Prospective International Randomized Phase II Study of Low-Dose Abiraterone With Food Versus Standard Dose Abiraterone In Castration-Resistant Prostate Cancer

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Prospective International Randomized Phase II Study of Low-Dose Abiraterone With Food Versus Standard Dose Abiraterone In Castration-Resistant Prostate Cancer


ABSTRACT

Purpose

Abiraterone acetate (AA) is a standard of care for metastatic castration-resistant prostate cancer (CRPC). Despite a large food effect, AA was administered under fasting conditions in its pivotal trials. We sought to test the hypothesis that low-dose AA (LOW; 250 mg with a low-fat meal) would have comparable activity to standard AA (STD; 1,000 mg fasting) in patients with CRPC.

Patients and Methods

Patients (n = 72) with progressive CRPC from seven institutions in the United States and Singapore were randomly assigned to STD or LOW. Both arms received prednisone 5 mg twice daily. Prostate-specific antigen (PSA) was assessed monthly, and testosterone/dehydroepiandrosterone sulfate were assessed every 12 weeks with disease burden radiographic assessments. Plasma was collected for drug concentrations. Log change in PSA, as a pharmacodynamic biomarker for efficacy, was the primary end point, using a noninferiority design. Progression-free survival (PFS), PSA response ($\geq 50\%$ reduction), change in androgen levels, and pharmacokinetics were secondary end points.

Results

Thirty-six patients were accrued to both arms. At 12 weeks, there was a greater effect on PSA in the LOW arm (mean log change, $-1.59$) compared with STD ($-1.19$), and noninferiority of LOW was established according to predefined criteria. The PSA response rate was 58% in LOW and 50% in STD, and the median PFS was approximately 9 months in both groups. Androgen levels decreased similarly in both arms. Although there was no difference in PSA response or PFS, abiraterone concentrations were higher in STD.

Conclusion

Low-dose AA (with low-fat breakfast) is noninferior to standard dosing with respect to PSA metrics. Given the pharmacoeconomic implications, these data warrant consideration by prescribers, payers, and patients. Additional studies are indicated to assess the long-term efficacy of this approach.

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Part D alone,
and according to the manufacturer, over 100,000 prescriptions for AA have been written in the first 5 years of availability,
at a wholesale acquisition cost of approximately $8,000 to $11,000 per month.

Early clinical studies of AA demonstrated that when administered with food, drug exposure was significantly increased compared with fasting administration. According to the drug label, food leads to a five- to seven-fold increase in drug concentration with a low-fat meal and a 10- to 17-fold increase with a high-fat meal. Nevertheless, the registration studies of AA were conducted in the fasting state, resulting in the current approved dosage of 1,000 mg daily.

Given the potential pharmacoeconomic implication of lowering the dose of AA for the treatment of CRPC, we hypothesized that a lower dose taken with food would have an effect on CRPC similar to the approved dose taken fasting. We used serum prostate-specific antigen (PSA), a well-established disease biomarker, to measure anticancer activity. We also examined changes in extragonadal androgen production and AA plasma concentrations.

**PATIENTS AND METHODS**

**Patient Selection**

Eligible patients had a diagnosis of CRPC, defined as disease progression despite a testosterone level < 50 ng/dL (or surgical castration). Progressive disease was defined radiographically as either two or more new lesions on bone scan or soft tissue progression on computed tomography/magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors 1.1 or serologic progression with increasing PSA per standard guidelines. Prior use of AA, enzalutamide, or other similar potent androgen pathway–targeted therapies was excluded. Prior use of chemotherapy and/or high-dose ketoconazole was allowed. Although high-dose ketoconazole has a similar mechanism of action to abiraterone, it does not preclude response to abiraterone and thus was allowed.

Other hormonal therapies, any herbal product known to decrease PSA levels, and any systemic corticosteroid (other than prednisone < 10 mg daily) were not allowed. Eligibility also included an Eastern Cooperative Oncology Group performance status ≤ 2, acceptable renal and hepatic function, and adequate baseline blood pressure and electrolytes.

