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The IMAAGEN Study: Effect of Abiraterone Acetate and Prednisone on Prostate-Specific Antigen and Radiographic Disease Progression in Patients with Non-Metastatic Castration-Resistant Prostate Cancer

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Abstract

Purpose: To evaluate the use of abiraterone acetate (1000 mg) plus prednisone (5mg) [AA+P] in patients with high-risk non-metastatic castration resistant prostate cancer (nmCRPC).

Materials and Methods: Patients considered at high risk for progression to metastatic disease (PSA 10 ng/mL or PSADT 10 months) received AA+P daily (28-day cycles). The primary endpoint was the proportion of patients achieving PSA50 during cycles 1–6. Secondary endpoints included time to PSA progression, time to radiographic evidence of disease progression, and safety.

Results: Of 131 enrolled patients, 44 (34%) remain on treatment, with a median follow-up of 40.0 months. Median age was 72 (48–90) years. Most patients (82.4%) were white; 14.5% were

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black. Median screening PSA was 11.9 ng/dL and PSADT was 3.4 months. PSA was significantly reduced ($p<0.0001$), with 86.9% PSA50 and 59.8% PSA90. Median time to PSA progression was 28.7 months (95% CI 21.2, 38.2). Median time to radiographic evidence of disease progression was not reached but was estimated to be 41.4 months (95% CI 27.6, NE) by sensitivity analysis with 15 patients. Baseline testosterone 12.5 ng/dL and PSA90 at cycle 3 were associated with longer times to PSA progression and radiographic evidence of disease progression. Outcomes for black patients were similar to other patients. Adverse events, Grade 3 AEs, and SAEs were reported in 96.2%, 61.1%, and 43.5% of patients respectively.

Conclusions: In patients with high-risk nmCRPC, treatment with AA+P demonstrated a significant reduction in PSA50 with encouraging results for the secondary endpoints including the safety of 5 mg P.

Keywords

abiraterone acetate; prostatic neoplasms

INTRODUCTION

Abiraterone acetate (AA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor that blocks 17 α hydroxylase/C17,20-lyase, thereby decreasing levels of testosterone produced by the testes, the adrenal glands, and prostate cancer tissue. Abiraterone acetate with 10 mg of prednisone (P) was approved by the U.S. Food and Drug Administration for the treatment of patients with metastatic castration resistant prostate cancer (mCRPC) and patients with metastatic high-risk castration-sensitive prostate cancer.¹ The magnitude of benefit, as measured by time to radiographic progression in pre-chemotherapy vs post-chemotherapy patients (16.5 months vs 5.6 months) as well as 50% reduction in PSA (PSA50) (62% vs 29%)^{2, 3}, suggested that patients treated earlier in disease progression may derive greater disease progression benefit. At the time that this study was initiated, there were no currently approved effective treatments for patients with high-risk non-metastatic (nm) CRPC. In February 2018, 2 prospective randomized controlled trials, one with apalutamide and one with enzalutamide, reported, positive results with significant prolongation in time to MFS. To date only apalutamide has received FDA approval for the treatment of patients with nmCRPC.⁴⁻⁶ We present the results of this phase 2 proof-of-concept study, IMAAGEN, herein.

MATERIALS AND METHODS

Study Design and Treatment

IMAAGEN ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01314118): NCT01314118) is a phase 2, multicenter, open-label, single-arm study. This study was institutional review board approved and all patients provided written, informed consent. Patients were enrolled from April 2011 to July 2013. After meeting all other entry criteria including prostate-specific antigen doubling time (PSADT) 10 months or absolute PSA of 10 ng/mL, patients underwent technetium bone scan as well as either CT or MRI scan to confirm non-metastatic status. Enrolled patients continued

ADT (unless post-orchietomy) and received once-daily, orally-administered AA 1000 mg and P 5 mg in customary 28-day treatment cycles.

