Cancer Therapy: Clinical

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. Clin Cancer Res; 17(14); 4854–61. ©2011 AACR.

Introduction

As data emerge suggesting that the progression of prostate cancer in an androgen-deprived milieu is, in part, mediated through the selective growth of tumor cells with a heightened sensitivity to androgens (1–4), progress and interest in the development of therapies that target extragonadal androgen synthesis have accelerated (5, 6). Abiraterone acetate is an orally available selective androgen biosynthesis inhibitor that specifically inhibits CYP17. Abiraterone has shown activity as a monotherapy in castration-resistant prostate cancer (CRPC) in both chemotherapy-naive and chemotherapy-exposed patients receiving a luteinizing hormone–releasing hormone (LHRH) analogue (7–12).

On the basis of the phase I experience with abiraterone acetate monotherapy, it was determined that the safety profile of this therapy could be improved through concomitant corticosteroid administration, an approach that reduces the compensatory elevations in adrenocorticotropic hormone (ACTH) and mineralocorticoid excess induced by CYP17 blockade. Because corticosteroids have shown modest antitumor efficacy when given as monotherapy, the current phase II study was designed to determine the efficacy and safety of the combination of abiraterone acetate and prednisone in patients with metastatic CRPC. In particular,
Castration-resistant prostate cancer (CRPC) is a lethal disease and depends on androgen production and androgen receptor signaling for growth, affecting bone more than other distant sites. Abiraterone acetate, a selective androgen biosynthesis inhibitor of CYP17, has been shown to inhibit persistent androgen synthesis from adrenal and intratumoral sources, thereby suppressing an important stimulus of CRPC growth. This phase II study is the first assessment of abiraterone acetate in CRPC not previously treated with docetaxel or androgen synthesis inhibitors such as ketoconazole. Serial changes in objective imaging (i.e., bone scans) were utilized to assess patient outcomes. Discordant findings between serologic (prostate-specific antigen) response and increases in bone scan lesion intensity, although previously described in treatment-naïve prostate cancer, are reported here for the first time in CRPC. In addition to reporting prolonged antitumor activity of abiraterone acetate, this study highlights the potential detriment for patients if increased bone scan intensity is erroneously interpreted as disease progression.

**Translational Relevance**

Castration-resistant prostate cancer (CRPC) is a lethal disease and depends on androgen production and androgen receptor signaling for growth, affecting bone more than other distant sites. Abiraterone acetate, a selective androgen biosynthesis inhibitor of CYP17, has been shown to inhibit persistent androgen synthesis from adrenal and intratumoral sources, thereby suppressing an important stimulus of CRPC growth. This phase II study is the first assessment of abiraterone acetate in CRPC not previously treated with docetaxel or androgen synthesis inhibitors such as ketoconazole. Serial changes in objective imaging (i.e., bone scans) were utilized to assess patient outcomes. Discordant findings between serologic (prostate-specific antigen) response and increases in bone scan lesion intensity, although previously described in treatment-naïve prostate cancer, are reported here for the first time in CRPC. In addition to reporting prolonged antitumor activity of abiraterone acetate, this study highlights the potential detriment for patients if increased bone scan intensity is erroneously interpreted as disease progression.

the present trial is the first trial with abiraterone to focus on patients who had not been treated with either docetaxel or an androgen synthesis inhibitor, such as ketoconazole. A well-recognized barrier to therapy development in CRPC is the lack of reliable surrogate markers of response to treatment coupled with a potentially exaggerated reliance on changes in serum prostate-specific antigen (PSA) as an indicator of treatment efficacy. This is particularly true with agents that have the potential for PSA modulation such as abiraterone acetate or ketoconazole. Consequently, changes in bone scan images have been advocated as important markers of disease response and progression. However, the utility of bone scans has been called into question because of a transient “flare” of bone lesion intensity in the context of treatment response resulting in a false determination of disease progression (13, 14). Although the bone scan flare has been described in breast cancer and in hormone-sensitive prostate cancer, no systemic evaluation of the flare phenomenon has been undertaken in CRPC (15, 16). Therefore, changes in objective imaging, particularly bone scans, were incorporated into this study in addition to PSA decline and time to PSA progression. As noted, these imaging changes are particularly important in the context of a novel agent that can potentially modulate PSA, potentially rendering it a less useful biomarker.

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 × 10⁹/L, platelets >100 × 10⁹/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
Defense Prostate Cancer Clinical Trials consortium and sponsored by Cougar Biotechnology. The primary study endpoint was the proportion of patients achieving a 50% or more decline in PSA levels by week 12 of therapy. Secondary endpoints included durability of response as determined by time to PSA progression, objective radiographic response rate according to RECIST guidelines (18), radiographic progression-free survival time, overall survival time, clinical benefit as determined by disease stabilization, change in ECOG performance status, and overall treatment safety.

Bone scan flare was prospectively defined as discordant results after 3 months of therapy based on the combination of an interpreting radiologist’s report indicating “disease progression,” typically based on increased lesion intensity or number that occurred in the context of a 50% or more decline in PSA levels, which on subsequent reevaluation 3 months later showed improvement or stability in the scan. Thus, patients evaluable for bone scan flare included all patients who had bone scans available at baseline, after 3 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. Distributions 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 principles 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 demographics 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 LHRH 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 estrogen or glucocorticoids. 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. Treatment had been discontinued secondary to disease progression 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 evaluable 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 baseline 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 resolution 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.
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 new 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.

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 close communication between clinicians and interpreting radiologists. This phase II study did not mandate 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>0</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>
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<tr>
<td>Dizziness</td>
<td>7 (21)</td>
<td>6 (18)</td>
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<td>1 (3)</td>
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<tr>
<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>
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<tr>
<td>Muscle spasms</td>
<td>6 (18)</td>
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<tr>
<td>Constipation</td>
<td>5 (15)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<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>
<td>1 (3)</td>
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<tr>
<td>Hyperglycemia</td>
<td>5 (15)</td>
<td>2 (6)</td>
<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>
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<td>0</td>
<td>0</td>
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<tr>
<td>Nausea</td>
<td>4 (12)</td>
<td>3 (9)</td>
<td>1 (3)</td>
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<tr>
<td>Musculoskeletal pain</td>
<td>4 (12)</td>
<td>2 (6)</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>
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</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>
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<tr>
<td>Vomiting</td>
<td>4 (12)</td>
<td>3 (9)</td>
<td>1 (3)</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.

Disclosures of Potential Conflicts of Interest

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

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