**Study Design and End Points**

This was a multinational randomized open-label study conducted at six sites in two countries, the United States and Singapore. Enrolled participants were randomly assigned in a one-to-one ratio to receive AA 1,000 mg was taken fasting. We used serum prostate-specific antigen (PSA), a well-established disease biomarker, to measure anticancer activity. We also examined changes in extragonadal androgen production and AA plasma concentrations.

Clinical Practice guidelines of the International Conference on Harmonization. All patients signed a written informed consent before the conduct of any study procedures and after a full explanation of the study to the patient by the study investigator.

The primary objective of the study was to compare the antitumor activity of LOW AA with the STD AA dose, as assessed by change in serum PSA. Although not a clinically validated surrogate end point, PSA is an androgen receptor–regulated gene, and changes in PSA have been correlated with overall survival on abiraterone. Secondary objectives were to compare AA pharmacokinetics between the arms, PSA response rate (≥ 50% reduction in PSA after 12 weeks of therapy), and PFS; to compare the safety profile of LOW with STD; and to evaluate the pharmacodynamic effect of LOW as assessed by reduction in the androgens testosterone and DHEA-S.

**Study Procedures**

Visits occurred weekly for the first 2 weeks, at week 4, and then monthly. PSA, standard chemistries, and blood counts were assessed monthly by local laboratories and reported centrally. The clinical-grade laboratory accreditation served to ensure assay constancy and sensitivity of PSA measurements. Disease burden assessed with standard nuclear medicine bone scan and abdomen/pelvis cross-sectional imaging was conducted every 12 weeks in accordance with the standard working group guidelines.

Plasma was collected for drug pharmacokinetic (abiraterone and metabolite) analysis after 8 days of therapy (before and 2, 3, and 4 hours after dosing) and monthly for the first 4 months (2 hours after dosing). The 2-hour time point was selected for collection because it is the time of maximum concentration after dosing for AA in prior studies. These analyses were conducted within the National Cancer Institute Pharmacology Laboratory using liquid chromatography–mass spectrometry with electrospray ionization, as detailed in the Data Supplement.

**Statistical Analysis**

Randomization was stratified by prior ketoconazole use and was accomplished using the method of permuted blocks and the random number generator in Stata software (Stata, College Station, TX). Block sizes were varied and known only to the study statistician. The primary end point of the study was change in PSA from baseline to 12 weeks. The benchmark data for our power calculations were adapted from the phase II trial by Danila et al and the much larger, randomized phase III trial in the postdocetaxel CRPC setting conducted by de Bono et al, which used the standard, high-dose fasting regimen. Pooling these data (weighted by sample size) yielded a historical PSA response rate (reduction in PSA by ≥ 50% of 30%). This study used a noninferiority trial design, with analysis of PSA change as a continuous variable (transformed to the log scale). Additional details are provided in the Data Supplement. A total sample size of 72 patients (36 per treatment arm) provided 80% power for the noninferiority test, using a one-sided alpha level of .10.

The Kaplan–Meier approach was used to estimate PFS rates, and the stratified log-rank test was performed to compare PFS between the two treatment arms, adjusting on the stratification factor. PSA and radiographic progression were defined according to Working Group criteria.

Patient progression for the PFS end point was defined as either PSA or radiographic progression, whichever occurred first. For patients without disease progression at the time of analysis, PFS was censored at the time of the patient’s last available tumor assessment.

The drug and hormone concentrations were analyzed at the time points outlined previously. Group comparisons were performed using two-sample t tests or nonparametric, Wilcoxon rank sum tests. Correlation between trough concentration and PSA change was summarized by the Spearman correlation coefficient, and intrapatient and interpatient pharmacokinetic variability was assessed by analysis of variance.
Randomized Study of Low-Dose Abiraterone in CRPC

RESULTS

Patients and Treatments

Between January 2012 and March 2016, 72 patients with CRPC were enrolled and underwent randomization, with 36 patients randomly assigned to each treatment arm. Four patients withdrew consent before initiating therapy (two in each arm) and were not followed. Thus, 34 patients per arm were treated per protocol (Fig 1). Patient characteristics were well balanced between the two groups, representing a typical CRPC population, with the majority of patients in this study receiving AA in the predocetaxel setting (Table 1). The only apparent difference between arms was that the LOW arm had a higher percentage of patients who self-identified as African American (31% vs 14% in the STD group).