This study was only statistically powered for the primary endpoint of the proportion of patients achieving a PSA50 during cycles 1–6. Secondary endpoints were time to PSA progression, time to radiographic evidence of disease progression, proportion of patients achieving a 30% (PSA30), 50% or 90% (PSA90) reduction in PSA by the end of cycle 6, proportion of patients achieving PSA50 by the end of cycle 3, changes in PSA over time and from baseline and testosterone levels after cycle 3 and 6, change from baseline, and safety.

Adverse events (AEs) were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. A central laboratory performed all study laboratory assessments. Efficacy was assessed by PSA and testosterone levels as well as imaging studies (bone scans and CT or MRI of the chest, abdomen, and pelvis) at baseline, after cycles 3 and 6, and every 2 and 3 cycles thereafter for PSA and imaging, respectively. For patients with imaging studies suspicious for radiographic progression of disease, confirmatory imaging was to be performed 6–8 weeks later per Prostate Cancer Clinical Trials Working Group (PCWG2)⁷ guidance. Time to radiographic progression of disease was the time between initiation of AA+P and time to first scan noting disease progression, per modified RECIST 1.1 criteria. Time to PSA progression was the time between initiation of AA+P and the time that a 25% increase and 2 ng/mL absolute increase in PSA from nadir occurred and was confirmed by a second PSA value 3 weeks thereafter, as outlined by the PCWG2.

Following achievement of the primary endpoint—first reported at ASCO 2014—data have been updated and reported annually.^{8–10} Results included herein are through data cutoff of 13 October 2015, after which the study was amended to allow for patients who had not progressed, to continue to receive treatment; however, central laboratory and imaging requirements were removed. The study is ongoing.

Key Eligibility Criteria

Men aged ≥18 years who had confirmed nmCRPC, with screening serum testosterone level <50 ng/dL or <2.0 nM, and a rising PSA level (PSA ≥10 ng/mL at screening or a PSADT of ≤10 months) were enrolled. Patients who had local disease progression or metastatic disease per modified RECIST criteria, chemotherapy for CRPC, prior therapy with aminoglutethimide or ketoconazole, or current antiandrogen therapy were excluded.

Statistical analyses

Efficacy endpoints were analyzed in the efficacy-evaluable population (ie, patients who completed ≥1 treatment cycle with ≥75% treatment compliance in AA+P and had ≥1 postbaseline PSA assessment). The primary endpoint was analyzed using a normal approximation to the binomial distribution compared with the observed proportion to a reference of 0.35.

Time to PSA progression and time to radiographic evidence of disease progression were summarized using the Kaplan-Meier method. After a median of 40 months of follow up, some patients withdrew due to suspected disease progression without obtaining confirmatory scans, a sensitivity analysis, also using the Kaplan-Meier method, was conducted and included patients whose “unconfirmed” progressions had led to initiation of new therapies. All secondary endpoints were summarized using descriptive statistics.

Safety variables of AEs summarized by grade and occurring within 30 days of last dose of study drug, laboratory values, vital sign measurements, and deaths reported during the study were analyzed. Safety variables were tabulated by descriptive statistics using the safety-evaluable set (all patients receiving study medications).

Post hoc analyses were conducted to explore factors associated with response and safety. The Kaplan-Meier method was used to explore the effects of race, baseline levels of PSA and testosterone. Landmark analyses were conducted to evaluate effect of PSA reduction after 3 cycles of treatment on time to PSA progression and time to radiographic evidence of disease progression.

RESULTS

Baseline Demographics and Disease Characteristics

A total of 297 patients were screened, imaging performed on 208 patients and 131 patients enrolled at 39 sites in the United States. A preplanned analysis was conducted when all enrolled patients had either completed or withdrawn from the initial 6 cycles of treatment; 111 (85%) patients completed cycles 1–6, while 20 (15%) patients discontinued. Study discontinuation was attributed to AEs (6.1%), disease progression (1.5%), physician decision (1.5%), protocol violation (3.8%) or withdrawal of consent (2.3%) (Fig 1). There were 82.4% of patients that were white and 14.5% that were black. The median age was 72 (range: 48–90) years (Table 1) [available online at <http://xxx> (per the editor’s direction-post Table 1 on The Journal’s website at no charge)]. At the time of this data cutoff, patients had received a median of 25 (range: 1–57) cycles of AA+P. Median treatment duration was 22.14 (range: 0.1–52.0) months, and median follow-up was 40.0 months; 44 (34%) patients have no evidence of disease progression and are continuing on treatment (Figure 1).

