Clinical Cancer Research

Safety and Antitumor Activity of Apalutamide (ARN-509) in Metastatic Castration-Resistant Prostate Cancer with and without Prior Abiraterone Acetate and Prednisone

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Abstract

Purpose: To evaluate the efficacy of apalutamide before or after treatment with abiraterone acetate and prednisone (AAP) in patients with progressive metastatic castration-resistant prostate cancer (mCRPC).

Experimental Design: Two cohorts were studied: AAP-naïve and post-AAP patients who had received ≥6 months of AAP. Patients had progressive mCRPC per rising prostate-specific antigen (PSA) and/or imaging, without prior chemotherapy exposure. All received apalutamide 240 mg/day. Primary endpoint was ≥50% decline in 12-week PSA according to Prostate Cancer Working Group 2 criteria. Secondary endpoints included time to PSA progression and time on treatment.

Results: Forty-six patients enrolled in the AAP-naïve ($n = 25$) and post-AAP ($n = 21$) cohorts. The 12-week PSA response rate was 88% (22/25) and 22% (4/18), median time to PSA progression was 18.2 months [95% confidence interval (CI), 8.3 months–not reached) and 3.7 months (95% CI, 2.8–5.6 months), and median time on treatment 21 months (range, 2.6–37.5) and 4.9 months (range, 1.3–23.2), for the AAP-naïve and post-AAP cohorts, respectively. Eighty percent (95% CI, 59–93) and 64% (95% CI, 43–82) of AAP-naïve and 43% (95% CI, 22–66) and 10% (95% CI, 1–30) of post-AAP patients remained on treatment for 6+ and 12+ months, respectively. Common treatment-emergent adverse events in both cohorts were grade 1 or 2 fatigue, diarrhea, nausea, and abdominal pain.

Conclusions: Apalutamide was safe, well tolerated, and demonstrated clinical activity in mCRPC, with 80% of AAP-naïve and 43% of post-AAP patients, remaining on treatment for 6 months or longer. *Clin Cancer Res; 23(14); 3544–51. ©2017 AACR.*

Introduction

Apalutamide (formerly ARN-509) is a next-generation androgen receptor (AR) antagonist (1), targeting known oncogenic changes in AR signaling that contribute to the lethal castration-resistant phenotype (2). The prostate cancer therapeutic landscape has changed significantly since the development of apalutamide as six life-prolonging therapies are now approved, including two AR-signaling–directed therapies, abiraterone and enzalutamide, which has broad indications in metastatic castration-resistant prostate cancer (mCRPC) (3–10). A major challenge in successful drug development for the benefit of CRPC patients is to identify active drugs and to learn how best to utilize them in sequence or in combination.

Apalutamide selectively and irreversibly binds with high affinity to the ligand-binding domain of the AR, inducing a conformational change in the AR that impairs translocation of the receptor complex into the nucleus of the cell and thereby prevents binding of androgen response elements. In mice CRPC xenograft models, apalutamide produced dose-dependent tumor regressions superior to those achieved with bicalutamide or enzalutamide (1). In addition, maximal antitumor effects occurred in animals bearing CRPC tumors at 4-fold lower concentrations in the central nervous system, a 3-fold lower dose, and approximately 9-fold lower plasma levels of apalutamide relative to enzalutamide, indicative of higher tumor-to-plasma penetration. A first-in-human phase I open-label study (ARN-509-001; NCT01171898) of apalutamide confirmed proof of mechanism and safety of apalutamide, and identified an optimal biologic dose for further study (11). In the phase II portion of trial ARN-509-001 in nonmetastatic CRPC patients, apalutamide demonstrated significant antitumor effects in men, with a favorable safety profile (12).

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi: 10.1158/1078-0432.CCR-16-2509

Translational Relevance

This study addressed the effect of activity of apalutamide in metastatic castration-resistant prostate cancer patients who were naïve to prior abiraterone plus prednisone (AAP) therapy as well as in patients who had received prior exposure to AAP. As expected, the apalutamide response was less in post-AAP versus AAP-naïve patients—22% versus 80% using a ≥50% PSA decline endpoint. Using newly defined Prostate Cancer Working Group 3–recommended swim plots, which illustrate time on treatment, the outcomes are radically different as the proportion of patients who remained on treatment for ≥6 months with apalutamide was 80% in the AAP-naïve cohort versus 43% in the post-AAP cohort. This represents a new standard that demonstrates the patient experience, useful for physicians when considering options to continue treatment until the patient is no longer clinically benefitting.