Efficacy

Subsequent to treatment with AA, the magnitude of reduction in PSA from baseline to 12 weeks was actually greater in the low-dose group, that is, the mean log change was −1.59 in LOW versus −1.19 in STD (with a pooled standard deviation of 1.62). The upper one-sided 90% confidence limit for the difference between the two arms (LOW − STD) was 0.11 (standard deviation, 0.068). Thus, according to the predefined criteria (Appendix, online only), noninferiority of LOW was established. It should be noted that the translation of PSA response rates to differences on a continuous log scale is highly dependent on the assumption of normality of the distribution of log PSA changes. Normal probability plots (Appendix Figs A1B and A1C, online only) indicate that the normality assumption is reasonably well satisfied here.

PSA changes while receiving treatment were consistent with prior studies. At 12 weeks, there were only three of 34 evaluable patients (9%) with primary PSA progression (post-treatment PSA increase as best response) within the STD group. Similarly, in the LOW group, one patient (3%) had primary PSA progression. The majority of patients experienced a decrease in PSA at 12 weeks in both arms (Fig 2A). Not only were the PSA changes similar on a continuous log scale, there was a similar absolute PSA response rate (as a dichotomous variable) at 12 weeks in both arms: 50% in the STD arm and 58% in the LOW arm. The lower one-sided 90% confidence limit for the difference between the two arms in PSA response rates (LOW − STD) was −7%. Therefore, we can assert with 90% confidence that the LOW arm is at most 7% worse than STD. PSA change from baseline to nadir for both groups was also assessed (Fig 2B). The nadir PSA response rate was 61% in the STD group and 69% in the LOW group (lower, one-sided 90% confidence limit of −6%). For reference, the PSA response rate was 62% in the landmark prechemotherapy phase III abiraterone study. Notably, not only was PSA response similar between arms, but duration of response was also comparable, with a median PFS of 8.6 months in both arms (P = .38; Fig 3). Because only four patients per arm received prior ketoconazole, no additional analysis was undertaken for the efficacy end points on the basis of the stratification factor.

Pharmacokinetics

Average abiraterone trough concentrations were significantly higher in the STD arm compared with the LOW arm (t test log trough concentration P < .001; Fig 4A). Interestingly, despite

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>STD (n = 36)</th>
<th>LOW (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Median (range) 74 (54-82)</td>
<td>72 (66-88)</td>
</tr>
<tr>
<td></td>
<td>&gt; age 75, No. (%) 16 (44)</td>
<td>15 (42)</td>
</tr>
<tr>
<td>ECOG performance status, No. (%)</td>
<td>0 or 1 34 (94)</td>
<td>33 (92)</td>
</tr>
<tr>
<td></td>
<td>2 2 (6)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td>White 26 (72)</td>
<td>17 (47)</td>
</tr>
<tr>
<td></td>
<td>African American 5 (14)</td>
<td>11 (31)</td>
</tr>
<tr>
<td></td>
<td>Asian 5 (14)</td>
<td>7 (19)</td>
</tr>
<tr>
<td></td>
<td>NA 1 (3)</td>
<td>I (3)</td>
</tr>
<tr>
<td>Prior systemic treatment of CRPC, No. (%)</td>
<td>0 8 (22)</td>
<td>9 (25)</td>
</tr>
<tr>
<td></td>
<td>1-2 23 (64)</td>
<td>22 (61)</td>
</tr>
<tr>
<td></td>
<td>≥ 3 5 (14)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Prior ketoconazole, No. (%)</td>
<td>4 (51)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Prior chemotherapy, No. (%)</td>
<td>0 29 (81)</td>
<td>30 (83)</td>
</tr>
<tr>
<td></td>
<td>1 7 (19)</td>
<td>3 (8)</td>
</tr>
<tr>
<td></td>
<td>≥ 2 0 (0)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Disease location, No. (%)</td>
<td>Bone 25 (69)</td>
<td>25 (69)</td>
</tr>
<tr>
<td></td>
<td>Visceral 5 (14)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Prostate-specific antigen (ng/mL), median (range)</td>
<td>48.4 (0.73-1789)</td>
<td>48.4 (1.01-1768)</td>
</tr>
<tr>
<td>Androgen levels, mean (standard deviation)</td>
<td>Testosterone (ng/dL) 14.0 (9.5)</td>
<td>11.4 (7.2)</td>
</tr>
<tr>
<td></td>
<td>DHEA-S (µg/dL) 51.3 (48.1)</td>
<td>71.0 (67.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CRPC, castration-resistant prostate cancer; DHEA-S, dehydroepiandrosterone-sulfate; ECOG, Eastern Cooperative Oncology Group; LOW, 250 mg abiraterone acetate with a low-fat meal; NA, not available; STD, standard dose of 1,000 mg abiraterone acetate fasting.
previous literature suggesting similar maximum concentration (C\text{max}) between 250 mg with food compared with 1,000 mg fasting (approximately 500 nM),\textsuperscript{11} we found that the C\text{max} was also higher in the STD arm compared with the LOW arm (t test log C\text{max} P = .012; Data Supplement). However, interindividual variability was higher in the STD arm (coefficient of variation, 151% v 106%; P, .001). Similar results were observed when the 2-hour sample was analyzed (AppendixFig 2B).

