cycles. Patients were evaluated monthly for efficacy and safety. Bone scan flare was defined as the combination, after 3 months of therapy, of an interpreting radiologist’s report indicating “disease progression” in context of a 50% or more decline in PSA level, with scan improvement or stability 3 months later.

Results: A 50% or more decline in PSA level at week 12 was confirmed in 22 of 33 (67%) patients. Declines in PSA level of 50% or more were seen in 26 of 33 (79%) patients. Undetectable PSA levels (<0.1 ng/mL) occurred in 2 patients. Median time on therapy and time to PSA progression were 63 weeks and 16.3 months, respectively. Twenty-three patients were evaluable for bone scan flare. Progression was indicated in radiologist’s report in 12 of 23 (52%), and 11 of 12 subsequently showed improvement or stability. As prospectively defined, bone scan flare was observed in 11 of 23 (48%) evaluable patients or 11 of 33 (33%) enrolled patients. Adverse events were typically grade 1/2 and consistent with prior published abiraterone reports.

Conclusion: Clinical responses to abiraterone plus prednisone were frequent and durable in men with metastatic CRPC. Further investigation is needed to clarify the confounding effect of bone scan flare on patient management and interpretation of results.
Abiraterone Acetate Phase II Study in CRPC

Patients and Methods

Patients

Eligibility required histologically confirmed adenocarcinoma of the prostate progressing on androgen deprivation therapy (either an LHRH agonist or orchiectomy, and following antiandrogen withdrawal, as appropriate). PSA progression was defined according to Prostate-Specific Antigen Working Group (PSAWG) criteria (17), and all patients had to have baseline lesions identified by bone scan, computed tomography (CT), or MRI. Prior ketoconazole therapy or chemotherapy was not permitted, with the exception of neoadjuvant or adjuvant chemotherapy completed at least 1 year before study entry. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate renal [serum creatinine ≤1.5 × upper limit of normal (ULN)], hepatic [bilirubin ≤1.5 × ULN, aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN], and bone marrow (hemoglobin >9 gm/dL, absolute neutrophil count >1.5 × 10^9/L, platelets >100 × 10^9/L) function, serum potassium level 3.5 mmol/L or more, and a castrate level of testosterone (<50 ng/dL). Patients with clinically significant electrocardiogram (ECG) abnormalities were ineligible, as were patients with uncontrolled hypertension, New York Heart Association Class III or IV congestive heart failure, those with active autoimmune disease requiring corticosteroid therapy, or any other serious medical or psychiatric illness. Radiation therapy or initiation of bisphosphonate therapy within 4 weeks of study entry was not permitted, although maintenance of a stable bisphosphonate dose was allowed. Use of hormonal therapies, systemic corticosteroids, or any other agent known to decrease PSA levels within 4 weeks prior to study initiation was not permitted. Written informed consent was obtained from all patients.

Treatment and evaluations

Treatment consisted of abiraterone acetate 1,000 mg daily with prednisone 5 mg twice daily. Abiraterone was administered without food in 28-day cycles. Treatment was given continuously until there was evidence of disease progression in patients not experiencing unacceptable toxicity.

Screening evaluations included a history and physical examination, performance status evaluation, and a 12-lead ECG. Laboratory assessments included complete blood cell count, serum chemistries and electrolytes, blood clotting evaluation (prothrombin time, partial thromboplastin time, international normalized ratio), and serum PSA and testosterone levels. Baseline tumor imaging was done by bone scan, CT, MRI, or other imaging procedure. Selected physical and laboratory assessments were repeated on days 1 and 8 of cycle 1, on day 1 of each subsequent cycle, and at the end of study. PSA values were obtained monthly. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3. Bone scans and tumor imaging studies were repeated every 3 cycles.

Study design and statistical considerations

This was a single-arm, open-label, multicenter phase II study conducted under the auspices of the Department of
levels (median 8.5 ng/dL; range, 0.9–24.1 ng/dL). The
withdrawal. All patients had castrate serum testosterone
received an antiandrogen and undergone antiandrogen
Clinical Cancer Research
31) or orchiectomy (32), and 32 (97%) had also
bone metastases. All patients had received androgen
evidence of metastatic disease and 26 of 33 (79%) had
The median baseline PSA level was 23 ng/mL and ranged
graphics and clinical characteristics are shown in Table 1.
centers within the United States. Baseline patient demo-
castrate level of testosterone were enrolled across 5 study
with metastatic prostate cancer progressing despite a
primary study endpoint, was confirmed in 22 (67%) of 33
or more decline in PSA levels, which on subsequent reevaluation
3 months later showed improvement or stability in the
Thus, patients evaluable for bone scan flare included
all patients who had bone scans available at baseline, after
months of therapy, and after 6 months of therapy. An
initial flare at 3 months followed by continued declines in
PSA levels and stable scans was also considered to be of
interest and is reported separately from true flare.
A sample size of 32 evaluable patients was determined as
necessary to detect a response rate of 50% or more, with
response defined as 50% or more decline in PSA levels at
12 weeks from baseline measurement, at a significance
level of 0.04 for a directional test and 81% power. Dis-
tributions of time-to-event variables were estimated using
the Kaplan–Meier product limit method. All patients who
received a minimum of 3 cycles of therapy were considered
evaluable for response. All patients who received at least 1
dose of abiraterone acetate were evaluable for safety.
Adverse events were summarized by worst grade of
severity per patient. The study protocol was approved by
the institutional review boards at all participating sites
and was conducted in accordance with the ethical prin-
ciples of the World Medical Association Declaration of
Helsinki.

