Sequential Use of the Androgen Synthesis Inhibitors Ketoconazole and Abiraterone Acetate in Castration-Resistant Prostate Cancer and the Predictive Value of Circulating Androgens

Won Kim1, Li Zhang1, John H. Wilton2, Gerald Fetterly2, James L. Mohler3, Vivian Weinberg1, Allison Morse1, Russell Z. Szmulewitz4, Terence W. Friedlander1, Lawrence Fong1, Amy M. Lin1, Andrea L. Harzstark1, Arturo Molina5, Eric J. Small1, and Charles J. Ryan1

Abstract

**Purpose:** Patients previously treated with ketoconazole were excluded from phase III trials of abiraterone acetate due to potential overlapping mechanism of action. The purpose of this study was to determine the clinical utility of abiraterone and its impact on circulating androgens following ketoconazole.

**Experimental Design:** Chemotherapy-naive patients with progressive metastatic castration-resistant prostate cancer (mCRPC) and prior ketoconazole therapy ≥28 days received abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. The primary endpoint was the proportion of patients with PSA response, defined as ≥30% PSA decline at 12 weeks. H0 = 0.30 versus H1 = 0.50 (α = 0.05, power = 0.83). Circulating androgen levels were measured using liquid chromatography tandem mass spectrometry.

**Results:** Thirty-nine patients were included in the final analysis. Twenty (51%; 95% confidence interval, 36%–66%) patients had ≥30% PSA decline; the null hypothesis was rejected. Sixteen (41%) had ≥50% PSA decline. Median PFS (progression-free survival) was 16 weeks; median radiographic PFS (rPFS) was 36 weeks. Samples for measurement of baseline androgens were available in 37 patients. The PSA response proportion was 59% in 29 patients with DHEA ≥ limit of quantitation (LOQ), compared with 13% in 8 patients with DHEA < LOQ (P = 0.042). Median PFS was 6 and 16 weeks in DHEA < LOQ and DHEA ≥ LOQ patients, respectively (P = 0.017); median rPFS was 14 and 36 weeks in DHEA < LOQ and DHEA ≥ LOQ patients, respectively (P < 0.001).

**Conclusions:** Abiraterone demonstrates modest clinical efficacy in mCRPC patients previously treated with ketoconazole. Patients with DHEA ≥ LOQ were more likely to demonstrate PSA responses and longer PFS. Analysis of circulating androgens merits further investigation as a biomarker for response to androgen synthesis inhibitor therapy. *Clin Cancer Res; 20(24); 6269–76. ©2014 AACR.*

Introduction

Ketoconazole, an imidazole antifungal agent with inhibitory activity of the cytochrome P450 17A1 complex (CYP17A1), has demonstrated clinical activity in patients with metastatic castration-resistant prostate cancer (mCRPC) in prospective clinical trials (1, 2) and has been used for decades in the treatment of this disease (3). Combined with the understanding that retained androgen receptor (AR) signaling is integral to the progression of prostate cancer to its lethal phenotype, the clinical utility of ketoconazole provided a framework for the development of novel androgen synthesis inhibitors. Abiraterone acetate, an oral CYP17A1 inhibitor with greater specificity and potency than ketoconazole (4, 5), significantly improved the survival of patients with progressive mCRPC in pivotal phase III trials (6, 7), and is now in broad clinical use. A phase I study of abiraterone in patients who experienced disease progression (or excessive toxicities) on ketoconazole demonstrated PSA responses comparable with those of ketoconazole-naive patients (8). However, concerns regarding the overlapping mechanism of action (and of resistance) between ketoconazole and abiraterone led to the exclusion of patients previously treated with ketoconazole from the pivotal phase III abiraterone trials (6, 7). Therefore, the clinical efficacy of
Translational Relevance

The CYP17A1 inhibitor abiraterone acetate has significantly improved the survival of men with metastatic castration-resistant prostate cancer (mCRPC), in both the after-chemotherapy and chemotherapy-naïve settings. The clinical utility of abiraterone following ketoconazole, however, is unknown. Ketoconazole, an imidazole antifungal agent with less potent and specific CYP17A1 inhibitory activity, remains a part of the clinical armamentarium for clinicians, particularly in areas of the world where abiraterone has not received regulatory approval. This phase II study demonstrated that abiraterone has modest clinical activity in patients with disease progression on ketoconazole. Patients with higher circulating androgen levels before starting abiraterone had significantly higher PSA response proportion and longer progression-free survival. The role of circulating androgens in mCRPC disease biology, and their potential as biomarkers for response to androgen synthesis inhibition therapy, merits further investigation.