Efficacy

One hundred six (86.9%) patients (95% CI=80.9%, 92.9%) achieved a 50% reduction in PSA by the end of cycle 6; 104 (85%) patients (95% CI=79%, 92%) achieved this reduction by the end of cycle 3. Maximum PSA reductions achieved by each patient are depicted in Figure 2. One hundred eleven (91%) patients (95% CI=86%, 96%) and 73 (59.8%) patients (95% CI=51%, 69%) achieved 30% and 90% reductions in PSA through cycle 6, respectively. Twenty-seven (22.1%) patients had PSA levels that were considered undetectable (<0.2 ng/mL), and 7 (5.7%) had PSA levels that were <0.02 ng/mL (Table 2). Median (95% CI) time to PSA progression was 28.7 (21.2, 38.2) months. Testosterone levels were reduced by approximately 96% by the end of cycle 3 and remained so by the end of cycle 6 (Table 3).

Thirty-one (23.7%) patients had confirmed radiographic evidence of disease progression based upon investigator assessment. The remaining 100 (76.3%) patients were censored, having discontinued treatment prior to disease progression, or were continuing on study without confirmed progression. At 48 months, 62% of patients were estimated to be progression-free. Median time to radiographic evidence of disease progression was not reached; however, in a sensitivity analysis including 15 unconfirmed progressions that led to initiation of new therapies, median time to radiographic evidence of disease progression was estimated at 41.4 months (95% CI: 27.6, not estimable) (Table 4 and Kaplan-Meier estimates, Figure 3).

Safety

Most (126/131 [96%]) patients reported AEs (Grades 1/2: 35%, and Grades 3/4: 57%). The most common AEs were hypertension (55 [42.0%] patients), fatigue (52 [39.4%] patients), and hypokalemia (44 [33.6%] patients). In 8 patients (6.1%), study discontinuation was attributed to AEs of atrial fibrillation, acute renal failure, asthenia, mesothelioma, fatigue, dementia and increased aminotransferase (2). Fifty-seven (43.5%) patients experienced serious AEs. (Table 5) The most common serious AEs were sepsis, pneumonia, and urinary retention (Supplementary Table 1). Seven (5%) patients experienced AEs resulting in death.

AEs of special interest are included in Table 5. Overall, AEs of special interest were mostly Grade 1/2 events. Black patients more frequently reported an event of Grade 3 hypertension (47% vs 20%). No patient discontinued AA+P due to a hypertensive event. Forty-four (33.6%) of 131 patients experienced hypokalemia, mostly Grade 1/2, (35/131, 27%). No patient discontinued AA+P due to mineralocorticoid excess or required prednisone dose escalation to manage this (Supplementary Table 2).

Post hoc Analyses

Patients with baseline testosterone ≥ 12.5 ng/dL (n=29) experienced significantly longer times to PSA progression (p=0.03) and a non-significant increase in radiographic evidence of disease progression (p=0.12) as compared with patients with baseline testosterone <12.5ng/dL (n=94). The positive association between higher baseline testosterone and improved outcomes was also observed in a large phase III randomized controlled study.¹¹ The median time for both endpoints was not reached in these patients. For patients with baseline testosterone <12.5ng/dL, median time to PSA progression was 24.9 months and median time to radiographic evidence of disease progression was 33.2 months (Supplementary Figures 1A and B).

