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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

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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 (≥ 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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INTRODUCTION

Abiraterone acetate (AA) is a potent selective and irreversible inhibitor of CYP17, the primary enzyme complex responsible for the production of extragonadal (adrenal, intratumoral) androgens, including hormones dehydroepiandrosterone-sulfate (DHEA-S), androstenedione, and others.[1] AA was approved by the Food and Drug Administration (FDA) in 2012 for metastatic castration-resistant prostate cancer (CRPC) on the basis of the results of a phase III randomized trial of AA

(1,000 mg) plus prednisone (5 mg twice daily) versus placebo plus prednisone in chemotherapy-pretreated patients with CRPC, in which AA improved overall survival and progression-free survival (PFS) and mitigated the deterioration of quality of life in patients with metastatic CRPC.[2,3] More recently, AA has been demonstrated to improve survival when administered in conjunction with standard initial androgen deprivation therapy for metastatic castration-sensitive prostate cancer.[4,5] AA is currently the most widely prescribed first-line medication for CRPC.[6] In 1 year, there were over 70,000 claims through Medicare

Part D alone,[7] and according to the manufacturer, over 100,000 prescriptions for AA have been written in the first 5 years of availability,[8] at a wholesale acquisition cost of approximately $8,000 to $11,000 per month.[9,10]

Early clinical studies of AA demonstrated that when administered with food, drug exposure was significantly increased compared with fasting administration.[11,12] 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.[13,14] 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[15] or serologic progression with increasing PSA per standard guidelines.[16] 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.[17] 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 fasting (STD) or 250 mg with a low-fat meal (LOW). The only stratification factor was prior history of high-dose ketoconazole treatment of CRPC. Treatment was administered on an outpatient basis continuously. The commercially available drug was procured by patients through their pharmacy. For patients in the STD arm, AA 1,000 mg was taken first thing in the morning after an overnight fast of at least 8 hours and at least 2 hours before any food intake, per the prescribing information. For the LOW arm, AA 250 mg per day was taken either concomitantly or within 30 minutes of a conventional low-fat breakfast. The nature of the breakfast was at the discretion of the patient; however, patients were told to avoid consumption of high-fat items (eg, sausage, bacon, deep-fried foods, etc) with AA. Food diaries completed by study participants were reviewed by study personnel for adherence. All patients received prednisone at a dose of 5 mg orally twice daily and kept both food and drug dosing diaries, which were reviewed by research staff for compliance.

The review boards at all participating institutions approved the study, which was conducted according to the Declaration of Helsinki and Good 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.[18] 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.[16] Serum testosterone (high throughput liquid chromatography) and DHEA-S (chemi-immunoassay) were also assessed locally within a clinical-grade laboratory every 12 weeks.

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.[14] 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[19] and the much larger, randomized phase III trial in the postdocetaxel CRPC setting conducted by de Bono et al,[2] 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[20] (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[21] 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.[16] 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.

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% *v* 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 the continuous log PSA 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.[2,3] 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.[3] 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
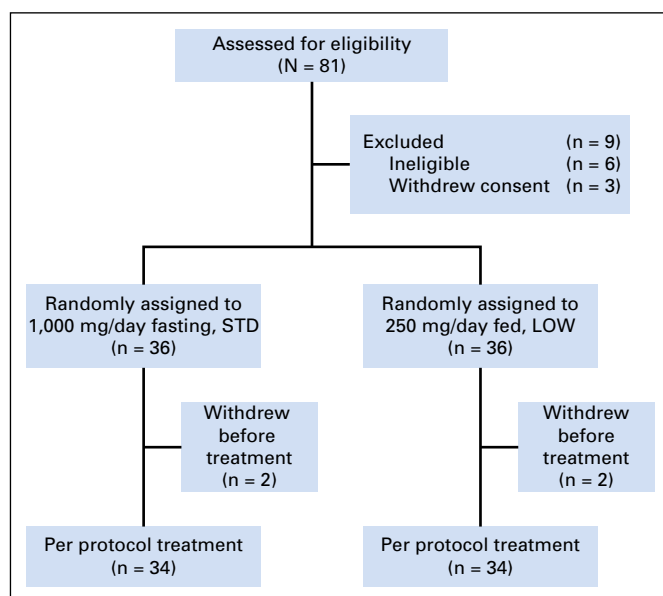

Fig 1. CONSORT diagram. LOW, 250 mg abiraterone acetate with a low-fat meal; STD, standard dose of 1,000 mg abiraterone acetate fasting.