Patients and Methods

Patients

Eligible patients had mCRPC and were treated with ketoconazole for more than 28 days, with evidence of disease progression or grades 3/4 toxicities requiring discontinuation of therapy. Disease progression was defined as a confirmed rise in PSA >2 ng/mL above the nadir (or baseline, if no response to ketoconazole), the appearance of new lesions on bone scan, or objective progression defined using RECIST criteria, while on ketoconazole. A minimum washout period of 27 days was required between the final dose of ketoconazole and the first dose of abiraterone acetate. Other key eligibility criteria included: Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; absolute neutrophil count ≥1.5 × 10⁹/L, hemoglobin ≥9.0 g/dL, and platelets ≥100 × 10⁹/L; serum creatinine and bilirubin ≤1.5× the institutional upper limit of normal (ULN), potassium ≥3.5 mmol/L, and AST and ALT ≤2.5× the institutional ULN. Patients previously treated with chemotherapy for mCRPC were excluded from the study.

The study was conducted in compliance with the study protocol and in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by regulatory authorities and Institutional Review Boards (IRB) of participating institutions. Signed and informed written consent was obtained from all patients before study entry.

Study design and treatment

This was a single-arm, prospective phase II study conducted through the Prostate Cancer Clinical Trials Consortium, at the University of California, San Francisco (UCSF; San Francisco, CA), and the University of Chicago (UOfC; Chicago, IL). Enrolled patients received abiraterone acetate 1,000 mg by mouth daily and prednisone 5 mg by mouth twice daily, in 28-day cycles. Abiraterone was taken on an empty stomach (at least 2 hours after and 1 hour before meals). Dosing was interrupted for grades 3/4 toxicities related to study treatment, and restarted at 25% dose reduction once toxicities resolved to grade 1 or less. Up to two dose reductions (to 750 and 500 mg by mouth, once daily) were permitted. Patients who required more than 4 weeks to recover from grade 3/4 toxicities were discontinued from study participation. Patients underwent clinical and laboratory assessment before their first dose and on day 1 of each subsequent cycle; radiographic assessments occurred every three cycles.

Treatment continued until disease progression according to Prostate Cancer Working Group 2 (PCWG2) criteria (9). Patients were allowed to continue therapy at the investigators’ discretion if they met the PSA criteria for progression but did not experience unequivocal clinical progression, objective progression per RECIST criteria or ≥2 new bone lesions. Abiraterone was discontinued for unacceptable toxicity, if the patient withdrew consent, or if the patient was withdrawn from the study at the investigators’ discretion.

Study endpoints and assessments

PSA response was defined as ≥30% PSA decline. The primary endpoint was PSA response proportion, defined as the proportion of patients with ≥30% PSA decline at 12 weeks of abiraterone treatment. Secondary endpoints included time to PSA progression (TTP), safety of abiraterone following prior ketoconazole therapy, and the proportion of patients with ≥50% PSA decline at 12 weeks. Exploratory endpoints included assessment of circulating androgen levels at baseline and their change over time on abiraterone.

Patients were assessed at the beginning of each 28-day cycle for safety and response. Soft tissue and bone imaging were performed every three cycles (12 weeks). PSA measurements were taken at baseline and with each cycle of treatment. Androgen levels were measured every two cycles (8 weeks) beginning with cycle 1, day 1 (baseline, before first dose of abiraterone).