In this report of mCRPC cohorts of trial ARN-509-001, we evaluate apalutamide activity in patients with and without prior abiraterone acetate and prednisone (AAP) therapy using Prostate Cancer Working Group 2 (PCWG2) criteria (13), including swim lanes that illustrate the duration of treatment as an additional indicator of meaningful clinical benefit that reflects the total patient experience on this trial (14).

Materials and Methods

Patients

Patients with mCRPC were enrolled in one of two cohorts: an AAP-naïve cohort (AAP-naïve) and an AAP-pretreated cohort (post-AAP). Results from a third cohort of patients with non-metastatic CRPC were reported separately (12). All patients had pathologically proven prostate adenocarcinoma and had received ongoing androgen deprivation therapy with a gonadotropin-releasing hormone analogue or orchiectomy, and had castration levels of serum testosterone of ≤50 ng/dL within 4 weeks of study enrollment; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1; a life expectancy of ≥3 months; corrected QT interval of ≤ 450 ms; and adequate cardiac, renal, hepatic, and bone marrow function.

Patients in the AAP-naïve cohort had disease progression, based on either a rising prostate-specific antigen (PSA) ≥2 ng/mL (within 2 weeks of study enrollment) or measurable disease (new or progressive tissue disease based on CT/MRI scans) by modified Response Evaluation Criteria in Solid Tumors (RECIST 1.0; ref. 15) or radiographic progression (≥2 new bone lesions, PCWG2 criteria; ref.13). Patients in both cohorts were excluded if they had been treated previously with enzalutamide, ketoconazole, or chemotherapy for mCRPC or had a history of seizure or conditions that predispose to seizures. Patients in the post-AAP cohort were also required to have received ≥6 months of abiraterone acetate treatment to ensure therapeutic benefit prior to disease progression.

Institutional review boards approved the study, which was conducted according to the principles set forth in the Declaration of Helsinki, the International Conference on Harmonisation, and the Guidelines for Good Clinical Practice. Data were anonymized to protect the identities of subjects involved in the research. All patients gave written informed consent.

Study design

Patients received apalutamide 240 mg/day (11) on a continuous daily dosing regimen, and remained on study treatment until either evidence of both PSA progression and radiographic progression or clinical progression alone, development of unacceptable toxicity, or withdrawal of consent (Supplementary Fig. S1A). Dose modifications (e.g., short treatment breaks or dose reduction) were allowed in case of treatment-related toxicities.

Endpoints

PSA response rate was assessed using the PCWG2 criteria (13), with slight modifications. The primary endpoint was a 50% or greater decline in PSA from baseline at 12 weeks (or earlier for those who discontinued therapy). The maximal PSA change at any time on the study was also reported for each patient. The secondary endpoints were time to PSA progression, measured from the start of treatment until the criteria for PSA progression were met, according to the modified PCWG2 (≥25% and ≥2 ng above nadir, confirmed ≥3 weeks later or ≥25% and ≥2 ng/mL after 12 weeks in the absence of decline); progression-free survival (PFS), measured from the start of the treatment until radiographic disease progression or death (based on investigator's assessment); and objective response rate, measured as changes in target and nontarget lesions relative to baseline reported every 12 weeks using modified RECIST 1.0 (15) and PCWG2 criteria (13).

Tumor evaluations were performed every three cycles (12 weeks). Safety was assessed continuously from the first dose until 30 days after the last dose or until the resolution or stability of any NCI Common Terminology Criteria for Adverse Events Version 4.0 treatment-emergent or treatment-emergent drug-related toxicity. Disease progression was defined as evidence of both PSA progression (≥25% and > 2 ng/mL above PSA nadir confirmed ≥3 weeks later or > 2 ng/mL above baseline PSA after 12 weeks) and radiographic progression (soft tissue metastases by modified RECIST; ref. 15) seen on CT/MRI scans and/or bone metastases by ^{99m}Tc-methylene diphosphate bone scans by PCWG2 criteria, and clinically by the occurrence of a skeletal-related event, pain progression, or worsening of disease-related symptoms requiring new systemic anti–prostate cancer therapy. Per Prostate Cancer Working Group 3 (PCWG3) recommendations (14), swim lane plots were generated to track the time on apalutamide treatment for individual patients with duration of ≥6 months as a measure of clinical benefit.

Statistical analysis

The study was expected to enroll 20 patients in the AAP-naïve cohort. In the post-AAP cohort, enrollment was staged such that if at least 1 in 10 patients achieved ≥50% PSA decline at 12 weeks, expansion to 20 total patients was planned.

