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Apalutamide in the treatment of castrate-resistant prostate cancer: evidence from clinical trials

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Abstract: Apalutamide (ARN-509) is a second-generation androgen receptor (AR) antagonist that was developed to inhibit AR-mediated prostate cancer cell proliferation. Following the initial promising clinical efficacy results in phase I and II clinical trials of patients with metastatic castrate-resistant prostate cancer (CRPC), apalutamide has been investigated in several phase III trials. Particular interest has focused on the development of effective therapy for the prevention of disease progression in patients with nonmetastatic (nm or M0) CRPC, especially patients who have a rapid prostate-specific antigen (PSA) doubling time that is indicative of shorter bone metastasis-free survival and associated with significant morbidity and mortality. The results from the phase III SPARTAN trial were recently published and reported a significant benefit of apalutamide relative to placebo in patients with nmCRPC and a high risk of metastatic progression. The study noted marked improvement in the primary endpoint of metastasis-free survival as well as several relevant secondary clinical endpoints, including time to symptomatic progression. These results led to the United States Food and Drug Administration (US FDA) approval of apalutamide in the nmCRPC setting in February 2018. This review summarizes the clinical development of apalutamide, culminating with the pivotal SPARTAN trial as well as other phase III trials which may further expand potential indications for this agent in the near future.

Keywords: androgen receptor, apalutamide, castration-resistant prostate cancer, clinical trials, metastasis-free survival, nonmetastatic castration-resistant prostate cancer

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Introduction

The natural history of prostate cancer is highly variable and can extend over many years. However metastatic castrate-resistant prostate cancer (mCRPC) is an incurable disease that has a median survival of about 2.5–3 years.[1] mCRPC can arise from earlier prostate cancer through a number of pathways. First, following definitive primary treatment for localized prostate cancer, patients may experience disease progression, most commonly manifesting as a rise in prostate-specific antigen (PSA). At this point their disease is still castrate-sensitive and treatment with androgen deprivation therapy (ADT) can suppress PSA and delay further progression, frequently for several years. Alternatively, patients can be diagnosed with *de novo* metastatic prostate cancer, with metastatic disease apparent on conventional imaging at the time of diagnosis. In this situation too, prostate cancer is still sensitive to testosterone suppression, and ADT remains a mainstay of therapy. However, eventually, in either situation prostate cancer will develop resistance to ADT, progressing to a castrate-resistant state. Here the distinction can be made between metastatic and nonmetastatic CRPC (nmCRPC), the former with detectable metastases on scans, and the latter as a systemic disease which has also developed resistance to ADT, manifesting as rising PSA, but with no detectable metastases on scans. A number of agents have been approved by the United States Food and Drug Administration

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(US FDA) for the treatment of patients with mCRPC, but until very recently, there were no US FDA-approved agents in the nmCRPC space.

Just as there is considerable heterogeneity in localized prostate cancer, nmCRPC is also highly heterogeneous, with some patients having aggressive disease that can rapidly metastasize and lead to death, while others experience a much more indolent course. PSA measurements in these patients are one indicator of worse prognosis. Both elevated absolute PSA level and shorter PSA doubling time (PSADT) have been demonstrated to be associated with worse clinical outcomes including shorter time to first bone metastasis, shorter bone metastasis-free survival and shorter overall survival (OS).[2–4] In particular there is an inflection point at a PSADT of around 8 months, where shorter PSADTs are associated with a dramatically increased risk of metastasis or death.[2] Bone metastases are a common manifestation of disease progression in CRPC and are associated with significant morbidity and mortality.[5] Thus, delaying or preventing progression to a detectable metastatic state was an unmet clinical need in this patient population. The recently published results of SPARTAN, a placebo-controlled phase III trial of apalutamide, a next-generation AR inhibitor, in men with nmCRPC, demonstrated clinical benefit in this patient population leading to the US FDA approval of apalutamide in nmCRPC.[6] This review summarizes the development of apalutamide, and presents the data of its activity in prostate cancer, culminating in the approval of this agent in nmCRPC as well as ongoing phase III trials in other prostate cancer settings.