An association between plasma trough concentration and PSA response to AA has been previously reported.\textsuperscript{22} However, within our data set, there was no evidence of a clinically significant correlation between the trough concentration and change in PSA (Spearman correlation coefficient, −0.12; P = .37; Fig 4B). There was also no statistically significant association between PSA response (50% reduction in PSA) regardless of arm and trough concentration (t test P = .11; Appendix Fig 2C, online only). In sum, although there were higher drug concentrations in the STD arm compared with the LOW arm, there was higher pharmaco-kinetic variability and no clear association within this study between drug concentration and efficacy.

**Endocrine Pharmacodynamic Effects**

A hallmark of AA on-target efficacy is change in androgen levels. We therefore sought to assess the association of dose with this important endocrine biomarker. Baseline circulating testosterone levels were in the castrate range in both treatment groups (Table 1). Subsequent to AA administration, overall testosterone levels fell in both arms to a similar extent, although the magnitude of this decrease was not able to be determined with accuracy because of the sensitivity of the commercial assay. DHEA-S is the most abundant extragonadal serum androgen in this patient population; its levels predictably fall after abiraterone administration\textsuperscript{17,23} with this background and because its standard of care measurement uses a highly sensitive assay with a dynamic range at low levels, DHEA-S was measured serially in this study. Like testosterone, baseline levels of DHEA-S are prognostic in an abiraterone-treated population.\textsuperscript{23} Baseline DHEA-S levels were similar in both arms (Table 1) and declined robustly with AA in the LOW arm, to 10.2 (5.9) µg/dL at cycle 4 and to 8.9 (6.1) µg/dL at the end of the study time point. This decrease in DHEA-S mirrored the levels seen with STD, which were 13.3 (6.4) µg/dL and 9.1 (6.2) µg/dL at cycle 4 and at the end of the study, respectively (Fig 5). Therefore, despite higher drug concentrations in the STD arm, the LOW arm showed equivalent activity with respect to endocrine effects, in addition to the associated change in PSA metrics.

**Safety**

Overall, the adverse events were consistent with prior studies of AA, with all adverse events, regardless of attribution, observed in at least 15% of patients in either arm listed in Table 2. Adverse events of special interest, as defined in the phase III studies\textsuperscript{2,3} were similar in both arms (Table 2). Although there were numerically more patients with grade 3 or higher events in the LOW arm, this was not statistically significant (32.4% v 17.6%; P = .26). There were two lethal adverse events, both in the STD arm (sepsis and small intestinal obstruction); neither was attributed to AA.