Table 1. Baseline Patient Characteristics		
Characteristic	STD (n = 36)	LOW (n = 36)
Age, years		
Median (range)	74 (54-82)	72 (56-88)
> age 75, No. (%)	16 (44)	15 (42)
ECOG performance status, No. (%)		
0 or 1	34 (94)	33 (92)
2	2 (6)	3 (8)
Race, No. (%)		
White	26 (72)	17 (47)
African American	5 (14)	11 (31)
Asian	5 (14)	7 (19)
NA		1 (3)
Prior systemic treatment of CRPC, No. (%)		
0	8 (22)	9 (25)
1-2	23 (64)	22 (61)
≥ 3	5 (14)	5 (14)
Prior ketoconazole, No. (%)	4 (11)	4 (11)
Prior chemotherapy, No. (%)		
0	29 (81)	30 (83)
1	7 (19)	3 (8)
≥ 2	0 (0)	3 (8)
Disease location, No. (%)		
Bone	25 (69)	25 (69)
Visceral	5 (14)	5 (14)
Prostate-specific antigen (ng/mL), median (range)	48.4 (0.73-1789)	48.4 (1.01-1768)
Androgen levels, mean (standard deviation)		
Testosterone (ng/dL)	14.0 (9.5)	11.4 (7.2)
DHEA-S (μg/dL)	51.9 (48.1)	71.0 (57.8)

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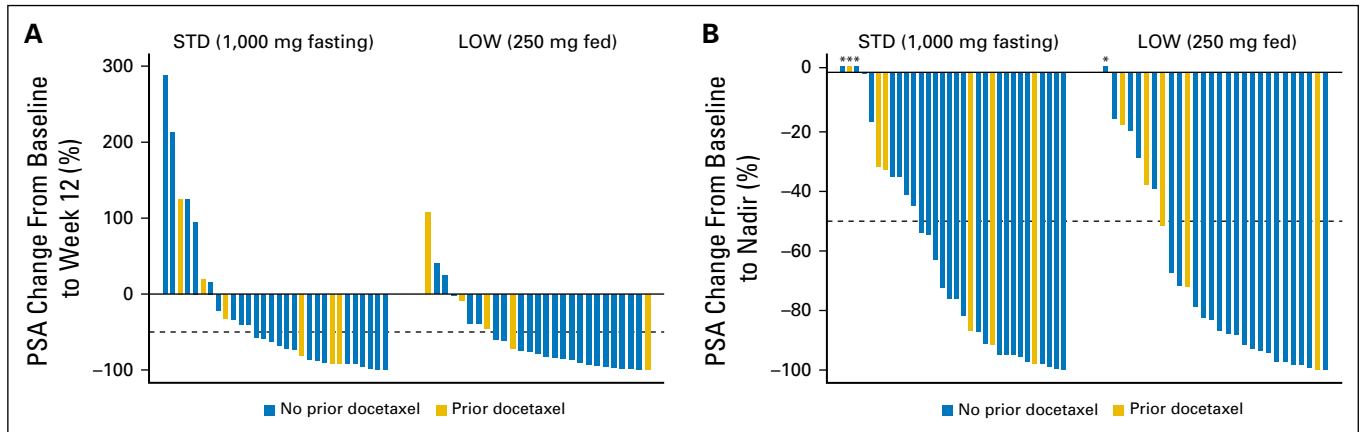
Fig 2. Decrease in prostate-specific antigen (PSA) while receiving treatment. Waterfall plot showing percent reduction in PSA at (A) landmark 12-week time point and (B) maximum nadir. Patients whose best PSA response was progression are denoted with (*). LOW, 250 mg abiraterone acetate with a low-fat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

previous literature suggesting similar maximum concentration (C_{max}) between 250 mg with food compared with 1,000 mg fasting (approximately 500 nM),[11] we found that the C_{max} was also higher in the STD arm compared with the LOW arm (t test log C_{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 (Appendix Fig 2B).