Androgen receptor antagonists and ARN-509

The importance of androgen receptor (AR) signaling in the pathophysiology of prostate cancer has been recognized for many decades ever since the pioneering work of Charles Huggins in using ADT for metastatic prostate cancer.[7] Even once CRPC develops, AR signaling continues to play a role through a number of proposed mechanisms, including AR gene mutation or amplification, increased AR expression, changes in coregulatory molecules, as well as increased intra-tumoral androgen synthesis.[8] The first-generation AR antagonists ('anti-androgens') include flutamide, nilutamide and bicalutamide. These agents have been used in combination with ADT as part of a combined androgen blockade (CAB) in castrate-sensitive prostate cancer. Although the benefit of adding an AR antagonist to either medical or surgical castration has not consistently demonstrated an OS benefit in randomized trials in this patient population, a large meta-analysis of 27 trials did suggest a 3% OS improvement of CAB compared with monotherapy.[9] These agents are frequently used as a lead-in therapy when initiating ADT with a gonadotropin-releasing hormone (GnRH) agonist in patients with high PSA or other evidence of high-volume metastatic disease with the aim of avoiding disease flares due to an initial testosterone surge at the beginning of treatment. Bicalutamide is a commonly used AR antagonist in contemporary clinical practice for castrate-sensitive prostate cancer. Like all AR antagonists, bicalutamide can undergo an antagonist to agonist transformation in the setting of CRPC resulting in increased PSA and tumor progression.[10] Anti-androgen withdrawal is a potential therapeutic maneuver in this situation which can lead to PSA response and potentially prolong progression-free survival (PFS) in a minority of patients.[11–14]

The limitations of first-generation AR antagonists, including a weak affinity for the AR and potential for agonist activity, led to further efforts to develop more potent second-generation AR antagonists.[15] Enzalutamide is one such agent that demonstrated clinical activity in CRPC, and was initially selected to move forward into clinical testing based on data suggesting greater affinity for the AR relative to bicalutamide. Clinical efficacy of enzalutamide in mCRPC patients was demonstrated by the AFFIRM trial,[16] in patients who previously received docetaxel-based chemotherapy, and in the PREVAIL trial,[17] among patients who were chemotherapy-naïve. Both trials were placebo-controlled and showed an OS advantage of enzalutamide in their respective settings. Abiraterone acetate is another agent targeting the androgen-signaling axis which has been used extensively in CRPC patients, although it is not a direct AR inhibitor. As an inhibitor of CYP17A, an enzyme critical for both testicular and extragonadal androgen synthesis, abiraterone acetate exerts its anticancer effects by dramatically lowering testosterone levels. When given in combination with low dose prednisone to avoid mineralocorticoid excess, abiraterone has been shown to prolong OS in mCRPC patients following chemotherapy as well as in chemotherapy-naïve patients in COU-AA-301 and COU-AA-302 trials respectively.[1,18]

Apalutamide, initially known as ARN-509, is another next-generation AR antagonist which was shown to bind with high affinity to the ligand-biding domain of the AR, inhibiting its transport to the nucleus and DNA binding capacity.[15] The potential advantages of apalutamide relative to enzalutamide that came to light during its preclinical development included greater antitumor activity at a lower dose, higher tumor/plasma ratio and lower concentrations in the central nervous system, potentially indicating a lower risk of seizure activity.[19]

Preclinical evidence for apalutamide

Apalutamide is a synthetic compound that was discovered using structure/activity relationship-guided medicinal chemistry.[20] It was identified for further development based on an initial assessment of its agonist and antagonist activity of AR signaling in a prostate cancer cell line, LNCaP/AR(cs), engineered to overexpress AR.[19] Apalutamide binds AR in the same ligand-binding domain as bicalutamide but with greater affinity, and unlike bicalutamide, retains full antagonist activity in the setting of AR overexpression. Furthermore, apalutamide was shown in competitive-binding assays to be selective for AR *versus* other nuclear hormone receptors.[19] Apalutamide was additionally shown in preclinical studies to impair AR nuclear localization and consequently DNA binding (both essential steps for AR-mediated transcriptional regulation) more effectively than bicalutamide. In mouse xenograft tumor models of LNCaP/AR(cs) cells that overexpressed AR, apalutamide more effectively reduced tumor volume than bicalutamide and was more efficacious at reducing tumor volume per unit dose and per unit steady-state plasma levels than enzalutamide.[21] When measured in mice, tumor/plasma ratios of apalutamide were considerably higher than tumor/plasma ratios of enzalutamide, which was hypothesized to be due to decreased plasma protein binding of apalutamide, and allowed for more robust intratumoral AR antagonism. Both apalutamide and enzalutamide are thought to be weak antagonists of γ-aminobutyric acid $(GABA)_A$ receptors in the brain, which is hypothesized to contribute to seizure activity observed with enzalutamide.[22] However, penetrance of the blood–brain barrier is potentially different among the two agents as apalutamide brain levels measured in mice were lower than enzalutamide levels following treatment, which suggested the possibility of a lower seizurogenic potential of apalutamide.