Results

Patient characteristics and treatment
Between October 2007 and May 2008, a total of 33 men
with metastatic prostate cancer progressing despite a
castrate level of testosterone were enrolled across 5 study
centers within the United States. Baseline patient demo-
graphics and clinical characteristics are shown in Table 1.
The median baseline PSA level was 23 ng/mL and ranged
from 5.9 to 1,110 ng/mL. All patients had radiographic
evidence of metastatic disease and 26 of 33 (79%) had
bony metastases. All patients had received androgen
deprivation therapy with an LHHR antagonist (N =
31) or orchiectomy (N = 2), and 32 (97%) had also
received an antiandrogen and undergone antiandrogen
withdrawal. All patients had castrate serum testosterone
levels (median 8.5 ng/dL; range, 0.9–24.1 ng/dL). The
majority of patients (88%) had received 2 prior hormonal
therapies, with 3 patients (9%) having received up to 4
hormonal therapies including estrogens or glucocorti-
coids. No patient had undergone prior treatment with
abiraterone, ketoconazole, or chemotherapy. At the time
of analysis (January 2010), the study population had
received a median of 63 weeks (range, 8–104 weeks) of
treatment with abiraterone acetate plus prednisone, with
15 patients (46%) continuing to receive therapy. Treat-
ment had been discontinued secondary to disease pro-
gression in 14 patients (42%) and adverse events in 3
patients (9%); 2 patients discontinued treatment as a
result of grade 3 adverse events (1 each for back pain and
pathologic fracture). Twenty-three patients were eval-
uable for the bone flare phenomenon. All 33 patients
were evaluable for response and safety.

PSA response and durability
Changes in PSA levels, both after 3 months of therapy
and maximal, for each patient are depicted in Figure 1. A
decline in PSA level of 50% or more after 3 months, the
primary study endpoint, was confirmed in 22 (67%) of 33
patients. Confirmed maximal declines in PSA levels of 50%
or more and 90% or more were seen in 26 (79%) and 15
(46%) patients, respectively. In 2 patients, PSA levels
became undetectable (<0.1 ng/mL), declining from base-
line values of 204 ng/mL and 9 ng/mL, respectively. These
patients continued to receive study therapy after 20 and 21
months, both with continued stable bone scans and reso-
lation of adenopathy in 1 patient.
Median follow-up time for this analysis was 19.3
months. The median time to PSA progression was 16.3
months [95% CI 9.2 months, not estimable; Fig. 2]. Nineteen (58%) patients received study treatment for at least 12 months.

**Objective tumor response**

Of 13 patients with measurable disease consisting of lymphadenopathy, 9 (69%) had a partial response and 3 (23%) had stable disease.

**Bone scan results and bone scan flare**

At baseline, 26 patients had positive bone scans. One had a solitary bone metastasis, 7 patients had between 2 and 4 metastases, and 18 patients had more than 4 discrete metastases. Twenty-three patients had the combination of a positive baseline bone scan, a 50% or more decline in PSA after 3 months, and bone scans at 3 and 6 months and thus were available for evaluation of bone scan flare. Reports were available on 92 total bone scans from 41 unique radiologists dispersed geographically among the study sites. Of the 23 eligible patients, bone scan progression was indicated in the radiologists’ reports in 12 (52%) of the scans taken after 3 months of therapy. Four of the 12 patients had a report worded specifically as “progression of disease” without new lesions (e.g., based solely on increased intensity of existing lesions), whereas for 8 of 12 patients, progression of disease due to new lesions was noted. For imaging following 6 months of therapy, the radiologists’ reports indicated subsequent improvement in 4 of 12 and stability in 7 of 12 patients. One patient had a worsened scan at 6 months despite continued PSA decline, showing a new lesion. Thus, overall, bone scan flare, as defined by the combination of PSA decline, initial flare, and subsequent improvement or stability in bone scans at 6 months, was observed in 4 of 23 (17%) and 7 of 23 (30%) evaluable patients and 4 of 33 (12%) and 7 of 33 (21%) enrolled patients, respectively.