All patients who received at least one dose of apalutamide were included in the efficacy and safety analyses. In the post-AAP cohort, 3 patients were excluded (1 without evidence of progressive mCRPC, 2 who did not receive prior abiraterone acetate for at least 6 months) from the efficacy analysis. Summary statistics were reported for demographics, baseline characteristics, adverse events, vital signs, and clinical laboratory evaluations. The change in PSA at 12 weeks relative to baseline (primary endpoint) and the maximal change in PSA at any time on study relative to baseline are presented in waterfall plots and

descriptively summarized. The Kaplan–Meier method was used to estimate the median time to events and 95% confidence intervals (CI).

Results

Patients

Patients were enrolled in the phase II portion of the study from November 2011 to June 2012. The cut-off date for the final data analysis was December 31, 2014. Patients had a median age of 68 years in the AAP-naïve cohort and 67 years in the post-AAP cohort, median times since initial diagnosis were 61 months and 107 months, respectively (Table 1). Roughly half of the patients had an ECOG PS of 0 (52% and 62% in the AAP-naïve and post-AAP cohorts, respectively). Gleason score ≤ 7 at initial diagnosis was observed in 28% and 67% of the AAP-naïve and post-AAP cohorts, respectively. Three patients were excluded from the efficacy analysis in the post-AAP cohort; 1 failed to meet criteria for progressive metastatic disease and 2 did not receive abiraterone acetate for $\geq$6 months (Supplementary Fig. S1B).

PSA responses

The 12-week PSA response rate was 88% (22/25; 95% CI, 69–97) for AAP-naïve patients and 22% (4/18; 95% CI, 6–48) for post-AAP patients (Table 2; Fig. 1A and B). The maximal percent PSA decline from baseline for patients (i.e., $\geq$50% decline at any time) was 92% (23/25) for AAP-naïve patients and 28% (5/18) for post-AAP patients (Fig. 1C and D).

The median duration of apalutamide treatment was 21 months (range: 2.6–37.5) for AAP-naïve and 4.9 months (range: 1.3–23.2) for post-AAP cohorts. The duration of apalutamide treatment in individual patients ordered sequentially from lowest to highest 12-week PSA response rate is shown in swim lane plots (14) for AAP-naïve patients (Fig. 2A) and post-AAP patients (Fig. 2B). These plots illustrate the individual patient experience over time. Notable is the disconnect between the degree of PSA decline and time on therapy in many patients. By cohort, a total of 80% (20/25; 95% CI, 59–93) and 64% (16/25; 95% CI, 43–82) of AAP-naïve patients and 43% (9/21; 95% CI, 22–66), and 10% (2/21; 95% CI, 1–30) of post-AAP patients remained on treatment with apalutamide for 6+ and 12+ months, respectively.

Table 1. Patient characteristics

	AAP-naïve mCRPC ($n = 25$)	Post-AAP mCRPC ($n = 21$)
Age, years, median (range)	68 (53–91)	67 (48–83)
Baseline PSA, ng/mL		
n	25	21
Median (range)	14.7 (1.1–2552.1)	58.4 (1.1–6074.3)
Baseline LDH, U/L		
n	18	18
Median (range)	192.5 (89–518)	233.0 (149–1075)
Baseline ALK-P, U/L		
n	25	20
Median (range)	78.0 (44–802)	96.5 (33–737)
ECOG PS, *n* (%)		
0	13 (52)	13 (62)
1	12 (48)	8 (38)
Gleason score at initial diagnosis, *n* (%)		
$\leq$7	7 (28)	14 (67)
8–10	18 (72)	6 (29)
Missing	0	1 (5)
Time since initial diagnosis, months, median (range)	61 (10–191)	107 (16–236)
Primary treatment, *n* (%)		
Prostatectomy ± salvage radiation	10 (40)	13 (62)
Primary radiation	11 (44)	12 (57)
No primary or salvage radiation	13 (52)	5 (24)
Metastases		
Bone	11 (44)	8 (38)
Soft tissue	9 (36)	5 (24)

Abbreviations: ALK-P, alkaline phosphatase; LDH, lactate dehydrogenase.