A waterfall plot was constructed to graphically display the PSA response at 12 weeks for each patient (9). PSA progression was defined as ≥25% PSA increase and absolute increase ≥2 ng/mL from the nadir, or for patient without PSA decline, ≥25% PSA increase and absolute increase ≥2 ng/mL from baseline. Progression-free survival (PFS) was a prespecified assessment. PCWG2 criteria were used to define disease progression, and included PSA progression, unequivocal clinical progression, radiographic progression, initiation of new therapy or death.
Measurement of circulating androgens

Analysis of circulating androgen levels was performed at Roswell Park Cancer Institute. Study samples were analyzed for testosterone (T), DHT, DHEA, androsterone (AND), and androsterone (AND), using high-pressure liquid chromatography (HPLC) and tandem mass spectrometric detection (LC/MS-MS), a previously validated method (10). Briefly, samples were prepared as follows: A 250 μL aliquot of a calibrator, quality controls, plasma blank, or study sample was mixed with 750 μL of HPLC grade water, 100 μL internal standard solution (75/225 pg/mL d₃-T/d₃-DHT in 75% methanol), and extracted with 4.0 mL methyl-tert-butyl ether (MTBE). Tubes were rotated for 15 minutes and centrifuged at 3,000 rpm and 4°C for 15 minutes to separate liquid phases. The aqueous phase was frozen in a dry-ice acetone bath and the upper MTBE layer poured into a glass conical tube. MTBE was evaporated with nitrogen at 37°C and the residue reconstituted with 60 μL of 60% methanol. The suspension was centrifuged at 3,000 rpm and 4°C for 5 minutes to separate insoluble materials. A 20 μL aliquot of the supernatant was injected.

LC/MS-MS was performed using a Shimadzu Prominence UFLC System (Shimadzu Scientific Instruments Inc.) interfaced with an AB SCIEX QTRAP 5500 mass spectrometer (AB SCIEX) in positive ion mode. Voltages for maximum parent/fragment ion pair intensities were optimized using direct infusion and flow injection analysis.

The limits of quantitation (LOQ) for the androgens measured are as follows: Testosterone <0.0125 ng/mL; DHT <0.025 ng/mL; ASD <0.250 ng/mL; DHEA <0.250 ng/mL; AND <0.250 ng/mL.

Serum and plasma specimens were used for analysis of circulating androgen levels. Comparison of androgen concentrations between the two specimen types in a subset of 10 patients in whom serum and plasma were drawn at the same time demonstrated no significant differences.

Statistical analysis

The study was designed to test the hypothesis that abiraterone retains clinical activity in patients with mCRPC that is refractory to ketoconazole. The null hypothesis of a 30% PSA response proportion (i.e., ≥30% of patients would experience a PSA decline ≥30% at 12 weeks of abiraterone) was compared with an alternative hypothesis of 50% PSA response proportion (i.e., ≥50% of patients would experience a PSA decline ≥30% at 12 weeks), using a Simon two-stage minimax design. Accrual of 39 patients was required assuming directional level of significance 0.05 and power 0.83 using an exact binomial test. Nineteen patients were to be accrued to the first stage, and if 7 achieved a ≥30% PSA decline, then 20 patients were to be accrued to the second stage. If 17 patients entered on the study achieved ≥30% PSA decline, then the null hypothesis would be rejected in favor of the alternative hypothesis. Frequency distribution and percentage were used to summarize categorical measurements, whereas mean (with SD) and median (with range) were used to describe symmetric and skewed continuous measurements, respectively. Univariate analysis among variable were assessed using the two-sample t test, the Wilcoxon rank-sum test, and the χ² test, as appropriate. The distribution of time-to-event variables (such as PFS, TTPP) was estimated using the Kaplan–Meier method, and log-rank tests were used for comparison.