Landmark analyses after 3 cycles of therapy were performed, and the maximum reductions in PSA were grouped into ranges of <50% (n=17), 50% to <90% (n=46), or >90% (n=55) of PSA reduction. A greater reduction in PSA was associated with prolonged time to PSA progression (median 15.7, 21.3, and 38.2 months, respectively [p=0.003]) and prolonged time to radiographic evidence of disease progression (median 14.8 months, 24.8 months, and not reached, respectively [p=0.002]) (Supplementary Figures 2A and B).

While black patients (n=19) had baseline PSA levels higher than other races (n=112) (median: 27.8 vs.12.7 ng/mL), time to PSA progression (median: 29.0 vs. 28.6 months

[$p=0.57$]) and time to radiographic evidence of disease progression (median: 41.4 vs not reached [$p=0.82$]) were similar as compared with other patients (Supplementary Figures 3A and B).

DISCUSSION

The findings of the IMAAGEN study demonstrate that a very high proportion of men with **nmCRPC** treated with AA 1000 mg and prednisone 5 mg, experience sustained PSA reductions as well as prolonged time to radiographic evidence of metastatic disease. While 10 mg of prednisone remains the standard of care in combination with AA, the use of 5 mg of prednisone demonstrated a safety profile similar to earlier trials of AA using either 5 or 10 mg of prednisone. This trial met its goal of enrolling the percent of black men consistent with the general US population¹² and noted no differences in overall response to treatment in black patients.

It is important to note that the IMAAGEN trial has a number of limitations. First, there is no comparator arm which limits the interpretation of these results. Prior studies have suggested that CRPC patients with lower disease burdens, including those with non-metastatic disease, experience more favorable outcomes on androgen targeted therapies than those with a higher burden, and the present data are consistent with that.^{13, 14}

Second, estimated time to metastatic progression was only reached using a sensitivity analysis and is based on just 15 patients. The PCWG2 criteria require a subsequent confirmatory scan for new lesions developed in the first 3–6 months (mCRPC) after initiating a new therapy; however, it is unrealistic to expect a patient to delay subsequent therapies when a first metastatic lesion appears after years of therapy. Therefore, patients with no confirmatory scans who withdrew from the study due to suspected disease progression, leading to the initiation of new therapies were included in the sensitivity analyses. The median difference in time to PSA progression and time to radiographic evidence of disease progression was just over a year (28.7 vs 41.4 months), with greater declines of PSA response by the end of 3 months of treatment being associated with longer time to radiographic evidence of disease progression. While the question of whether the length of time between PSA progression and radiographic progression is due to continued study drug efficacy cannot be answered in the present analysis; it is useful for clinicians to understand that rising PSA does not temporally coincide with the development of radiographic evidence of metastatic disease. This study confirms that, irrespective of the length time between PSA rise and radiographic progression, patients should remain on therapy as was done in the phase 3 studies with AA+P.^{3, 15}

Third, there was no OS endpoint; however, since the inception of this trial, data have come to light that demonstrate a strong relationship in patients with localized disease between metastasis free survival and OS.¹⁶ Moreover, a growing body of literature suggests the value of delaying the onset of metastatic disease in terms of physical and emotional well-being as well as cost.^{17–19}

Lastly, IMAAGEN was conducted using technetium bone and CT/MRI scans. With this technology, 37% of these “high-risk” patients were found to have unsuspected metastatic disease at the time of screening and were not enrolled in the study.²⁰ With the availability of newer imaging modalities such as PSMA PET scanning, which may have higher sensitivity and specificity, and thus greater diagnostic accuracy, it is foreseeable that many more of these patients at “high-risk” for progression to metastatic disease will be found to have radiographic evidence of metastatic disease. Nonetheless, this does not diminish the observation that the IMAAGEN patients had a profound PSA response and subsequent longer time to conventional radiographic evidence of disease progression than patients treated in first-line mCRPC trials. For example, radiographic PFS was 16.5 months vs. 8.2 months for placebo in the COU-AA-302 study of mCRPC chemotherapy naive patients and in fact, the radiographic PFS in IMAAGEN exceeded overall survival (median 35.3 months) of those patients receiving AA+P in the COUAA-302 study.²¹

While most patients in IMAAGEN reported AEs, these were manageable with only 6% of patients discontinuing due to AEs by cycle 6. The full risk-benefit profile of treating patients with nmCRPC with AA+P would need to be further studied in a prospective, randomized controlled trial.