Phase I trial of apalutamide

The first-in-human phase I study of apalutamide enrolled 30 patients with progressive mCRPC.[23] Eligibility criteria included patients with histologically confirmed prostate adenocarcinoma without neuroendocrine differentiation who had progressive mCRPC based on new or progressive soft tissue or bone metastases on scans, or a minimum of three rising PSA levels at least 1 week apart with the last PSA $\geq$ 2 ng/ml. Patients were required to maintain castrate levels of testosterone (<50 ng/dl) and were excluded from the trial if they had received prior ketoconazole (a first-generation androgen synthesis inhibitor) or more than two prior regimens of taxane-based therapy. About 9 months into the trial, the protocol was amended to exclude patients previously treated with enzalutamide or abiraterone. Patients were assigned sequentially to escalating doses of apalutamide using a 3 + 3 design, with an initial dose at 30 mg daily and escalated up to 480 mg daily across nine different dose levels. At doses $\geq$300 mg, patients were allowed to switch to twice-daily regimens. Dose-limiting toxicities in this trial were defined as any grade 3/4 nonhematologic toxicity or grade 4 hematologic toxicity persisting for more than 5 days. The primary objectives of the trial were to determine a recommended phase II dose for apalutamide, as well as to assess pharmacokinetics, safety and tolerability of the drug.

Enrolled patients had a median age of 68 years and a median PSA of 42 ng/ml, with 87% having bony metastases and 53% having soft tissue metastases. The median duration of study participation was 9.5 months, and no patients discontinued the study due to drug-related toxicity. Overall, apalutamide was well tolerated with the most common adverse event (AE) being fatigue (47%), all restricted to grade 1 or 2. No grade 4 or 5 toxicities were observed and only four grade 3 toxicity events of any kind were noted, all considered unrelated to study treatment. No seizures were reported at any dose level.

Reduction of uptake of fluoro-5α dihydrotestosterone (FDHT) on positron emitted tomography (PET) was used as a pharmacodynamic marker, with the plateau in the reduction in FDHT uptake reflective of effective targeting of drug to AR. The apalutamide dose level with optimal FDHT-PET uptake was determined to be $\geq$120 mg, consistent with saturation of AR binding. The recommended phase II dose was determined to be 240 mg daily

based on the integration of clinical data and data from preclinical models, although two additional doses of 300 mg and 480 mg daily were also tested to establish the safety margin of the drug. Dose escalation to 480 mg daily did not identify a maximum-tolerated dose. Overall, across all cohorts, PSA declines at 12 weeks of ⩾50% reduction from baseline were observed in 14 of 30 patients (46.7%) and the median PSA change from baseline at 12 weeks was −43.2%, suggesting substantial clinical activity.

Phase II trial of apalutamide

Following these initial encouraging phase I results, clinical investigation of apalutamide proceeded into a phase II study in CRPC patients, with three expansion cohorts: (1) patients with nmCRPC (2) patients with mCRPC who were abiraterone-naïve and (3) patients with mCRPC following treatment with abiraterone.

Results from the nmCRPC cohort were first published in 2016.[24] This cohort included patients who had histologically confirmed prostate cancer and had received ongoing ADT with a GnRH analog or orchiectomy. All patients had castrate levels of serum testosterone (⩽50 ng/dl) and no radiographic evidence of distant metastases assessed on (conventional) central imaging review. Patients previously treated with enzalutamide, abiraterone or ketoconazole were excluded as were patients with prior history of seizures or on medications known to increase seizure potential. This trial selected patients at high risk for developing metastases, based on a PSA ⩾ 8 ng/ml measured within 3 months of enrollment or a PSADT ⩽ 10 months. There was no prespecified PSA threshold for study inclusion. The primary endpoint of the study was a 12-week post-treatment percentage change in PSA relative to the baseline and a maximal change in PSA at any time during the study, assessed using Prostate Cancer Working Group 2 (PCWG2) criteria.[25] Secondary endpoints included time to PSA progression and metastasis-free survival according to response evaluation criteria in solid tumors (RECIST), with imaging evaluations done every 16 weeks and independently verified by central review.