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**Fig 2.** Decrease in prostate-specific antigen (PSA) while receiving treatment. Waterfall plot showing percent reduction in PSA at (A) landmark 12-week time point and (B) maximum nadir. Patients whose best PSA response was progression are denoted with (*). LOW, 250 mg abiraterone acetate with a low-fat meal; STD, 1,000 mg abiraterone acetate fasting

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**Fig 3.** Prostate-specific antigen (PSA) progression. Kaplan-Meier plot of time to progression while receiving 250 mg abiraterone acetate with a low-fat meal (LOW) or standard dose of 1,000 mg abiraterone acetate fasting (STD), showing a median progression-free survival of 8.6 months in both arms (log-rank P = .38).
This prospective randomized study comparing low-dose AA with food with standard dose fasting suggests noninferiority of a 75% dose reduction of AA, if given in the prandial state. Importantly, both PSA response and time to progression in both arms within this study were comparable to previous studies.3,11,24 In further support of the central hypothesis, serum androgen levels decreased to a similar extent within both arms in the study. Although the sensitivity of the testosterone assay used was not sufficient to measure testosterone changes at the lowest measured levels, DHEA-S, which has been used in measuring abiraterone efficacy,17,23 was able to be measured with high sensitivity (because of the relative abundance of this androgen in circulation) and fell to the same extent in both arms of the study. Thus, the two pharmacodynamic end points examined, changes in PSA and androgen levels, point to similarity between LOW and STD dosing of AA for patients with CRPC.

Notably, despite prior studies and the FDA label citing a large food effect on bioavailability, the pharmacokinetic analyses within this larger randomized study suggest that the food effect on AA absorption and bioavailability may not be as robust as previously reported. Within all pharmacokinetic time points analyzed, STD dosing resulted in higher drug levels. This is somewhat consistent with a recently reported study that found that the Cmax increased only 150% to 200% with food, even with a high-fat meal.25 Furthermore, the less robust food effect observed in this study may have been due to a more fat-restrictive low-fat diet compared with standard low- and high-fat diets used in FDA-directed food-effect studies. It has been argued that patients with cancer cannot be routinely relied on to follow dietary instructions with respect to oral medications, which could lead to high exposure variability in the fed state despite a constant dose.26 In contrast, our study demonstrated a statistically higher variability in pharmacokinetics within the standard fasting arm. This improved pharmacokinetic variability with food is consistent across orally bioavailable oncology medications when taken in the prandial state that maximizes bioavailability.27 Although there were no discrepancies in patient drug diaries, the composition and timing of food intake after AA may have contributed to the high observed variability.28 Importantly, our study found no significant correlation between steady-state (trough) abiraterone concentration and PSA response, although the three patients with the highest drug concentrations experienced robust PSA responses. These three patients with abiraterone levels approximately triple the median heavily contributed to the higher variability in the STD arm and the higher abiraterone concentration in general within this arm compared with the LOW arm. Given the equivalence between the arms on PSA response and adrenal androgen synthesis, our study suggests that LOW dosing achieves pharmacologically sufficient AA exposure and raises the possibility that a lower dose of AA, even in the fasted state, may be sufficient. Within oncology, there continues to be a focus on equating the optimal dose with the maximally

![Graph A](fig4a.png)  
**Fig 4.** Abiraterone drug levels. (A) The abiraterone trough drug concentration (Cmin) was higher in the standard dose of 1,000 mg abiraterone acetate fasting (STD) arm compared with the 250 mg abiraterone acetate with a low-fat meal (LOW) arm (P < .001). (B) There was no correlation between abiraterone Cmin and change in prostate-specific antigen (PSA; P = .37).

![Graph B](fig4b.png)  
**Fig 5.** Effect of dehydroepiandrosterone-sulfate (DHEA-S) levels on treatment. DHEA-S levels decreased substantially and to a similar extent regardless of treatment arm. C4, cycle 4; LOW, 250 mg abiraterone acetate with a low-fat meal; STD, standard dose of 1,000 mg abiraterone acetate fasting.
Anorexia 3 (8.8) 0 (0) 2 (5.9) 0 (0)
AST increased 4 (11.8) 0 (0) 2 (5.9) 0 (0)
Anemia 7 (20.6) 0 (0) 5 (14.7) 0 (0)
Diarrhea 6 (17.6) 0 (0) 4 (11.8) 1 (2.9)

**Table 2. Adverse Events Summary: Adverse Events of Grade 1 to 4 in ≥15% of Patients in Either Cohort**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>STD (n = 34)</th>
<th>LOW (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>16 (47.1)</td>
<td>16 (47.1)</td>
</tr>
<tr>
<td>Pain</td>
<td>9 (26.5)</td>
<td>15 (44.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (30)</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (20.6)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5 (14.7)</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>6 (17.6)</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>6 (17.6)</td>
<td>2 (5.9)</td>
</tr>
</tbody>
</table>