In conclusion, IMAAGEN showed that treatment with AA+P demonstrated a significant reduction in PSA50 with encouraging results for the secondary endpoints including the safety of 5 mg P in nmCRPC patients. These results suggest that potentially earlier treatment of CRPC with effective therapies might result in improved clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

AA+P	abiraterone acetate + prednisone 5mg
AE	adverse event
ADT	androgen-deprivation therapy
CI	confidence interval
CRPC	castration-resistant prostate cancer
CT	computed tomography

CTCAE	Common Toxicity Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
IMAAGEN	Impact of Abiraterone Acetate on Prostate Specific AntiGEN
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
nmCRPC	nonmetastatic castration-resistant prostate cancer
PCWG	Prostate Cancer Clinical Trials Working Group
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PSA30	30% reduction in prostate-specific antigen
PSA50	50% reduction in prostate-specific antigen
PSA90	90% reduction in prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
SD	standard deviation

REFERENCES

1. Zytiga [package insert]. Horsham, PA: Janssen Biotech, Inc, 2018.
2. Ryan CJ, Smith MR, de Bono JS et al.: Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*, 368: 138, 2013 [PubMed: 23228172]
3. de Bono JS, Logothetis CJ, Molina A et al.: Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*, 364: 1995, 2011 [PubMed: 21612468]
4. Smith MR, Saad F, Chowdhury S et al.: Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med*, 2018
5. Erleada [package insert]. Horsham, PA: Janssen Products, LP; 2018.
6. Hussain M, Fizazi K, Saad F, et al.: PROSPER: A phase 3, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic castration-resistant prostate cancer (M0 CRPC). *J Clin Oncol* 36, 2018 (suppl 6S; abstr 3).
7. 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, 2008 [PubMed: 18309951]
8. Ryan CJ, Crawford ED, Shore ND et al.: Effect of abiraterone acetate and low-dose prednisone on PSA in patients with nonmetastatic castration-resistant prostate cancer: the results from IMAAGEN core study. *J Clin Oncol* 2014; 32 (15 suppl): 5s Abstract 5086.
9. Ryan CJ, Crawford ED, Shore ND et al.: IMAAGEN trial update: effect of abiraterone acetate and low dose prednisone on PSA and radiographic disease progression in patients with non metastatic castration-resistant prostate cancer. *J Clin Oncol* 2015; 33 (15 suppl). Abstract 5053.
10. Ryan CJ, Crawford ED, Shore ND et al.: IMAAGEN trial safety and efficacy update: effect of abiraterone acetate and low-dose prednisone on prostate-specific antigen and radiographic disease progression in patients with nonmetastatic castration-resistant prostate cancer. *J Clin Oncol* 2016; 34 (suppl). Abstract 5061.