An association between plasma trough concentration and PSA response to AA has been previously reported.[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 pharmacokinetic 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 and mirror the decline of the other androgens testosterone and androstenedione.[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.[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[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.
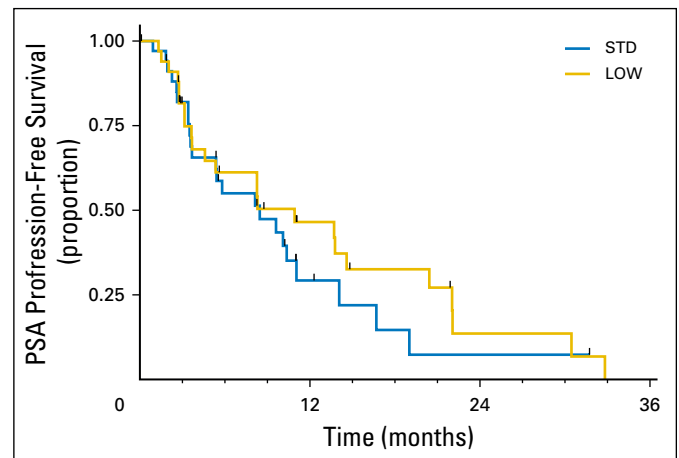
Fig 3. Prostate-specific antigen (PSA) progression. Kaplan-Meier plot of time to progression while receiving 250 mg abiraterone acetate with a low-fat meal (LOW) or standard dose of 1,000 mg abiraterone acetate fasting (STD), showing a median progression-free survival of 8.6 months in both arms (log-rank $P = .38$).
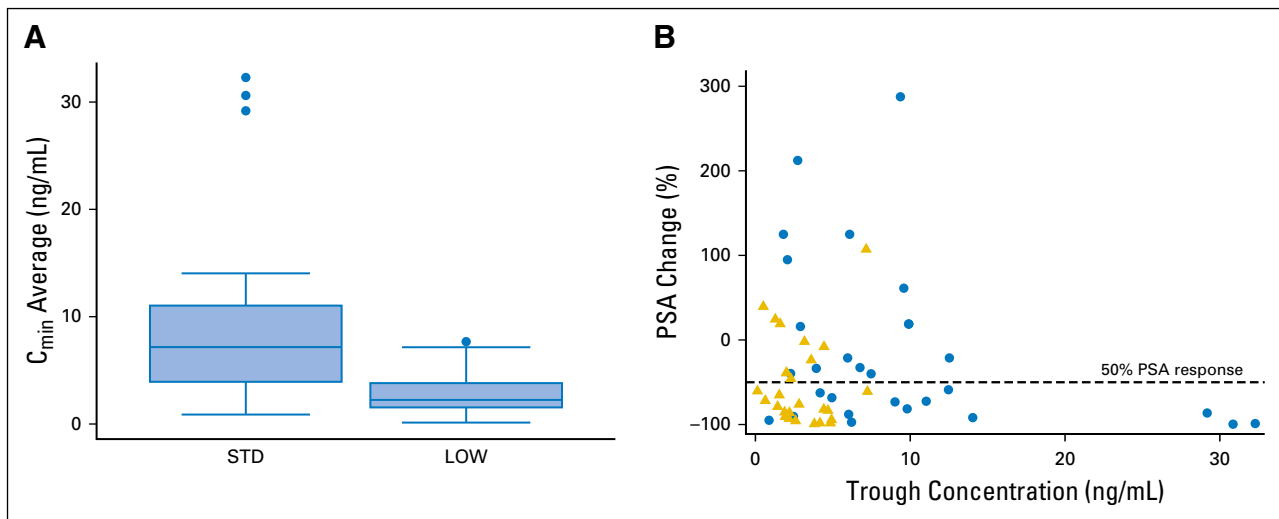
Fig 4. Abiraterone drug levels. (A) The abiraterone trough drug concentration (C_{min}) was higher in the standard dose of 1,000 mg abiraterone acetate fasting (STD) arm compared with the 250 mg abiraterone acetate with a low-fat meal (LOW) arm ($P < .001$). (B) There was no correlation between abiraterone C_{min} and change in prostate-specific antigen (PSA; $P = .37$).