Overall, 51 patients were enrolled in this high-risk nmCRPC phase II expansion cohort, although 4 patients were excluded from efficacy analyses due to the presence of metastatic disease. Patients were treated with 240 mg apalutamide daily until documented disease progression, based on the dose defined in the phase I study. The median patient age was 71, the median baseline PSA was 10.7 ng/ml (range 0.5–201.7) and 80% of patients had received prior therapy with a first-generation AR antagonist (bicalutamide, nilutamide or flutamide). After a median follow up of 28.0 months, 18 patients (35%) still remained on the study whereas 9 (18%) dropped out due to AEs and 11 (22%) dropped out due to disease progression, defined as evidence of both PSA progression (according to PCWG2 criteria) and radiographic progression or evidence of clinical progression alone (significant pain requiring intervention or a skeletal-related event). The median treatment duration was 26.9 months, with 89% of patients experiencing a ⩾50% PSA decline at 12 weeks. The median PSA change from baseline to week 12 was −85% while median maximal change in PSA was −93%. Median time to PSA progression was 24.0 months while the median metastasis-free survival was not reached. Apalutamide was well tolerated in this patient population with fatigue once again the most common AE (61% any grade, 4% grade ⩾3). These promising results in the nmCRPC population supported the further development of apalutamide in this patient population and influenced the design of SPARTAN phase III randomized trial.

The results from the remaining two cohorts of the phase II study of apalutamide in CRPC patients were published in 2017.[26] These two cohorts of men with metastatic CRPC, included 25 patients who were chemotherapy and abiraterone-naïve and 21 patients who had received prior abiraterone treatment. The general patient inclusion criteria and treatment (apalutamide 240 mg daily) in these two cohorts were similar to the high-risk nmCRPC cohort described previously. Patients in the post-abiraterone cohort were required to have received at least 6 months of prior abiraterone treatment. The median age in the abiraterone-naïve and post-abiraterone cohorts were similar at 68 and 67 respectively. Not surprisingly, the median baseline PSA level was higher in the more heavily pretreated cohort (58.4 ng/ml compared with 14.7 ng/ml.) The primary endpoint of 12-week PSA response rate (at least 50% decline from baseline) was 88% for abiraterone-naïve patients and 22% for post-abiraterone patients. The median time to PSA progression was 18.2 months for abiraterone-naïve patients and only 3.7 months for post-abiraterone patients. The median duration of apalutamide treatment

was 21 months for abiraterone-naïve and 4.9 months in the post-abiraterone cohort. However, 80% and 43% of patients in abiraterone-naïve and post-abiraterone cohorts respectively remained on treatment for at least 6 months suggesting that almost half of patients in the post-abiraterone cohort still benefited from apalutamide treatment, showing no evidence of clinical or radiographic progression, despite having suboptimal PSA responses. The safety profile of apalutamide in these two cohorts was consistent with previously reported data in the phase I trial and the high-risk nmCRPC cohort. These results informed the design of a number of phase III trials, discussed below.

SPARTAN phase III trial of apalutamide in nmCRPC

SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) was an international, randomized, double-blind, placebo-controlled phase III trial of apalutamide in patients with nmCRPC.[6] The trial was conducted at 332 sites in 26 countries in North America, Europe and the Asia-Pacific region and enrolled a total of 1207 patients from October 2013 to December 2016. In order to be eligible for this trial, patients had to have histologically or cytologically confirmed adenocarcinoma of the prostate, to have castrate-resistant disease, and to have no distant metastases, as detected by a technetium-99 m bone scan and computed tomography (CT) of the head, chest, abdomen and pelvis. Patients with pelvic lymph nodes measuring <2 cm in the short axis and located below the aortic bifurcation (N1 disease), were eligible for the trial, as were N0 patients. Eligible patients additionally were at high risk of developing metastases, defined by having a PSADT $\leqslant$ 10 months while receiving continuous ADT, and were continued on ADT during the trial. Eligible patients were stratified according to PSADT ($>$ 6 months *versus* $\leqslant$ 6 months), use of bone-sparing agents and nodal disease (N0 *versus* N1) and were randomly assigned in a 2:1 ratio to receive apalutamide 240 mg daily or placebo. Patients in both groups were treated on a continuous daily dosing regimen until progression, AEs, or withdrawal of consent.