11. 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, 2013 [PubMed: 23816964]
12. United States Census Bureau 2010 census. <https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml>
13. Ryan CJ, Weinberg V, Rosenberg J et al.: Phase II study of ketoconazole plus granulocyte-macrophage colony-stimulating factor for prostate cancer: effect of extent of disease on outcome. *J Urol*, 178: 2372, 2007 [PubMed: 17936834]
14. Ryan CJ, Kheoh T, Li J et al.: Prognostic Index Model for Progression-Free Survival in Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer Treated With Abiraterone Acetate Plus Prednisone. *Clin Genitourin Cancer*, 2017
15. Ryan CJ, Smith MR, Fizazi K et al.: Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*, 16: 152, 2015 [PubMed: 25601341]
16. Xie W, Regan MM, Buyse M et al.: Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. *J Clin Oncol*, 35: 3097, 2017 [PubMed: 28796587]
17. Klaassen Z, Howard LE, de Hoedt A et al.: Factors predicting skeletal-related events in patients with bone metastatic castration-resistant prostate cancer. *Cancer*, 123: 1528, 2017 [PubMed: 28026865]
18. Kirby M, Hirst C, Crawford ED: Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract*, 65: 1180, 2011 [PubMed: 21995694]
19. Li TT, Shore ND, Mehra M et al.: Impact of subsequent metastases on costs and medical resource use for prostate cancer patients initially diagnosed with localized disease. *Cancer*, 123: 3591, 2017 [PubMed: 28542732]
20. Crawford ED, Kantoff PW, Shore ND et al.: Unsuspected metastases found during screening for a trial of patients with non-metastatic castration resistant prostate cancer. Poster presented at: 24th International Prostate Cancer Update; February 19–22, 2014; Vail, Colorado.
21. Rathkopf DE, Smith MR, de Bono JS et al.: Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol*, 66: 815, 2014 [PubMed: 24647231]

Figure 1.
Patient disposition.

Figure 2.
Maximum PSA reduction achieved during Cycles 1–6.

Figure 3. Kaplan-Meier estimates of (A) radiographic progression-free survival and (B) sensitivity analysis of radiographic progression-free survival.

Table 1.**Baseline patient demographics and disease characteristics**

	Abiraterone Acetate + Prednisone
Enrolled patients, N (%)	131
Age, years	
Median (range)	72.0 (48.0, 90.0)
Race, n (%)	
White	108 (82.4)
Black	19 (14.5)
Asian	2(1.5)
Other	1 (0.8)
Not reported	1 (0.8)
Screening PSA, ng/mL	
Median (range)	11.9 (1.3, 167.8)
10	79 (60.3)
<10	52 (39.7)
PSADT, n (%)	52 (39.7)
Median (range), months	3.4(1.1, 9.4)
Primary tumor stage at initial diagnosis, n (%)	119
1	39 (32.8)
2	44 (37.0)
3	36 (30.3)
4	0
Time from initial diagnosis to first dose of AA, years	
Median (range)	10.2 (1.5, 26.0)
Time from 1st castration* to first AA dose, n (%)	130 (99.2)
Median (range), years	5.9(0.1, 26.0)
ECOG performance status	
0	112 (85.5)
1	18 (13.7)
2	1 (0.8)
Calculated Gleason Score, n (%)	125 (95.4)
<7	17 (13.6)
7	59 (47.2)
8	49 (39.2)
Median (range)	7.0 (4.0; 10.0)

* Castration via surgery or gonadotropin-releasing hormone.

AA, abiraterone acetate; PSADT, prostate-specific antigen doubling time

Table 2.

Summary of prostate-specific antigen responses

Abiraterone Acetate + Prednisone	
Efficacy-evaluable patients, n	122
50% reduction in PSA during Cycles 1–6, n (%)	106 (86.9)
95% CI	80.9, 92.9
P-value ^a	<0.0001
PSA reduction by category, n (%)	
0	6 (4.9)
0 to <30%	5 (4.1)
30 to <50%	5 (4.1)
50 to <90%	33 (27.0)
90%	73 (59.8)
Undetectable PSA, n (%)	
<0.20 ng/mL	27(22.1)
<0.02 ng/mL	7 (5.7)
PSA progression-free rates, n	
12 months (% , 95% CI)	0.797 (0.705, 0.863)
18 months (% , 95% CI)	0.674 (0.570, 0.758)
24 months (% , 95% CI)	0.557 (0.449, 0.651)

^aResponse compared against the fixed proportion of 0.35 using a 1-sample and 1-sided test for a binomial proportion by normal approximation. CI, confidence interval

Table 3.