Results

Demographics

Between August 2010 and December 2012, a total of 42 patients were enrolled at UCSF and UoC. Three patients were replaced during the first stage of accrual due to adverse patient selection: 1 patient with a history of oxygen-dependent pulmonary fibrosis and cardiac disease died of a myocardial infarction before week 12 evaluation without evidence of disease progression; 1 patient with rapidly progressing disease at the time of enrollment discontinued therapy after just 9 days and died a few days thereafter; a third patient with symptomatic pleural effusion at the time of enrollment discontinued therapy after 5 weeks with worsening respiratory status and died shortly thereafter. Approvals were obtained from the Data and Safety Monitoring Committees and the IRBs of both institutions before study expansion and continued accrual. These 3 patients were excluded from all analyses. Therefore, 39 patients were included in the final analysis (Supplementary Fig. S1).

Baseline demographics and clinical characteristics are summarized in Table 1. Thirty-seven patients discontinued ketoconazole for disease progression; 1 patient discontinued because of QT prolongation and another discontinued because of transaminitis and rash and disease progression. Seven of the 14 patients who had pain due to metastatic disease at baseline before starting abiraterone required opiate analgesics. Ninety-two percent had bone metastases; 48.5 (2.1–1,144.0)
38% had lymph node metastases; and 5% had visceral metastases, which is consistent with the typical metastatic disease burden in this patient population. At the time of final analysis, 2 patients remained on study and on abiraterone.

**Clinical responses**

Three patients discontinued study treatment before 12 weeks due to disease progression (1 by PSA only and 2 by pain). After 12 weeks of abiraterone treatment, 20 patients [51%; 95% confidence interval (CI), 36%–66%] had ≥30% PSA decline. Therefore, the null hypothesis of 30% PSA response proportion was rejected. In addition, 16 patients (41%; 95% CI, 26%–56%) experienced ≥50% PSA decline after 12 weeks of abiraterone. PSA responses at 12 weeks of abiraterone treatment are summarized on a waterfall plot (Fig. 1). Median TTPP was 16 weeks (range, 4–71). Clinical responses to abiraterone, by PSA and radiographic assessment, are summarized in Table 2.

The relationship between duration of prior ketoconazole therapy and PSA response was explored in a post hoc analysis, given the long median duration of ketoconazole therapy in enrolled patients. Median duration of prior ketoconazole therapy was significantly shorter in patients who had ≥30% PSA decline (20 vs. 72 weeks, \( P = 0.001 \); Supplementary Fig. S2).

**Progression-free survival**

Median PFS (Fig 2A) was 16 weeks (range, 4–71 weeks), which was identical to the median TTPP; PSA progression constituted disease progression in all but 2 patients. Both of these patients had clear evidence of clinical disease progression (increasing pain) despite neither PSA nor radiographic progression.

**Radiographic PFS**

Recent studies of abiraterone (COU-AA-302; ref. 7) and enzalutamide (PREVAIL; ref. 11) in chemotherapy-naïve patients used a novel definition of radiographic PFS (rPFS), which was defined as death, soft tissue progression per RECIST criteria, bone progression (per modified PCWG2 criteria), or unequivocal clinical progression (defined as worsening symptomatic disease or the need for another therapeutic intervention such as palliative radiation, chemotherapy, or surgery). PSA changes were not included in the rPFS definition. rPFS was a coprimary endpoint of both studies.

rPFS, similarly defined, was reported for the present study cohort (Fig. 2B). For the most conservative estimate of rPFS, 3 patients who discontinued study treatment for PSA progression only (all before 12 weeks of therapy) were considered to have radiographic progression at the time of PSA progression. On the basis of this definition, median rPFS was 36 weeks (range, 8–170 weeks).

**Safety**

The most common adverse events (Table 3) were fatigue (46%), hypophosphatemia (21%), hypertension (18%), transaminitis (13%), and hypokalemia (13%); most of these were grade 1/2 events. Twelve patients (31%) experienced a total of 23 grade 3/4 adverse events, of which one was a grade 4 event (anemia). Hypophosphatemia was the most common grade 3 adverse event, occurring in 3 patients (8%); no other grade 3 adverse event occurred in more than
2 patients. There were no patients who permanently discontinued abiraterone due to adverse events.

**Androgen analysis**

Baseline androgen levels were available in 37 patients. Median DHEA was 0.614 ng/mL; median testosterone was 0.0467 ng/mL; median ASD was 0.194 ng/mL; DHT was <LOQ in all but 5 patients; AND was <LOQ in all patients.