DISCUSSION

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 C_{max} 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
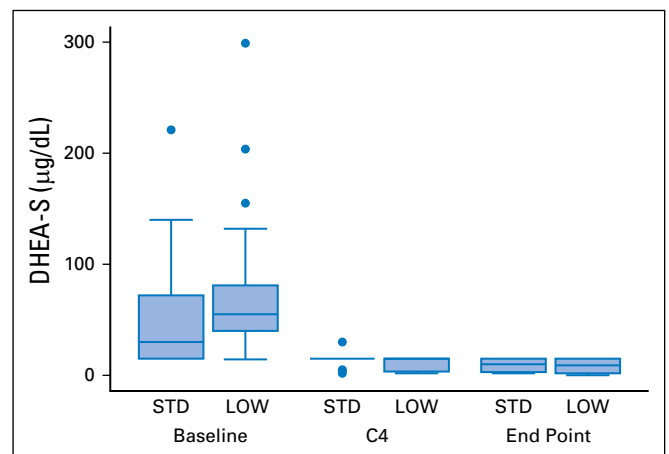
Fig 5. Effect of dehydroepiandrosterone-sulfate (DHEA-S) levels on treatment. DHEA-S levels decreased substantially and to a similar extent regardless of treatment arm. C4, cycle 4; LOW, 250 mg abiraterone acetate with a low-fat meal; STD, standard dose of 1,000 mg abiraterone acetate fasting.

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

Adverse Event	STD No., % (n = 34)		LOW No., % (n = 34)	
Fatigue	16 (47.1)		16 (47.1)	
Pain	9 (26.5)		15 (44.1)	
Hypertension	10 (34)		8 (23.5)	
Anemia	7 (20.6)		3 (8.8)	
Hypokalemia	5 (14.7)		7 (20.6)	
Hypocalcemia	6 (17.6)		5 (14.7)	
Hot flashes	6 (17.6)		2 (5.9)	
Adverse Event of Special Interest	Grade 1-4	Grade 3 or 4	Grade 1-4	Grade 3 or 4
Fluid retention or edema	5 (14.7)	0 (0)	4 (11.8)	0 (0)
Hypokalemia	5 (14.7)	1 (2.9)	7 (20.6)	0 (0)
Hypertension	10 (34)	0 (0)	8 (23.5)	2 (5.9)
ALT increased	4 (11.8)	0 (0)	2 (5.9)	0 (0)
AST increased	4 (11.8)	0 (0)	3 (8.8)	0 (0)
Anorexia	3 (8.8)	0 (0)	5 (14.7)	0 (0)
Diarrhea	5 (14.7)	0 (0)	4 (8.8)	1 (2.9)

Abbreviations: LOW, 250 mg abiraterone acetate with a low-fat meal; STD, standard dose of 1,000 mg abiraterone acetate fasting.

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 radiographic 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 an association 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]

REFERENCES

1. Ryan CJ, Molina A, Li J, et al: Serum androgens as prognostic biomarkers in castration-resistant prostate cancer: Results from an analysis of a randomized phase III trial. J Clin Oncol 31:2791-2798, 2013

2. de Bono JS, Logothetis CJ, Molina A, et al: Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 364:1995-2005, 2011

3. Ryan CJ, Smith MR, de Bono JS, et al: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-148, 2013

4. Fizazi K, Tran N, Fein L, et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 377:352-360, 2017

5. James ND, de Bono JS, Spears MR, et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 377:338-351, 2017

6. Malangone-Monaco E, Foley K, Varker H, et al: Prescribing patterns of oral antineoplastic therapies observed in the treatment of patients with advanced prostate cancer between 2012 and 2014: Results of an oncology EMR analysis. Clin Ther 38:1817-1824, 2016

7. Caram MEV, Borza T, Min HS, et al: Early national dissemination of abiraterone and enzalutamide for advanced prostate cancer in Medicare Part D. J Oncol Pract 13:e694-e702, 2017