Table 2. Efficacy outcomes

	AAP-naïve mCRPC ($n = 25$)	Post-AAP mCRPC ($n = 18$)
PSA response rate[a], *n* (%)		
12 weeks	22 (88)	4 (22)
24 weeks	20 (80)	1 (6)
36 weeks	17 (68)	0
Maximal PSA response[b], *n* (%)	23 (92)	5 (28)
Median time to PSA progression, months (95% CI)	18.2 (8.3–NR)	3.7 (2.8–5.6)
Median PFS[c], months (95% CI)	NR (16.7–NR)	NR (NR–NR)
ORR[d], n/N (%)	4/8 (50)	0/10 (0)

Abbreviations: ORR, objective response rate.

[a]$\geq$50% decline in PSA from baseline from PCWG2 criteria.

[b]Maximal PSA response is the maximal percent reduction post baseline for the individual patient at any time point.

[c]Per protocol, patients who had progressive disease that was not confirmed prior to subsequent therapy were censored back to their last assessment prior to subsequent therapy.

[d]Eight patients in the AA-naïve cohort and 10 patients in the post-AAP mCRPC cohort had measurable disease at baseline.

Secondary outcomes

The median time to PSA progression was 18.2 months (95% CI, 8.3 months–not reached [NR]) for AAP-naïve patients and 3.7 months (95% CI, 2.8–5.6 months) for post-AAP patients (Table 2; Fig. 3A). The median PFS was NR (95% CI, 16.7 months–NR) for AAP-naïve patients after 22.1 months of follow-up, and NR (95% CI, NR–NR) for post-AAP patients after 5.6 months of follow-up, respectively (Fig. 3B).

Based on RECIST, of the eight AAP-naïve patients with measurable target lesions at baseline, tumor regression to a partial response was observed in four and stable disease in two for 14 months and 2.8 months. There were no tumor regressions in the 10 post-AAP patients, although four had stable disease for 2.5, 3.8, 5.1, and 5.6 months, respectively.

Safety

The most common treatment-emergent adverse events in AAP-naïve patients were fatigue, nausea, and abdominal pain; fatigue, diarrhea, and nausea were the most common treatment-emergent adverse events in post-AAP patients (Table 3). Most treatment-emergent adverse events were of grade 1 or 2. The only grade 3 treatment-emergent adverse events reported in more than one patient in each cohort was anemia in 2 AAP-naïve patients (8%) and back pain in 2 post-AAP patients (10%). The most common drug-related treatment-emergent adverse events were fatigue (48% and 52%, respectively), diarrhea (32% and 19%, respectively), and nausea (32% and 24%). Serious adverse events were reported by 8 (32%) AAP-naïve patients and 6 (29%) post-AAP patients, but none were assessed as drug related. No adverse events of fall were reported