Median DHEA level was significantly higher in patients who had a ≥30% decline in PSA (0.71 ng/mL vs. 0.43 ng/mL, P = 0.028); median testosterone and ASD levels were not significantly different between the PSA responders and PSA nonresponders (Supplementary Fig. S3). Therefore, the relationship between baseline DHEA levels and clinical benefit of abiraterone was explored further. Eight patients had DHEA < LOQ and 29 patients had DHEA ≥ LOQ. One patient (13%) with DHEA < LOQ had a ≥30% PSA decline, compared with 17 patients (59%) with DHEA ≥ LOQ (P = 0.042). The median PFS was 6 and 16 weeks in the DHEA < LOQ and DHEA ≥ LOQ groups, respectively (P = 0.017; Fig. 3A). Median rPFS was 14 and 36 weeks in the DHEA < LOQ and DHEA ≥ LOQ groups, respectively (P < 0.001; Fig. 3B). All patients had undetectable DHEA levels by cycle 3, day 1 (after 8 weeks of treatment).

**Discussion**

Patients previously treated with ketoconazole were excluded from the phase III studies of abiraterone due to concerns regarding the potential overlapping mechanism of action and resistance of these CYP17A1 inhibitors. In this study, abiraterone demonstrated modest clinical activity in men with progressive mCRPC despite prior CYP17A1 inhibition therapy with ketoconazole. Over half the patients enrolled on this study had ≥30% PSA declines after 12 weeks of abiraterone treatment; thus, the study met its primary endpoint. Moreover, more than 40% of patients had ≥50% PSA declines after 12 weeks on abiraterone. Median PFS was 16 weeks, and median rPFS was 36 weeks. Abiraterone was well tolerated in this study population; 31% of patients experienced grade 3/4 adverse events.

**Table 2. Summary of clinical responses**

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 39)</th>
<th>DHEA &lt; LOQ (n = 8)</th>
<th>DHEA ≥ LOQ (n = 29)</th>
<th>P, DHEA &lt; LOQ vs. DHEA ≥ LOQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30% PSA decline at 12 wk, n (%)</td>
<td>(95% CI)</td>
<td>20 (51%; 36–66%)</td>
<td>1 (13%)</td>
<td>17 (59%)</td>
</tr>
<tr>
<td>≥50% PSA decline at 12 wk, n (%)</td>
<td>(95% CI)</td>
<td>16 (41%; 26–56%)</td>
<td>1 (13%)</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>≥30% PSA decline at any time, n (%)</td>
<td></td>
<td>24 (62%)</td>
<td>2 (25%)</td>
<td>22 (76%)</td>
</tr>
<tr>
<td>&gt;50% PSA decline at any time, n (%)</td>
<td></td>
<td>19 (49%)</td>
<td>1 (13%)</td>
<td>18 (62%)</td>
</tr>
<tr>
<td>TTPP, median (range), wk</td>
<td></td>
<td>16 (4–71)</td>
<td>6 (4–32)</td>
<td>16 (4–71)</td>
</tr>
<tr>
<td>Bone response at 12 wk (n = 33)</td>
<td>Stable disease, n (%)</td>
<td>31 (94%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft tissue response at 12 wk (n = 14)</td>
<td>Partial response, n (%)</td>
<td>4 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td></td>
<td>6 (43%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Kaplan–Meier curves representing: A, PFS (disease progression was defined per Prostate Cancer Working Group 2 criteria, and included death, radiographic progression, unequivocal clinical progression, and PSA progression); and B, rPFS (radiographic disease progression was defined as death, radiographic progression, or unequivocal clinical progression).
colleagues (13) demonstrated that >30% PSA decline satisfied the Prentice criteria (14) as a surrogate for overall survival (OS) in first-line chemotherapy studies of patients with mCRPC. It is important to note that the association between PSA decline and OS in these same studies is modest when reported using PTE, or proportion of treatment effect (15). Furthermore, surrogacy for PSA changes and OS has not been demonstrated for AR-targeted therapies. Despite these limitations, the study raises several points that merit further discussion and investigation.