The primary endpoint of this trial was metastasis-free survival, defined as the time from randomization to the first detection of distant metastasis on imaging or death from any cause. Although PSA levels were measured regularly at a central laboratory, patients and treating physicians remained blinded to PSA results. Disease assessment including CT of the chest, abdomen and pelvis and bone scans were obtained every 16 weeks (or at additional timepoints if metastasis was suspected) and were assessed centrally by reviewers blinded to clinical characteristics or course. Any new bone lesion detected on a bone scan required a second imaging study with either CT or magnetic resonance imaging in order to confirm metastasis. At the time of metastatic progression, patients remained blinded as to therapy, but all patients were offered open-label abiraterone acetate. Secondary endpoints included PFS (defined as the time from randomization to the first detection of local or distant metastatic disease on imaging or death from any cause), time to metastasis (defined as time from randomization to the first detection of distant metastasis in bone or soft tissue), time to symptomatic progression, time to the initiation of cytotoxic chemotherapy and OS. There were additionally a number of exploratory endpoints including time to PSA progression (defined according to PCWG2 criteria), PSA response rate (defined as percentage of patients who had a PSA decline from baseline of at least 50%), patient-reported outcomes assessed with the FACT-P questionnaire and EQ-5D-3L questionnaire, and second PFS (PFS2), defined as the time from randomization to progression on subsequent treatment, following study treatment.

Overall 806 patients were assigned to the apalutamide group and 401 patients were assigned to the placebo group. The groups were well balanced in terms of their baseline characteristics. The median age was 74 years in both groups and the median time from initial diagnosis to randomization was almost 8 years. The median PSADT at the time of diagnosis was 4.4 months in the apalutamide group and 4.5 months in the placebo group. The groups were also well balanced with regards to the proportion of patients with a PSADT $\leqslant$ 6 months (71%), the use of bone-sparing agents (10%), and the presence of N1 disease (16%).

The primary endpoint of metastasis-free survival significantly favored the apalutamide group (40.5 months compared with 16.2 months in the placebo group), representing a 2 year delay in the development of metastases with the use of apalutamide [hazard ratio (HR) for metastases or death, 0.28; 95% confidence interval (CI), 0.23–0.35; $p < 0.001$]. The favorable effect of apalutamide was consistent across all prespecified

subgroups. Apalutamide was additionally associated with improved outcomes relative to placebo for a number of secondary endpoints. Median PFS was 40.5 months in the apalutamide group and 14.7 months in the placebo group (HR: 0.29; 95% CI: 0.24–0.36; $p < 0.001$) while the median time to metastasis was 40.5 months *versus* 16.6 months (HR: 0.27; 95% CI: 0.22–0.34; $p < 0.001$). The median time to symptomatic progression was not reached in either group; however, time to symptomatic progression was improved significantly by apalutamide (HR: 0.45; 95% CI: 0.32–0.63; $p < 0.001$). In the apalutamide group, 89.7% of patients had a PSA response as opposed to only 2.2% in the placebo group, whereas the median time to PSA progression was not reached in the apalutamide group and was 3.7 months in the placebo group (HR: 0.06; 95% CI: 0.05–0.08). At the time of publication, it was premature to assess the impact of apalutamide on survival, as only 24% of events (deaths) had occurred. Nevertheless, median OS was not reached in the apalutamide group and was 39.0 months in the placebo group, showing a favorable hazard ratio which did not reach statistical significance (HR: 0.70; 95% CI: 0.47–1.04; $p = 0.07$).

The majority of patients who discontinued treatment in either group went on to receive subsequent US FDA-approved (life-prolonging) treatment. Treatment discontinuation occurred due to progressive disease in 19% (155 pts) in the apalutamide group and 53% (210 pts) in the placebo group, whereas discontinuation due to AEs occurred in 11% (85 pts) in the apalutamide group and 7% (28 pts) in the placebo group. Nearly 80% of placebo patients received US FDA-approved therapy of some type in the mCRPC setting. The most commonly used subsequent treatment was an androgen-signaling inhibitor (abiraterone or enzalutamide) in both the apalutamide group (46% of all patients) and the placebo group (68% of all patients). At the time of analysis, the PFS2 (PFS on subsequent treatment from time of trial randomization) was not yet reached in the apalutamide group and was 39.0 months in the placebo group. The hazard ratio was very favorable in the apalutamide group for this comparison (HR 0.49; 95% CI: 0.36–0.66, $p < 0.0001$), representing a 51% improvement in time to second progression with the early use of apalutamide. This was in spite of the significant use of androgen-signaling inhibitor agents as subsequent therapy in the placebo arm.