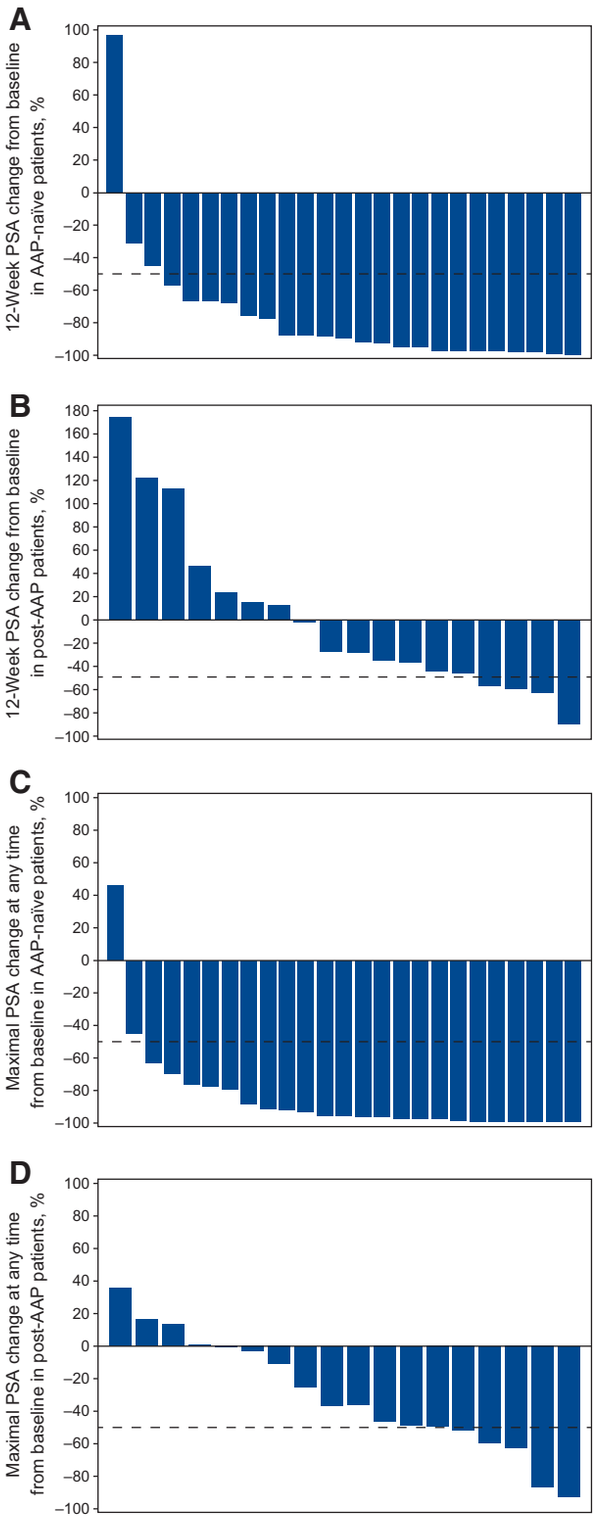

Figure 1.
Waterfall plots showing 12-week PSA response in patients with AAP-naïve mCRPC (**A**) and post-AAP mCRPC (**B**), and maximal PSA response at any time point in patients with AAP-naïve mCRPC (**C**) and post-AAP mCRPC (**D**).

as serious, and no seizures were reported. Dose modifications (reduction and/or interruption) occurred in 7 (28%) AAP-naïve patients and 8 (38%) post-AAP patients; one dose reduction occurred in 3 (12%) AAP-naïve patients and 1 (5%) post-AAP patient, and at least one dose interruption occurred in 5 (20%) AAP-naïve patients and 8 (38%) post-AAP patients. The median number of days with treatment interruption was 18 (range: 3–29) for AAP-naïve patients and 11 (range: 5–27) for post-AAP patients. Most dose reductions and interruptions were because of adverse events. The adverse events that led to permanent treatment discontinuation were abdominal pain [$n = 1$ (4%)], gastrointestinal hemorrhage [$n = 1$ (4%)], large intestinal hemorrhage [$n = 1$ (4%)], and arthralgia [$n = 1$ (4%)] in the AAP-naïve cohort (in 4/25 patients), and fatigue [$n = 1$ (5%)] and muscle disorder [$n = 1$ (5%)] in the post-AAP patient cohort (in 1 of 21 patients). Disease progression was the most common reason for treatment discontinuation. Discontinuation due to adverse events was observed in 12% (3/25 patients) of AAP-naïve patients and in 5% (1/21 patients) of post-AAP patients. Two patients in the AAP-naïve cohort died from disease progression.

Discussion

This is the first study to prospectively show the impact of prior AAP exposure on outcome, and underscores the limitations in relying solely on PSA response to assess treatment benefit. For AAP-naïve and AAP-exposed patients, the PSA response rates after 12 weeks on study following treatment with apalutamide were 88% (22/25) and 22% (4/18), and median time to PSA progression 18.5 and 3.8 months, respectively, suggesting that the drug was effective in the former and had limited efficacy for the latter. Arguably more important for the post-AAP group, however, was that 43% (9/21) of patients were still on treatment for 6 months or longer (95% CI, 22–66), including 5 who had a PSA decline of >50%. The results show that simple reliance on the ≥50% decline in PSA as the "indicator of a favorable treatment effect" for a defined clinical cohort can underestimate the proportion of patients who may benefit. The recognized heterogeneity of mCRPC can result in progression in individual lesions as opposed to systemic progression that is not always reflected by PSA response (16). It is for this reason that PCWG3 defined the outcome measure of "no longer clinically benefitting" to ensure that drugs from which patients are benefitting are not stopped prematurely (14).

Overall, the median duration of drug exposure in the AAP-naïve cohort (21 months) compared favorably with the median duration of exposure observed in those with chemotherapy-naïve mCRPC treated with other AR-targeted therapies such as abiraterone acetate (13.8 months; ref. 8) and enzalutamide (16.6 months) in the first-line setting (3). Direct comparisons, however, are limited by the small sample size enrolled. The most common adverse events (primarily grade 1 or 2) were fatigue, diarrhea, nausea, and abdominal pain. Grade 3 and 4 adverse events were infrequent. Most adverse events of rash or pruritus were grade 1 and 2 and did not lead to dose modifications. One patient in the post-AAP cohort had a grade 3 erythematous rash that led to dose interruption.