Thus, although not powered for a practice-changing clinically

 tolerated dose, a paradigm not well justified in an era of targeted therapy.29

 Although designed to demonstrate noninferiority, this study lacks the power to rule out a smaller difference between the two dosing arms than a predefined noninferiority margin of 15%. Our data yield a lower 90% confidence limit for the absolute difference in PSA response rates (LOW − STD) of −7%; therefore a smaller 10% noninferiority margin would also have been supported. However, with a more conservative one-sided 95% confidence limit, the lower bound between the difference in PSA response rates in our study is −11%.

 In addition, because the study did not mandate that patients stay in the study past PSA progression, nor did it collect radio-graphic progression past PSA progression, we were unable to capture fully validated CRPC end points of radiographic PFS and overall survival.30 However, prior larger studies in metastatic prostate cancer have shown a between PSA progression, according to standard criteria, and overall survival.31 Thus, although not powered for a practice-changing clinically

 validated end point, the equivalence in PSA PFS between the two arms is provocative, and additional studies should be undertaken.

 There are several other dosing strategies that could be studied on the basis of the results of this study. Given the prolonged effect on androgen synthesis after a single dose of AA,32 500 mg every other day with food or even every fourth day could be tested. Because lower drug concentrations than we predicted were seen with LOW, 250-mg dosing (or 500 mg intermittently) could also be explored using a high-fat meal.

 The pharmacoeconomic implications of this study’s findings are compelling. AA has an approximate retail cost of $10,000 per month. With a median time receiving treatment of 16.5 months in metastatic CRPC,3 the per-patient cost savings with the LOW dosing would exceed $100,000. Furthermore, AA was recently shown to improve survival in the metastatic castration-sensitive prostate cancer setting, with median PFS estimates of 33 to 44 months, potentially resulting in per-patient cost savings of more than $300,000.4,5 Given the prevalent paradigm of developing drugs with large food effects under fasting conditions, there are multiple other opportunities to lower drug costs by administration with food.28,33

Disclosures provided by the authors are available with this article at jco.org.

**AUTHOR CONTRIBUTIONS**

Conception and design: Russell Z. Szmulewitz, Theodore Karrison, Walter M. Stadler, Mark J. Ratain

Financial support: Walter M. Stadler, Mark J. Ratain

Administrative support: Russell Z. Szmulewitz, Walter M. Stadler

Provision of study materials or patients: Russell Z. Szmulewitz, Elia Martinez, Mark F. Kozloff, Bradley Carthon, R. Donald Harvey, Paul Fishkin, Wei Peng Yong, Edmund Chiong, Chadi Nabhan, Walter M. Stadler

Collection and assembly of data: All authors


Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Leadership: Cardinal Health
Stock or Other Ownership: Cardinal Health

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Research Funding: OncoTherapy Science (Inst), Dicerna (Inst)
Patents, Royalties, Other Intellectual Property: Royalties related to UGT1A1 genotyping for irinotecan, royalties related to UGT1A1 genotyping for irinotecan (Inst), pending patent related to a genomic prescribing system, pending patent related to a genomic prescribing system (Inst)
Expert Testimony: Multiple generic companies

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Appendix

Pharmacokinetic Analysis

Plasma samples were collected at participating institutions at the time points described, with careful annotation of collection time in relation to abiraterone acetate (AA) dose. All pharmacokinetic samples were stored as frozen samples, and batched analyses were conducted within the Pharmacology Laboratory at the National Cancer Institute within the National Institutes of Health by solid phase extraction. Plasma concentrations of abiraterone (Abi) and its pharmacologically active metabolite, delta-4-abi, were quantitatively measured using a sensitive ultrahigh performance liquid chromatography–tandem mass spectrometry assay with a calibration range of 1 to 1,000 nM. Briefly, abi and delta-4-abir were extracted from 100 μL of human heparinized plasma, with 1 mL of ethyl acetate containing 2[H]4-abiraterone (deuterated abiraterone). Extracts were evaporated and reconstituted before injection onto an ultrahigh performance liquid chromatography–tandem mass spectrometry, where the compounds were separated chromatographically using a gradient elution of 10 mM ammonium acetate and acetonitrile on a Waters ACQUITY(R) BEH C18 column (2.1 × 50 mm, 1.7 um). The compounds were selectively identified based on their unique product ion after multiple reaction monitoring analysis of mass to charge (m/z; abi: m/z 350.0 → 156.2; delta-4-abi: m/z 348.0 → 156.2; 2[H]4-Abi: m/z 354.5 → 160.4). All samples were run alongside freshly prepared calibration standards (in duplicate) and quality control standards (in quintuplet) daily, per Food and Drug Administration guidelines.