Two responding patients were not evaluable for bone scan flare: 1 had persistent declines in PSA levels (from baseline to the end of month 3 and from month 3 through month 6 of therapy), with a negative bone scan at baseline that was not repeated; the second discontinued study therapy after 4 months on therapy because of a pathologic femoral neck fracture despite a decline in PSA level of 91.7%.

In the 11 patients with bone flare at 3 months and stable or improved scans at 6 months, median age was 72 years (range, 54–85), median PSA level at baseline was 21.9 ng/dL (range, 6.8–204.3), and median alkaline phosphatase level at baseline was 88.5 units/L (range, 49.0–372.0), not significantly different from the study population as a whole. Alkaline phosphatase levels did not change in patients experiencing flare: median baseline value was 88.5 units/L. After 3 months of therapy, the median remained at 88.5 units/L and after 6 months, it was 83.5 units/L. Four patients had less than 4 metastases,
and 7 patients had multifocal disease. Patient disposition is summarized in Figure 3.

Radiologist interpretation of bone scans in these 11 patients was as follows: 4 patients had month 4 bone scans being read as having increased intensity of existing lesions; the other 7 patients had bone scans that were read as having new lesions (Fig. 4). Of these 11 patients with flare, 10 maintained a decline in PSA levels of 50% or more from baseline and 1 developed an increase in PSA level from month 4 to month 7 of 4.9 ng/dL (73% increase above nadir and 21% decline from baseline) after 6 months. The remaining patient with discordant results following 3 months of therapy continued to have decline in PSA levels past 3 months but had a bone scan after 6 months of therapy that was interpreted as progressive disease. This patient came off study after 8 months of therapy (and thus never underwent another bone scan).

Safety

Adverse events were most often grade 1 or 2 (see Table 2) and clinically manageable. The most common treatment-related adverse events were fatigue, hot flush, bone pain, peripheral edema, arthralgia, dizziness, and hypokalemia. In addition to those listed in Table 2, there was a single occurrence each of grade 3 supraventricular arrhythmia and atrial flutter. One incident each of grade 3 hypokalemia and hypertension was observed.

Discussion

In the current study, a large proportion of patients (67%) with CRPC experienced a 50% or more decline in serum PSA levels while on abiraterone acetate, an effect that persisted for more than 1 year in more than half of patients. An important and surprising observation in this study was that discordant bone scan findings after 3 months of therapy were observed in a large proportion of patients (36% of the total and 48% of those who experienced a ≥50% decline in PSA levels).

In this study, the potential clinical utility of abiraterone acetate in CRPC used determinants of efficacy that included decline in PSA levels, time to PSA progression, and changes in objective imaging with bone scan and CT scans. Evaluation of bone scans resulted in an observation of a high incidence of bone flare during the first 6 months of the study.

Potential confounding variables that may lead to erroneous determination that a flare has occurred were considered. These included the possibility of a significant delay between baseline bone scan and initiation of therapy (and therefore disease progression before starting therapy) and...
bisphosphonate initiation. All patients initiated treatment within 28 days of the baseline bone scan, and initiation of bisphosphonate therapy was not permitted within 28 days before starting or at any time while on the study, thus decreasing the possibility that these factors falsely elevated the incidence of diagnosed flare.

Figure 4. Examples of bone scan flare in patients receiving abiraterone acetate. A, example of a patient with a declining PSA level but a month 4 bone scan being read as having a new metastasis in the right pubic ramus, as indicated by the arrow (although in retrospect, one can see the lesion in the baseline bone scan). By month 7, this lesion shows improvement, indicating that this lesion seen at month 4 was present at baseline and thus was secondary to bone flare. B, example of a patient with a declining PSA level but a month 4 bone scan being read as progression in existing lesions. By month 7, this progression improved, indicating that the progression seen at month 4 was due to bone flare.