Given the potential for seizures due to off-target effects of AR antagonists on $GABA_A$ receptors (1, 17, 18), safety was an important component of this study. In preclinical models, apalutamide

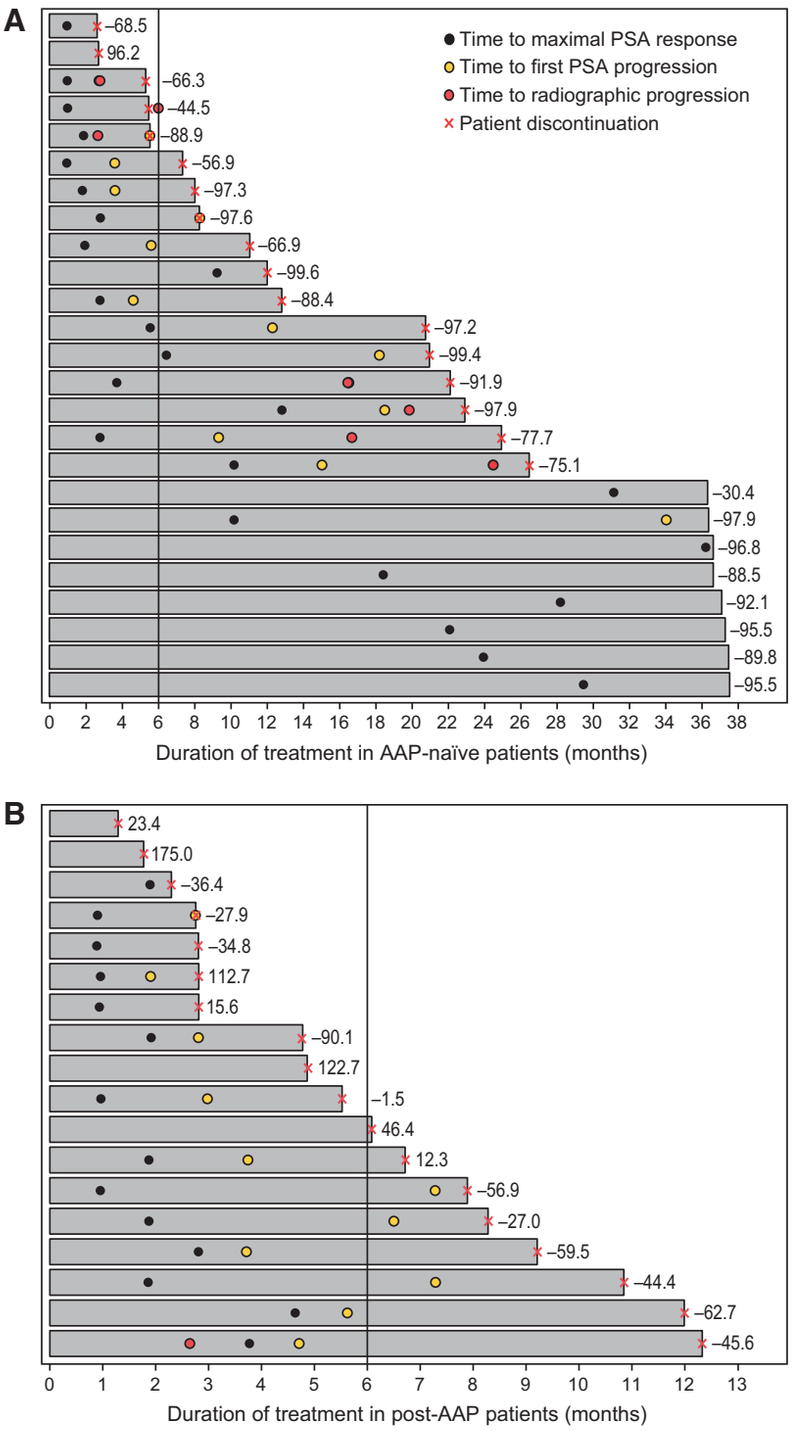

Figure 2.

Swim lane plots showing duration of apalutamide treatment (*x*-axis) aligned sequentially in individual patients from shortest (top lane) to longest (bottom lane) treatment duration (*y*-axis) in the AAP-naïve mCRPC (**A**) and post-AAP mCRPC (**B**) cohorts. Respective 12-week PSA response rates are shown to the right of the lanes. Vertical line demarcates patients on treatment for ≥6 months as a measure of clinical benefit.

demonstrated a promising profile, with relatively low brain penetration and a high therapeutic index. Importantly, no seizure activity was observed in this clinical study, which enrolled a total of approximately 100 patients (12). This not only suggests the potential to use apalutamide as a single agent, but supports development of future combination therapies in which the tolerability as well as the safety profile of a drug are important aspects to take into consideration when combining drugs.