Based on the substantial clinical benefit observed in the apalutamide group, in July 2017 the independent data and safety monitoring committee unanimously recommended unblinding of the study and giving placebo group patients the option of switching to apalutamide. Based on these data, on 14 February 2018 the US FDA approved apalutamide for the treatment of nmCRPC patients.[27]

The results of this trial showed apalutamide to be well tolerated. AEs led to the discontinuation of treatment in only 10.6% of patients in the apalutamide group and 7.0% in the placebo group. Overall, grade 3 or 4 AEs were observed in 45.1% of patients in the apalutamide group and 34.2% in the placebo group. Most common AEs independent of attribution included fatigue (30.4% in apalutamide group *versus* 21.1% for placebo), hypertension (24.8% *versus* 19.8%), rash (23.8% *versus* 5.5%), diarrhea (20.3% *versus* 15.1%), nausea (18.1% *versus* 15.8%), weight loss (16.1% *versus* 6.3%), arthralgia (15.9% *versus* 7.5%), and falls (15.6% *versus* 9.0%). In terms of AEs of interest, or attributed to the drug, the most commonly encountered were: fracture (11.7% in apalutamide *versus* 6.5% in placebo), dizziness (9.3% *versus* 6.3%), hypothyroidism (8.1% *versus* 2.0%) and mental impairment (5.1% *versus* 3.0%). Only 0.2% (two patients total) treated with apalutamide had a documented seizure (both in patients with predisposing conditions), whereas no seizures were noted in the placebo group. Among AEs more commonly encountered in the apalutamide group, rashes were generally low grade and self-limited and generally improved when the drug was held, whereas hypothyroidism was generally asymptomatic and observed in patients already on thyroid replacement. However, 10 patients treated with apalutamide had AEs associated with death, most commonly due to cardiac, cerebrovascular or infectious causes, whereas only one such death was observed in the placebo arm.

Patient-reported outcomes (PROs) in the SPARTAN trial were additionally reported at the 2018 European Association of Urology and 2018 American Urological Association meetings.[28,29] As part of this trial, PRO data were collected prospectively using FACT-P and EQ-5D-3L self-administered questionnaires to assess health-related quality of life (HRQoL) while on treatment with apalutamide or placebo. In general, this trial population of patients with nmCRPC was largely asymptomatic at their baseline assessment with a mean FACT-G

score of 83 in the apalutamide arm and 84 in the placebo arm (out of 108) as compared with the FACT-G population norm of 81. Following initiation of treatment with apalutamide, FACT-G scores remained consistent with this baseline value throughout the reported time window out to cycle 29 of treatment, indicating that HRQoL was maintained despite the use of apalutamide. A similar trend was seen in the placebo arm. There were no significant differences observed among the two arms suggesting a similar tolerability experience between apalutamide and placebo in the clinical trial. Overall, men with nmCRPC in this trial were shown to have similar HRQoL to the general population, as they were largely asymptomatic at baseline, while the addition of apalutamide treatment allowed them to maintain this HRQoL while deriving significant therapeutic benefit.

In summary, the significant improvement across multiple clinically relevant endpoints in this randomized, placebo-controlled trial support the use of apalutamide in patients with nmCRPC who are at risk for progression to metastatic disease based on a PSADT of 10 months or less. Overall, the use of apalutamide delayed metastasis by 2 years, and this benefit was consistent across all patient subsets including both older and younger patients, patients who were N0 or N1, and patients with both high and low PSA values and PSADTs. Treatment with apalutamide was associated with a tolerable side effect profile which was consistent with previously reported safety data in earlier trials of this agent. PROs also indicated that patients treated with apalutamide maintained their quality of life, as tolerability experience among the treatment arms in the trial were similar.

Ongoing trials and future directions

In addition to the completed pivotal SPARTAN trial, there are a number of ongoing randomized trials testing the utility of apalutamide in a number of settings (Table 1). The ACIS trial is a placebo-controlled phase III trial evaluating the utility of adding apalutamide to abiraterone/prednisone in men with mCRPC [ClinicalTrials.gov identifier: NCT02257736].[30] The TITAN trial is assessing the utility of adding apalutamide to ADT in metastatic hormone-sensitive prostate cancer [ClinicalTrials.gov identifier: NCT02489318].[31] The ATLAS trial is evaluating apalutamide in combination with ADT in patients with high-risk localized or locally advanced prostate cancer receiving primary radiotherapy [ClinicalTrials.gov identifier: NCT02531516],[32] and an Alliance Foundation trial is enrolling men with high-risk biochemically relapsed prostate cancer randomized into one of three arms to receive either degarelix, degarelix and apalutamide, or degarelix, apalutamide and abiraterone/prednisone [ClinicalTrials.gov identifier: NCT03009981].[33]

In addition to these ongoing trials, a number of other questions regarding apalutamide require further investigation. The mechanisms of resistance to apalutamide remain to be elucidated and can potentially guide further treatment of patients who progress on this therapy. Also, of paramount importance is the identification of novel predictive biomarkers to identify patients most likely to respond to apalutamide treatment or conversely patients least likely to derive benefit, who should be treated with other agents instead. The appropriate use of molecular imaging may additionally play a role in identifying both patient eligibility for treatment and response to treatment and should be investigated further.