Testosterone levels

	n	Mean	SD	Median	IQR	Base Mean	Change from Baseline		
							n	Mean	SD
Ultrasonic Assay Testosterone, ng/dL									
Baseline *	116	10.308	11.4926	8.200	6.190				
Cycle 4, Day 1	92	0.387	0.4397	0.260	0.280	10.640	87	-10.240	12.4870
Cycle 7, Day 1	87	0.378	0.2840	0.290	0.340	10.560	83	-10.174	12.9588

* One patient had a screening testosterone level of 6.78 ng/dL, meeting entry criteria, but reported 117.38 ng/dL at Cycle 1, Day 1. On Cycle 4, Day 1, the patient's testosterone was 3.15 ng/dL and on Cycle 7, Day 1 the patient's testosterone level was 0.59 ng/dL.

Table 4.

Time to radiographic progression

Abiraterone Acetate + Prednisone	
All enrolled patients	131
Radiographic progression event	31 (23.7)
Censored	100 (76.3)
Time to radiographic progression event	
Median (95% CI)	NE (41.4, NE)
Range	(0.0 ⁺ , 49.8 ⁺)
Progression-free rates, n	131
12 months (95% CI)	0.862 (0.782, 0.915)
24 months (95% CI)	0.746 (0.645, 0.822)
36 months (95% CI)	0.691 (0.582, 0.776)
48 months (95% CI)	0.615 (0.470, 0.732)
Sensitivity analysis [*]	Abiraterone Acetate + Prednisone
All enrolled patients	131
Radiographic progression event	46 (35.1)
Censored	85 (64.9)
Time to radiographic progression event	
Median (95% CI)	41.4 (27.6, NE)
Range	(0.0 ⁺ , 49.8 ⁺)
Progression-free rates, n	131
12 months (95% CI)	0.810 (0.723, 0.872)
24 months (95% CI)	0.665 (0.564, 0.747)
36 months (95% CI)	0.553 (0.445, 0.648)
48 months (95% CI)	0.492 (0.367, 0.606)

⁺ = censored observation; NE = not estimable.

^{*} Sensitivity analysis includes events that were not confirmed by a second scan due to patient or physician decision.

Table 5.

Summary of AEs

Abiraterone Acetate + Prednisone(N=131)		
Patients with AEs, n (%)	126(96.2)	
Drug-related	118(90.1)	
Patients with serious AEs, n (%)	57 (43.5)	
Drug-related	29(22.1)	
Patients with AEs leading to treatment discontinuation, n (%)	20(15.3)	
Patients with AEs leading to death, n (%) [*]	7(5.3)	
Common AEs (≥ 15% of patients)	Any Grade	Grade 3
Hypertension	55 (42.0)	31 (23.7)
Fatigue	52 (39.7)	1 (0.8)
Hypokalemia	44 (33.6)	9 (6.9)
Peripheral edema	33 (25.2)	2(1.5)
Nausea	28 (21.4)	1 (0.8)
Diarrhea	25 (19.1)	2(1.5)
Dizziness	25 (19.1)	1 (0.8)
Headache	22 (16.8)	1 (0.8)
Constipation	22 (16.8)	1 (0.8)
Cough	22 (16.8)	0
Back pain	21 (16.0)	2(1.5)
Vomiting	21 (16.0)	1 (0.8)
Upper respiratory tract infection	21 (16.0)	0
Arthralgia	20(15.3)	0
AEs of hypertension, hypokalemia, and fluid retention or edema events of special interest	Any Grade	Grade 3 ^{**}
Hypertension	55 (42.0)	31 (23.7)
Hypertensive crisis	1 (0.8)	1 (0.8)
Hypokalemia	44 (33.6)	9 (6.9)
Peripheral edema	33 (25.2)	2(1.5)
Pleural effusion	4(3.1)	1 (0.8)

^{*} Grade 5 AEs reported in 5 (4%) patients and 2 additional deaths due to Grade 4 injury (motorcycle accident) and Grade 3 pneumonia. Six patients had a single serious AE (injury, pneumonia, aspiration pneumonia, myocardial infarction, congestive cardiac failure, and coronary artery disease). One patient had sepsis, pneumonia, and acute respiratory failure.

^{**} No Grade 4 events reported.