Statistical Analyses

The study used a noninferiority trial design with a noninferiority margin of 15% for the difference in prostate-specific antigen (PSA) response rates. This margin was chosen to provide preliminary evidence to support additional larger studies. Specifically, letting \( p_L \) denote the true PSA response rate (50% or greater reduction in PSA from baseline to 12 weeks) for the low-dose fed regimen (LOW) and \( p_S \) the true PSA response rate for the standard high-dose fasting treatment (STD), we tested \( H_0: p_L \geq p_S + 0.15 \) versus \( H_A: p_L < p_S \). \( H_0 \) can be rejected at the one-sided, .10 alpha level if the lower 90% confidence bound for \( p_L - p_S \) is greater than \(-0.15\), which would mean that with high confidence, one could assert that the response rate for the lower dose is no more than 15 percentage points less than the rate for the standard dose.

To determine the required sample size, as described in the main text, we assumed a 30% response rate for the high-dose group on the basis of historical data. This would mean that the response rate under a low-dose regimen would need to be at least 15% to fall within our noninferiority margin. However, rather than analyzing PSA response rate, which is a dichotomous outcome variable, we analyzed PSA on a continuous scale to improve efficiency. Assuming the log ratio of the 12-week to baseline PSA levels, that is, \( \ln(\text{PSA}_{12}/\text{PSA}_0) \) is approximately normally distributed, we interpret a response rate of 30% to mean that the 30th percentile of the distribution of \( \ln(\text{PSA}_{12}/\text{PSA}_0) \) equals \( \log(0.5) \), because 0.5 (50% reduction) is the response cutoff value (Data Supplement, Figure A1). This relationship implies that the mean of the log ratio is \( \ln(0.5) - Z_{0.30} \times \text{SD} \), where \( Z_{0.30} \) equals \(-0.524\), the 30th percentile of the standard normal distribution, and \( \text{SD} \) is the standard deviation of the distribution of \( \ln(\text{PSA}_{12}/\text{PSA}_0) \). For the LOW group, the curve will be shifted to the right (smaller reductions in PSA), such that only 15% of the area is to the left of \( \ln(0.5) \), with mean \( \ln(0.5) - Z_{0.15} \times \text{SD} \), where \( Z_{0.15} \) equals \(-1.036\). A 15% (LOW) versus 30% (STD) difference in response rates therefore corresponds to a \( 1.036 - 0.524 = 0.512 \) SD difference in means. Letting \( \mu_L \) and \( \mu_S \) denote the respective true mean log changes in the LOW and STD groups, we tested \( H_0: \mu_L \geq \mu_S \) versus \( H_A: \mu_L < \mu_S \). \( H_0 \) can be rejected at the one-sided, .10 alpha level if the lower 90% confidence bound for \( \mu_L - \mu_S \) is greater than \(-1.51\), which would mean that with high confidence, one could assert that the mean log change for the lower dose is no more than 15 percentage points less than the rate for the standard dose.
Fig A1. Distribution of log PSA changes. A. Statistical assumption of normal distribution curves for STD (left) and LOW (Arm). B. Normal probability plot for STD arm. C. Normal probability plot for LOW arm.
Fig A2. Abiraterone drug concentrations. Abiraterone C\textsubscript{max} (A) and 2 hour post treatment drug levels (B) were higher in STD compared to LOW arms. (C) There was no significant difference in likelihood of PSA response based on AA trough concentration (p=0.11) irrespective of treatment arm (LOW, triangle; STD, circle).