The high incidence of the discordant interpretation of bone scans by radiologists in the presence of a 50% or more decline in PSA levels highlights several important issues related to study design and management of CRPC. First, this phenomenon is not systematically assessed in the setting of highly active, hormonal therapies that...
modulate PSA expression in CRPC. As a result, incorporation of these data into subsequent phase II and phase III designs may further clarify the clinical meaning of this phenomenon (e.g., whether it predicts a favorable long-term outcome). Second, it suggests that there may be an initial discordance between PSA and bone scan that will change with time, in many cases leading to the stable presence of bone lesions following an initial increase in tracer uptake. Of note, consensus criteria such as the Prostate Cancer Working Group 2 (PCWG2) formally addresses bone flare and includes the recommendation to carry out a first follow-up bone scan 12 or more weeks after the start of therapy; and furthermore defines progression in bone when a minimum of 2 new lesions are observed and confirmed on a second scan done 6 or more weeks later (19). These bone flare findings further highlight a need for closer communication between clinicians and interpreting radiologists. This phase II study did not mandate central review of scans, nor did it require that scans be carried out at the main clinical site of the study. Indeed, there were 41 individual radiologists from 4 different states (Massachusetts, Texas, New Mexico, and California) who interpreted 92 bone scans in this study, which suggests that these results are not the result of an institutional or regional bias. Therefore, it is necessary that this phenomenon be recognized to avoid prematurely discontinuing efficacious therapy on the basis of a potentially erroneous bone scan interpretation. Mandating central review of scans where possible is recommended. Finally, bone flare can potentially be evaluated by the measurement of markers of bone turnover, as changes in bone-specific isoenzyme of alkaline phosphatase and osteocalcin have been reported to be sensitive predictors of subsequent radiologic response (20). These parameters may provide useful clinical information to a physician after only 1 month of therapy, long before radiologic evidence of response can be expected (21). Imaging techniques, such as positron emission tomography, utilizing novel tracers such as radiolabeled dihydrotestosterone, are also in development as a potential means to more specifically image androgen receptor and ligand interactions.

The PSA response proportion of 67% in this study is slightly higher than that observed in previous phase II studies with abiraterone acetate (36%–55%; refs. 9, 12, 22). Potential explanations for this observation are many and include the fact that this was a population with less extensive disease than in past studies (e.g., median PSA level was 23 in this study), no patients were previously treated with either chemotherapy or CYP17 inhibitors such as ketoconazole, and finally that prednisone may contribute to a modest increase in the likelihood of a decline in PSA levels.

Table 2. Incidence of most frequent (≥10%) treatment-related adverse eventsa (N = 33)

<table>
<thead>
<tr>
<th>Toxicity by preferred term</th>
<th>Total grade 1–4</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>15 (46)</td>
<td>8 (24)</td>
<td>6 (18)</td>
<td>1 (3)</td>
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<tr>
<td>Hot flush</td>
<td>10 (30)</td>
<td>7 (21)</td>
<td>3 (9)</td>
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<td>0</td>
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<tr>
<td>Bone pain</td>
<td>8 (24)</td>
<td>6 (18)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>8 (24)</td>
<td>7 (21)</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
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<tr>
<td>Arthralgia</td>
<td>7 (21)</td>
<td>6 (18)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (21)</td>
<td>6 (18)</td>
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<td>1 (3)</td>
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<td>Hypokalemia</td>
<td>7 (21)</td>
<td>6 (18)</td>
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<td>1 (3)</td>
<td>0</td>
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<tr>
<td>Back pain</td>
<td>6 (18)</td>
<td>3 (9)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (18)</td>
<td>3 (9)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>6 (18)</td>
<td>6 (18)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Constipation</td>
<td>5 (15)</td>
<td>5 (15)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>5 (15)</td>
<td>4 (12)</td>
<td>1 (3)</td>
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<td>0</td>
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<tr>
<td>Hyperbilirubinemia</td>
<td>5 (15)</td>
<td>4 (12)</td>
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<tr>
<td>Hyperglycemia</td>
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<td>2 (6)</td>
<td>1 (3)</td>
<td>0</td>
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<tr>
<td>Contusion</td>
<td>4 (12)</td>
<td>4 (12)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Nausea</td>
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<td>3 (9)</td>
<td>1 (3)</td>
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<td>0</td>
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<tr>
<td>Musculoskeletal pain</td>
<td>4 (12)</td>
<td>2 (6)</td>
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<tr>
<td>Pain in extremity</td>
<td>4 (12)</td>
<td>3 (6)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (12)</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (12)</td>
<td>3 (9)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

*aMost frequent according to the total percentage observed.*
without steroid replacement therapy were rare (9–12). Although hypokalemia remained a common event, it occurred with lower incidence and severity than was observed in patients previously treated with steroid replacement therapy. This decrease was most likely due to suppression of the compensatory increase in ACTH levels by prednisone, as well as a heightened awareness of this potential toxicity and early intervention with potassium supplementation.

Collectively, these results, as well as the favorable long-term safety profile of this combination, suggest that this therapy is highly active in CRPC. Advancement of this dose and schedule of abiraterone to a pivotal phase III study in this patient population is warranted.

Disclosure of Potential Conflicts of Interest

C.M. Haag, A. Molina, and T. Khosr are employed by Cougar Biotechnology. E.J. Small is a compensated advisor to Cougar Biotechnology. C.J. Logothetis, M.R. Smith, and E. Efstathiou are uncompensated advisors to Cougar Biotechnology. The other authors disclosed no potential conflicts of interest.

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