Until 2010, docetaxel was the only approved treatment to show an overall survival benefit in mCRPC (19, 20). Now, several new therapeutic approaches have been shown to prolong life and are approved by the FDA (3–10). Given the rapid pace of drug development and drug approvals that continue to expand the range of treatment options available to patients with mCRPC, the questions of sequencing and testing combinatorial strategies have become paramount. As the biologic factors contributing

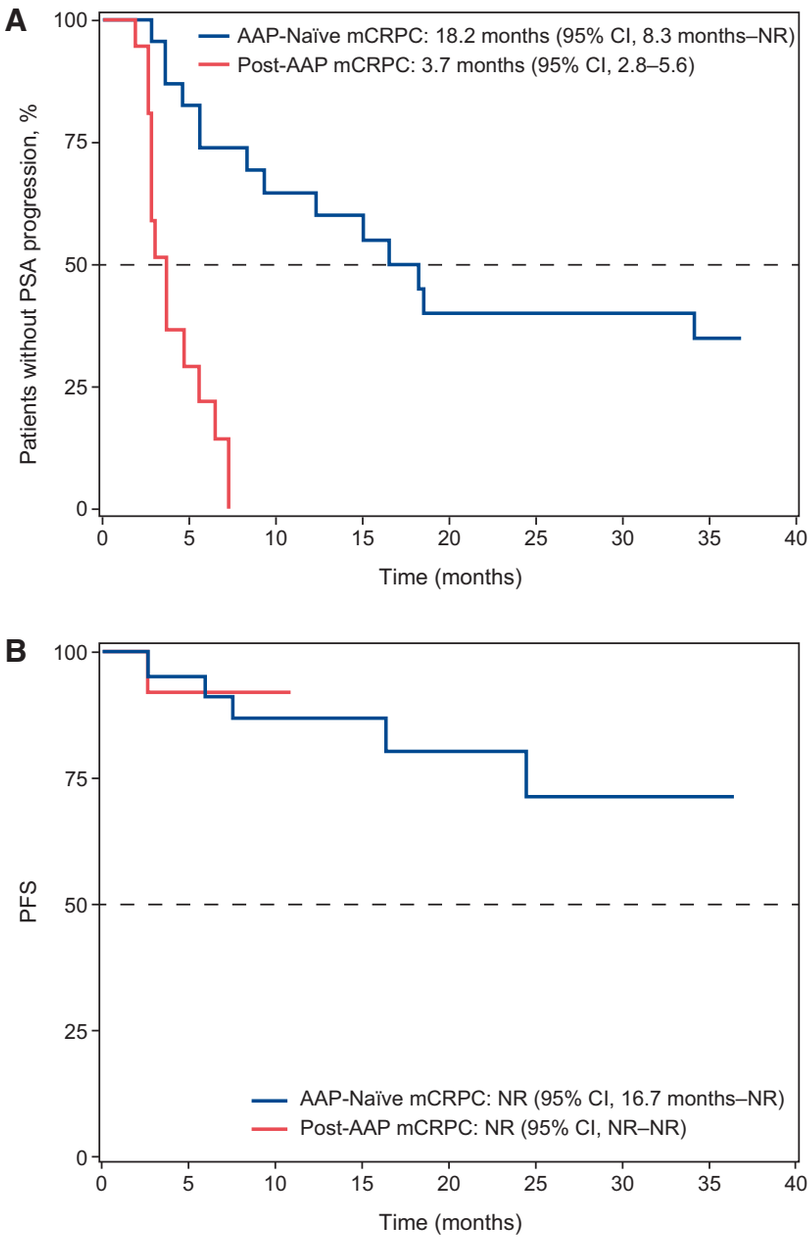

Figure 3.
Secondary outcomes. Time to PSA progression (**A**), and PFS (**B**). Per protocol, patients were allowed to discontinue treatment for PSA progression.

to intrinsic or early resistance to abiraterone acetate may differ from acquired resistance after an initial response and predict limited efficacy for subsequent treatment with AR-targeted agents (21), a minimum of 6 months of prior abiraterone acetate was an eligibility requirement in the post-AAP cohort, thereby ensuring that the patients had experienced prior therapeutic benefit to the first AR-targeted drug. The efficacy of apalutamide in patients who had shorter exposure times to AAP (3–6 months) remains an open question.