Conclusion

Apalutamide is a second-generation AR antagonist that directly binds to the AR, preventing its translocation, DNA binding and subsequent AR-mediated transcription, thus inhibiting AR-mediated prostate cancer cell growth and proliferation. Several prospective clinical trials over the past decade have assessed the efficacy and safety of apalutamide in prostate cancer patients generating a wealth of clinical data and experience that supports the clinical utility of apalutamide in various prostate cancer treatment settings. Most notably, the recent results of the phase III SPARTAN trial indicating significant improvement in metastasis-free survival of patients treated with apalutamide as opposed to placebo, in the setting of reasonable treatment tolerability and maintenance of HRQoL, led to the US FDA approval of this agent in nmCRPC. Further study of apalutamide in other treatment settings is ongoing with randomized phase III trials assessing its efficacy in patients with hormone-sensitive prostate cancer and also as part of rational combination regimens. Further study is needed to better characterize patients most likely to benefit from apalutamide in nmCRPC and other treatment settings and to inform future combination regimens that will maximize the benefit of this drug. The efficacy and safety data from completed trials of apalutamide

Table 1. Important phase III trials of apalutamide.

Acronym	Identifier	Patient population	Comparator arms	Primary endpoint
ACIS	NCT02257736	mCRPC	Apalutamide/abiraterone/prednisone *versus* placebo/abiraterone/prednisone	Radiographic progression-free survival
TITAN	NCT02489318	mHSPC	Apalutamide/ADT *versus* placebo/ADT	Radiographic progression-free survival and overall survival
ATLAS	NCT02531516	High-risk or locally advanced prostate cancer	Apalutamide/ADT + RT *versus* bicalutamide/ADT + RT	Metastasis-free survival
EORTC	NCT03488810	Intermediate and limited high-risk prostate cancer	Apalutamide/ADT + RT *versus* nonsteroidal anti-androgen / ADT + RT	Disease-free survival
ALLIANCE	NCT03009981	Biochemically recurrent prostate cancer with PSA doubling time ⩽9 months	Degarelix *versus* degarelix/apalutamide *versus* degarelix/apalutamide/abiraterone/prednisone	PSA progression-free survival
SPARTAN	NCT01946204	nmCRPC	Apalutamide/ADT *versus* placebo/ADT	Metastasis-free survival

ADT, androgen deprivation therapy; mCRPC, metastatic castrate-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castrate-resistant prostate cancer; PSA, prostate-specific antigen; RT, radiotherapy.

point to a promising future role for this agent in helping broader populations of patients with prostate cancer.

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Conflict of interest statement

Dr Koshkin reports no specific conflict of interest. Dr Small has been a member of an advisory board for Janssen and has received speakers' honoraria from Janssen.

References

1. 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* 2015; 16: 152–160.
2. Smith MR, Saad F, Oudard S, *et al.* Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. *J Clin Oncol* 2013; 31: 3800–3806.
3. Smith MR, Kabbinavar F, Saad F, *et al.* Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol* 2005; 23: 2918–2925.
4. Smith MR, Cook R, Lee K-A, *et al.* Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. *Cancer* 2011; 117: 2077–2085.
5. Scher HI, Solo K, Valant J, *et al.* Prevalence of prostate cancer clinical states and mortality in

the United States: estimates using a dynamic progression model. *PLoS One* 2015; 10: e0139440.