8. Janssen Biotech I: Zytiga. https://www.zytiga.com

9. Pilon D, Queener M, Lefebvre P, et al: Cost per median overall survival month associated with

abiraterone acetate and enzalutamide for treatment of patients with metastatic castration-resistant prostate cancer. J Med Econ 19:777-784, 2016

10. Astellas Pharma: Information for Vermont prescribers of prescription drugs (long form): Xtandi (enzalutamide) capsules. https://astellasuswebitms.blob.core.windows.net/vermont/Xtandi Long Form.pdf

11. Ryan CJ, Smith MR, Fong L, et al: Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. J Clin Oncol 28:1481-1488, 2010

12. Stuyckens K, Saad F, Xu XS, et al: Population pharmacokinetic analysis of abiraterone in

chemotherapy-naïve and docetaxel-treated patients with metastatic castration-resistant prostate cancer. Clin Pharmacokinet 53:1149-1160, 2014

13. Janssen Biotech: Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202379s021lbl.pdf

14. Center for Drug Evaluation and Research: Application number: 202379Orig1s000. Clinical pharmacology and biopharmaceutics review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202379orig1s000clinpharmr.pdf

15. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009

16. Scher HI, Halabi S, Tannock I, et al: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-1159, 2008

17. Kim W, Zhang L, Wilton JH, et al: Sequential use of the androgen synthesis inhibitors ketoconazole and abiraterone acetate in castration-resistant prostate cancer and the predictive value of circulating androgens. Clin Cancer Res 20:6269-6276, 2014

18. Xu XS, Ryan CJ, Stuyckens K, et al: Correlation between prostate-specific antigen kinetics and overall survival in abiraterone acetate-treated castration-resistant prostate cancer patients. Clin Cancer Res 21:3170-3177, 2015

19. Danila DC, Morris MJ, de Bono JS, et al: Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. J Clin Oncol 28:1496-1501, 2010

20. Karrison TG, Maitland ML, Stadler WM, et al: Design of phase II cancer trials using a continuous endpoint of change in tumor size: Application to a study of sorafenib and erlotinib in non small-cell lung cancer. J Natl Cancer Inst 99:1455-1461, 2007

21. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. Journal Am Stat Assn 53:457-481, 1958

22. Carton E, Noe G, Huillard O, et al: Relation between plasma trough concentration of abiraterone and prostate-specific antigen response in metastatic castration-resistant prostate cancer patients. Eur J Cancer 72:54-61, 2017

23. Ryan CJ, Peng W, Kheoh T, et al: Androgen dynamics and serum PSA in patients treated with abiraterone acetate. Prostate Cancer Prostatic Dis 17:192-198, 2014

24. Ryan CJ, Shah S, Efstathiou E, et al: Phase II study of abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. Clin Cancer Res 17:4854-4861, 2011

25. Chi KN, Spratlin J, Kollmannsberger C, et al: Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. J Clin Pharmacol 55:1406-1414, 2015

26. Jain RK, Brar SS, Lesko LJ: Food and oral antineoplastics: More than meets the eye. Clin Cancer Res 16:4305-4307, 2010

27. Kang SP, Ratain MJ: Inconsistent labeling of food effect for oral agents across therapeutic areas: Differences between oncology and non-oncology products. Clin Cancer Res 16:4446-4451, 2010

28. Devriese LA, Koch KM, Mergui-Roelvink M, et al: Effects of low-fat and high-fat meals on steady-state pharmacokinetics of lapatinib in patients with advanced solid tumours. Invest New Drugs 32:481-488, 2014

29. Ratain MJ: Targeted therapies: Redefining the primary objective of phase I oncology trials. Nat Rev Clin Oncol 11:503-504, 2014 [Erratum Nat Rev Clin Oncol 12:126, 2015]

30. Morris MJ, Molina A, Small EJ, et al: Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. J Clin Oncol 33:1356-1363, 2015

31. Hussain M, Goldman B, Tangen C, et al: Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: Data from Southwest Oncology Group Trials 9346 (Intergroup Study 0162) and 9916. J Clin Oncol 27:2450-2456, 2009

32. O'Donnell A, Judson I, Dowsett M, et al: Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br J Cancer 90:2317-2325, 2004