Although both groups had some degree of response to treatment, the different times on treatment for the two cohorts highlight the importance of characterizing patients based on prior exposure and response to prior therapy (14). Also unknown is whether outcomes would be better if combinations of agents that target different points on the AR-signaling axis, such as abiraterone acetate and apalutamide, were utilized, relative to sequencing the drugs as was done in this trial.

Overall, apalutamide was safe and well tolerated in patients with mCRPC. The safety profile is consistent with that of the phase I trial in mCRPC as well as the phase II data in nonmetastatic CRPC (12). Evidence of clinical benefit in patients with mCRPC was demonstrated in both AAP-naïve (80%) and post-AAP (43%) patients who remained on treatment for 6 months or longer. These results support further clinical development of apalutamide, which is ongoing across the spectrum of advanced prostate disease, including randomized phase III trials in nonmetastatic CRPC (NCT01946204; ref. 22) and mCRPC (NCT02257736; ref. 23).

Table 3. Safety

Treatment-emergent adverse events[a]	AAP-naïve mCRPC ($n = 25$) All grades	AAP-naïve mCRPC ($n = 25$) Grade ≥3	Post-AAP mCRPC ($n = 21$) All grades	Post-AAP mCRPC ($n = 21$) Grade ≥3
Fatigue	15 (60)	0	11 (52)	1 (5)
Nausea	14 (56)	0	7 (33)	0
Abdominal pain	12 (48)	1 (4)	2 (10)	0
Diarrhea	11 (44)	0	8 (38)	0
Dyspnea	7 (28)	1 (4)	3 (14)	0
Rash	7 (28)	0	0	0
Arthralgia	6 (24)	0	6 (29)	0
Back pain	6 (24)	0	4 (19)	2 (10)
Cough	6 (24)	0	2 (10)	0
Anemia	5 (20)	2 (8)	3 (14)	0
Hot flush	5 (20)	0	0	0
Decreased appetite	4 (16)	0	5 (24)	0
Dizziness	4 (16)	0	2 (10)	0
Insomnia	4 (16)	0	1 (5)	0
Peripheral edema	4 (16)	0	1 (5)	0
Upper respiratory tract infection	4 (16)	0	1 (5)	0
Musculoskeletal chest pain	4 (16)	0	3 (14)	1 (5)
Vomiting	4 (16)	0	4 (19)	1 (5)
Headache	3 (12)	0	4 (19)	0
Constipation	2 (8)	1 (4)	5 (24)	1 (5)
Flatulence	4 (16)	0	0	0
Musculoskeletal pain	2 (8)	0	6 (29)	1 (5)

[a]Based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 reported in >15% of patients in either cohort.

Disclosure of Potential Conflicts of Interest

D.E. Rathkopf is a consultant/advisory board member for Janssen. N.D. Shore reports receiving speakers bureau honoraria from AbbVie, Amgen, Astellas, Bayer, Dendreon, Ferring, Janssen, Medivation, Sanofi, and Tolmar. R.F. Tutrone reports receiving speakers bureau honoraria from Astellas/Medivation, Dendreon and Janssen, and reports receiving commercial research grants from Astellas, Bayer, Dendreon, and Janssen. J.J. Alumkal reports receiving commercial research grants from Aragon Pharmaceuticals. C.J. Ryan reports receiving speakers bureau honoraria from Janssen. M. Saleh reports receiving speakers bureau honoraria from Genentech. H.I. Scher is a consultant/advisory board member for Astellas, BIND Pharmaceuticals, Blue Earth Diagnostics, Bristol-Myers Squibb, Clovis Oncology, Elsevier's Practice Update website, Ferring Pharmaceuticals, Janssen, Med IQ, Medivation, Merck, Roche, Sanofi, Takeda Millennium, and WCG Oncology, reports receiving commercial research grants from Illumina Inc., Innocrin Pharma, Janssen, and Medivation, and is on the Board of Directors for Asterias Biotherapeutics. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

D.E. Rathkopf had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acknowledgments

Writing assistance was provided by Ira Mills, PhD, and Hajira Koeller, PhD, of PAREXEL, and was funded by Janssen Global Services, LLC. The current affiliation of Edna Chow Maneval is Ignyta, Inc., San Diego, CA.

Grant Support

This study was funded by Aragon Pharmaceuticals, Inc. Janssen Research & Development, LLC, is performing work on behalf of Aragon. The sponsor was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation and review of the manuscript.

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Received October 10, 2016; revised December 5, 2016; accepted January 22, 2017; published OnlineFirst February 17, 2017.

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