6. Smith MR, Saad F, Chowdhury S, *et al.* Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med* 2018; 378: 1408–1418.
7. Huggins C. Effect of orchiectomy and irradiation on cancer of the prostate. *Ann Surg* 1942; 115: 1192–1200.
8. Scher HI and Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. *J Clin Oncol* 2005; 23: 8253–8261.
9. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. *Lancet* 2000; 355: 1491–1498.
10. Taplin ME, Bubley GJ, Shuster TD, *et al.* Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N Engl J Med* 1995; 332: 1393–1398.
11. Sartor AO, Tangen CM, Hussain MHA, *et al.* Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). *Cancer* 2008; 112: 2393–2400.
12. Small EJ and Carroll PR. Prostate-specific antigen decline after casodex withdrawal: evidence for an antiandrogen withdrawal syndrome. *Urology* 1994; 43: 408–410.
13. Small EJ and Srinivas S. The antiandrogen withdrawal syndrome. Experience in a large cohort of unselected patients with advanced prostate cancer. *Cancer* 1995; 76: 1428–1434.
14. Small EJ, Halabi S, Dawson NA, *et al.* Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). *J Clin Oncol* 2004; 22: 1025–1033.
15. Rathkopf D and Scher HI. Androgen receptor antagonists in castration-resistant prostate cancer. *Cancer J* 2013; 19: 43–49.
16. Scher HI, Fizazi K, Saad F, *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; 367: 1187–1197.
17. Beer TM, Armstrong AJ, Rathkopf DE, *et al.* Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; 371: 424–433.
18. de Bono JS, Logothetis CJ, Molina A, *et al.* Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; 364: 1995–2005.
19. Clegg NJ, Wongvipat J, Joseph JD, *et al.* ARN-509: a novel antiandrogen for prostate cancer treatment. *Cancer Res* 2012; 72: 1494–1503.
20. Jung ME, Ouk S, Yoo D, *et al.* Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). *J Med Chem* 2010; 53: 2779–2796.
21. Tran C, Ouk S, Clegg NJ, *et al.* Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* 2009; 324: 787–790.
22. Foster WR, Car BD, Shi H, *et al.* Drug safety is a barrier to the discovery and development of new androgen receptor antagonists. *Prostate* 2011; 71: 480–488.
23. Rathkopf DE, Morris MJ, Fox JJ, *et al.* Phase I study of ARN-509, a novel antiandrogen, in the treatment of castration-resistant prostate cancer. *J Clin Oncol* 2013; 31: 3525–3530.
24. Smith MR, Antonarakis ES, Ryan CJ, *et al.* Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. *Eur Urol* 2016; 70: 963–970.
25. 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* 2008; 26: 1148–1159.
26. Rathkopf DE, Antonarakis ES, Shore ND, *et al.* Safety and antitumor activity of apalutamide (ARN-509) in metastatic castration-resistant prostate cancer with and without prior abiraterone acetate and prednisone. *Clin Cancer Res* 2017; 23: 3544–3551.
27. U.S. Food & Drug Administration. Research C for DE and Approved Drugs (14 February, 2018). FDA approves apalutamide for non-metastatic castration-resistant prostate cancer, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm596796.htm (accessed 5 July 2018).
28. Small EJ, Saad F, Hadaschik BA, *et al.* MP52-20 Patient-reported outcomes (PROs) in SPARTAN, a phase 3, double-blind, randomized study of apalutamide (APA) plus androgen deprivation therapy (ADT) vs placebo plus ADT in men with nonmetastatic castration-resistant prostate cancer (nmCRPC). *J Urol* 2018; 199: e703–e704.
29. Saad F, Small E, Hadaschik B, *et al.* 743 - Patient (pt) reported outcomes (PROs) in SPARTAN,

a phase 3, double-blind, randomized study of apalutamide (APA) plus androgen deprivation therapy (ADT) vs placebo (PBO) plus ADT in men with nonmetastatic castration-resistant prostate cancer (nmCRPC). *Eur Urol Suppl* 2018; 17: e1070–e1071.

30. Rathkopf DE, Attard G, Efstathiou E, *et al*. A phase 3 randomized, placebo-controlled double-blind study of ARN-509 plus abiraterone acetate (AA) in chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2015; 33: TPS5071–TPS5071.

31. Chi KN, Chowdhury S, Radziszewski P, *et al*. TITAN: a randomized, double-blind, placebo-controlled, phase 3 trial of apalutamide (ARN-509) plus androgen deprivation therapy (ADT) in metastatic hormone-sensitive prostate cancer (mHSPC). *Annals of Oncology* 2016; 27(6): 771TiP. Available at: https://doi.org/10.1093/annonc/mdw372.54

32. Sandler HM, McKenzie MR, Tombal BF, *et al*. ATLAS: a randomized, double-blind, placebo-controlled, phase 3 trial of apalutamide (ARN-509) in patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy. *J Clin Oncol* 2016; 34: TPS5087–TPS5087.

33. ClinicalTrials.gov. A study of androgen annihilation in high-risk biochemically relapsed prostate cancer - tabular view, https://clinicaltrials.gov/ct2/show/record/NCT03009981 (accessed 5 September 2018).