33. Szmulewitz RZ, Ratain MJ: Playing Russian roulette with tyrosine kinase inhibitors. Clin Pharmacol Ther 93:242-244, 2013

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■ ■ ■

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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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**Expert Testimony:** Multiple generic companies

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: $p_L - p_S \leq -0.15$ versus H_A: $p_L - p_S > -0.15$. 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.[20] Assuming the log ratio of the 12-week to baseline PSA levels, that is, $\ln(PSA_{12}/PSA_0)$ is approximately normally distributed, we interpret a response rate of 30% to mean that the 30th percentile of the distribution of $\ln(PSA_{12}/PSA_0)$ 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 $\ln(0.5) - Z_{0.30}{}^*SD$, where $Z_{0.30}$ equals -0.524, the 30th percentile of the standard normal distribution, and SD is the standard deviation of the distribution of $\ln(PSA_{12}/PSA_0)$. 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 $\ln(0.5) - Z_{0.15}{}^*SD$, 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 μ_L and μ_S denote the respective true mean log changes in the LOW and STD groups, we tested H_0: $\mu_L - \mu_S > 0.512$ SD versus H_A: $\mu_L - \mu_S < 0.512$ SD. Assuming the PSA response rates are truly equivalent, a total sample size of 72 patients (36 per treatment arm) provides 80% power for the noninferiority test, using a one-sided alpha level of .10.
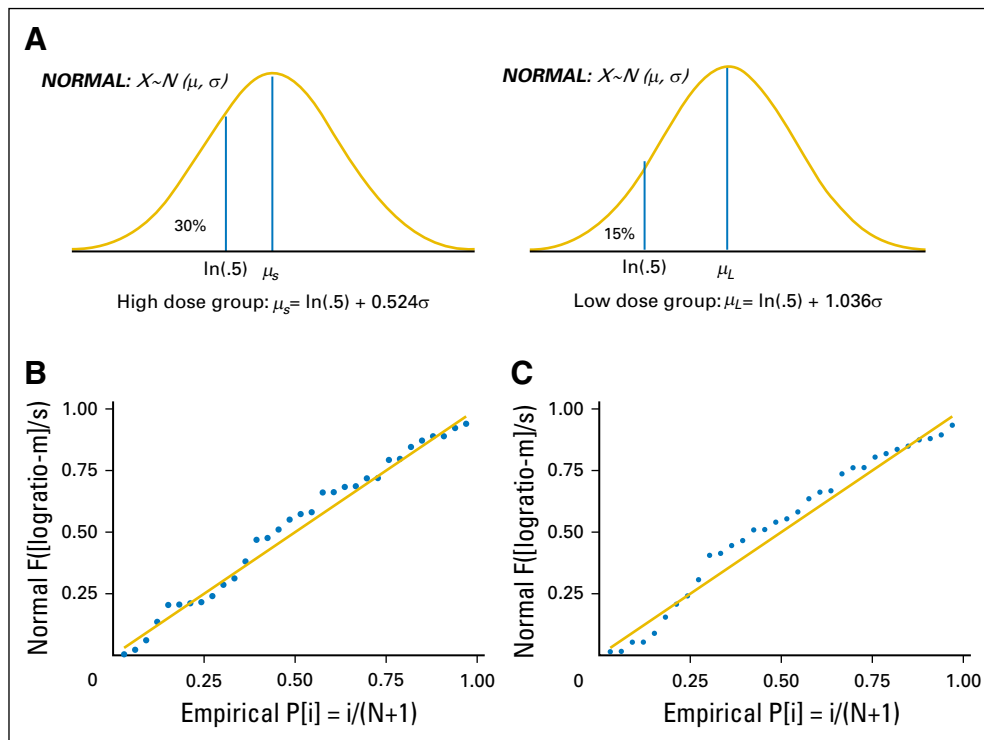
Fig A1. Distribution of log PSA changes. A. Statistical assumption of normal distribution curves for STD (left) and LOW (Arm). B. Normal probability plot for STD arm. C. Normal probability plot for LOW arm.
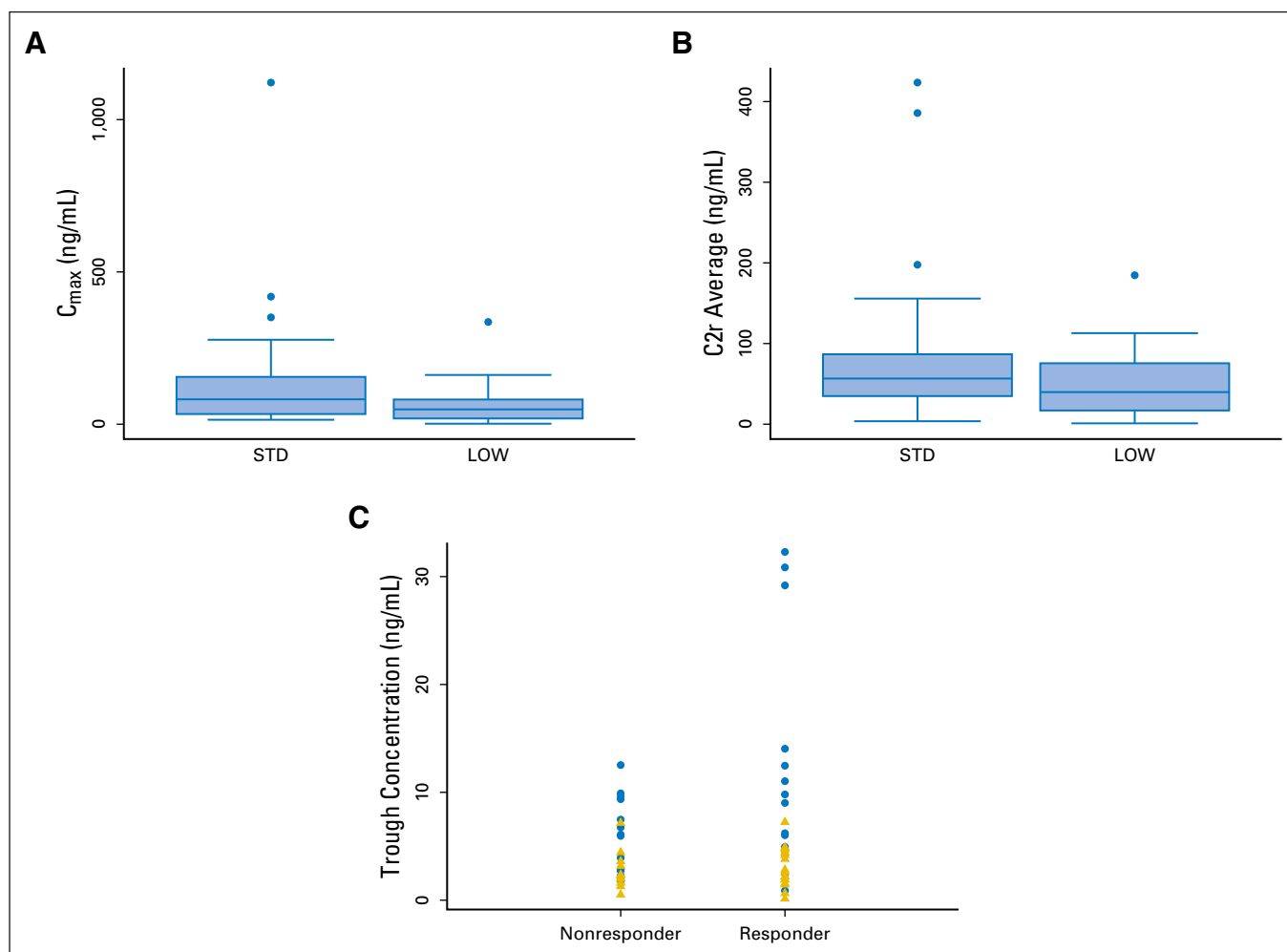
Fig A2. Abiraterone drug concentrations. Abiraterone C$_{max}$ (A) and 2 hour post treatment drug levels (B) were higher in STD compared to LOW arms. (C) There was no significant difference in likelihood of PSA response based on AA trough concentration (p=0.11) irrespective of treatment arm (LOW, triangle; STD, circle).