First is whether the greater target inhibitory potency of abiraterone compared with ketoconazole is clinically meaningful. A phase III trial of antiandrogen withdrawal with or without ketoconazole showed significant suppression of serum androgens in patients treated with ketoconazole with subsequent increase in serum androgen levels at the time of disease progression (2), suggesting upregulation of androgen production (perhaps via enhanced CYP17A1 activity) as a mechanism for ketoconazole resistance; intratumoral CYP17A1 expression has been shown to be increased in patients previously treated with ketoconazole (16). The ultrasensitive assessment of circulating androgens in this study showed most patients with detectable levels of T, ASD, and DHEA at baseline (after ketoconazole and before abiraterone therapy) had undetectable levels after 8 weeks of abiraterone treatment (all 37 patients had undetectable DHEA levels; testosterone remained undetectable in 5 patients, and ASD remained detectable in 2 patients). Furthermore, patients with detectable DHEA levels were more likely to respond to abiraterone than those with undetectable levels. Combined, these findings support the conclusions that: (i) upregulated androgen production may be a mechanism of ketoconazole resistance; (ii) the greater CYP17A1 inhibitory potency of abiraterone is indeed clinically meaningful, and can provide clinical benefit in a subset of patients following disease progression.

Second is whether analysis of circulating androgens informs our understanding of therapeutic resistance (as well as response) to androgen synthesis inhibition. Unlike in patients treated with ketoconazole, androgen levels do not rise at the time of disease progression in those treated with abiraterone (8). CYP17A1 is present in both the endocrine (adrenal) and intracrine (tumor) domains. Whether ketoconazole and abiraterone exert their clinical efficacy in the endocrine versus intracrine domain (or both), and to what degree in each compartment is unknown.

![Graph of progression-free survival](image)

**Figure 3.** Kaplan–Meier curves representing: A, PFS, and B, rPFS for patients with DHEA < LOQ (in red) and DHEA ≥ LOQ (in blue).
Although CYP17A1 expression has been shown to be increased in patients previously treated with ketoconazole (16), whether this is a resistance mechanism that is induced because of suppressed circulating androgens due to adrenal ablation, or in response to intracrine suppression of CYP17A1 activity, is unknown. In addition, it is unknown whether upregulation of intratumoral CYP17A1 expression is the source of the increased androgen concentrations at the time of disease progression on ketoconazole, although adrenal ablation may be incomplete and endocrine androgen synthesis may contribute. How these issues relate to primary and secondary resistance to androgen synthesis inhibition merit further investigation.

The fact that abiraterone can suppress circulating androgens in patients with previous disease progression with ketoconazole demonstrates that abiraterone can suppress CYP17A1 activity upregulated by ketoconazole. However, as stated above, it remains unclear whether abiraterone exerts its activity via the endocrine versus intracrine compartments (or both). A recent retrospective analysis of serum androgen levels in patients treated with abiraterone after cytotoxic therapy demonstrated that baseline levels (also measured using LC/MS-MS) were prognostic for survival (17). Interestingly, patients with higher androgens had improved survival compared with those with low androgens regardless of treatment arm, and the PSA response proportion was higher in patients with higher androgen levels. This suggests that mCRPC progressing in a low circulating androgen environment has a more aggressive phenotype; it is possible that patients with mCRPC who experience disease progression in this setting harbor tumors that may be adapted to CYP17A1 inhibition.

Baseline DHEA levels were highly associated with response to abiraterone following ketoconazole. Only 1 of 8 patients with undetectable DHEA levels experienced a PSA response, whereas 17 of 29 patients with detectable DHEA levels treated with abiraterone had a PSA response. Conversely, patients with PSA responses had higher baseline DHEA levels. Patients with detectable DHEA levels had significantly longer PFS and rPFS. These data suggest that DHEA levels may have a potential role as a biomarker for response to CYP17A1 inhibition therapy. Although ultra-sensitive assays for androgens are now commercially available, their broad clinical utility as a biomarker requires further investigation and prospective validation before incurring additional costs. Currently, testosterone < 50 ng/dL is the only broadly accepted androgen parameter used to guide the treatment of advanced prostate cancer. Patients with higher "castrate" testosterone levels have been shown to survive longer compared than those with lower "castrate" testosterone levels (17), which questions the adequacy of this parameter. Combined with the results of this study, the utility of circulating androgen levels in the care of patients with prostate cancer merits further investigation.

The median duration of prior ketoconazole treatment in this study population was 43 weeks, with nearly half (46%) of enrolled patients having been treated with ketoconazole for more than 1 year. Although this could be the result of selection bias to which any small phase II study might be subject, the demographic data are representative of chemotherapy-naïve patients with mCRPC (7, 11). In this CYP17A1 inhibitor–pretreated patient population, the median rPFS on abiraterone was 36 weeks. Although this was significantly shorter than the median rPFS reported in the COU-AA-302 phase III study of abiraterone in chemotherapy-naïve patients with mCRPC (16.5 months; ref. 7), this result was expected given the prior exposure to CYP17A1 inhibition, and consistent with ≥50% PSA decline rates (41% in this study, 62% in the COU-AA-302 study). Indeed, the median duration of total CYP17A1 inhibition therapy (ketoconazole and abiraterone) in the men enrolled on this study was 91 weeks. This compares more favorably with the median rPFS of patients on the COU-AA-302 phase III study (7). Although acknowledging the pitfalls of such analysis, this further supports the hypothesis that sequential CYP17A1 inhibition is a feasible treatment strategy, and is particularly relevant given the broad concerns for rising costs of cancer therapy (18). Although abiraterone is clearly the “better” drug (10-fold greater potency, favorable toxicity profile, and improved survival demonstrated in two phase III clinical trials), these data may support the concept of considering total time on androgen synthesis inhibition therapy and may inform the subsequent study of the sequential use of these therapies.

In summary, abiraterone acetate demonstrates clinical efficacy and safety in patients with mCRPC previously treated with ketoconazole. Patients with detectable DHEA levels were more likely to demonstrate a PSA response to abiraterone and longer PFS. Analysis of circulating androgens merits further investigation as a biomarker for response to androgen synthesis inhibitor therapy in patients with mCRPC.

Disclosure of Potential Conflicts of Interest

A. Molina is an employee of and has ownership interest (including patents) in Johnson & Johnson. C.J. Ryan reports receiving speakers bureau honoraria from and is a consultant/advisory board member for Janssen. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: V. Weinberg, E.J. Small, C.J. Ryan

Development of methodology: T.W. Friedlander, C.J. Ryan

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W. Kim, J.H. Wilton, G. Fetterly, J.L. Mohler, A. Morse, R.Z. Szmulewitz, T.W. Friedlander, L. Fong, A.M. Lin, A.L. Harzstark, A. Molina, C.J. Ryan


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): W. Kim, A. Morse

Study supervision: W. Kim, C.J. Ryan

Grant Support

J.L. Mohler was supported by the Roswell Park Cancer Institute and National Cancer Institute (NCI) grants P30-CA16656 and P01-CA77739.

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 June 20, 2014; revised September 6, 2014; accepted September 29, 2014; published OnlineFirst October 21, 2014.

www.aacrjournals.org  Clin Cancer Res; 20(24) December 15, 2014 6275

Published OnlineFirst October 21, 2014; DOI: 10.1158/1078-0432.CCR-14-1595
References


Sequential Use of the Androgen Synthesis Inhibitors Ketoconazole and Abiraterone Acetate in Castration-Resistant Prostate Cancer and the Predictive Value of Circulating Androgens

Won Kim, Li Zhang, John H. Wilton, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-14-1595

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2014/10/22/1078-0432.CCR-14-1595.DC1

Cited articles
This article cites 17 articles, 8 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/20/24/6269.full.html#ref-list-1

Citing articles
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
/content/20/24/6269.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.