Apalutamide and its use in the treatment of prostate cancer

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High-risk nonmetastatic castration-resistant prostate cancer is a lethal disease that previously lacked clear treatment options. Progression to bone metastases is associated with significant morbidity and high cost. Apalutamide, an androgen receptor inhibitor, has substantial clinical response in nonmetastatic castration-resistant prostate cancer. Apalutamide + androgen deprivation therapy is well tolerated and improves metastasis-free survival, progression-free survival and time to symptomatic progression, and is associated with a favorable trend of improved overall survival. Future research is needed to elucidate mechanisms of resistance to treatment with androgen signaling inhibitors.

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Background

Prostate cancer is the second leading cause of cancer related death among men in the USA [1]. Androgen deprivation therapy (ADT), or the reduction of serum testosterone to castrate levels (≤ 50 ng/ml) through medical or surgical approaches is a backbone of therapy for prostate cancer [2]. Continuous, rather than intermittent, ADT remains the standard of care for men with metastatic disease [3].

Unfortunately, despite initial disease control the resulting symptom palliation from ADT, resistance overtime to ADT is near-universal, and the disease takes the form of castration-resistant prostate cancer (CRPC). CRPC is an eventual lethal condition defined by cancer growth in the setting of castrate levels of serum testosterone [4,5]. When castration resistance develops, the standard of care is to obtain conventional imaging with a technetium-99m scintigraphy (bone scan) and computed tomography of chest, abdomen and pelvis to categorize the disease as metastatic or nonmetastatic [5,6].

Metastatic CRPC is a uniformly fatal disease with a median survival of approximately 2.5 years [7]. This disease state may develop either from metastatic hormone sensitive prostate cancer (HSPC) or from nonmetastatic prostate cancer that has developed resistance to ADT. Patients with biochemically recurrent prostate cancer after definitive prostate-directed therapy (i.e., surgery and local radiation) and without evidence of metastases on imaging have nonmetastatic HSPC (nmHSPC) [6]. Patients with nmHSPC are treated with intermittent ADT, however at the time of metastases or castration resistance, patients require continuous ADT [6,8].

Nonmetastatic castration-resistant prostate cancer

Nonmetastatic CRPC (nmCRPC) is a clinically heterogeneous state that is indicated by an increasing prostate-specific antigen (PSA), in the setting of castrate levels of serum testosterone, with no evidence of metastases on conventional imaging, generally consisting of a technetium bone scan and cross-sectional imaging of abdomen and pelvis [6,9]. Prostate Cancer Working Group (PCWG2) defines PSA progression as a 25% or greater increase and an absolute increase of at least 2 ng/ml from the nadir on consecutive lab draws while the patient is on ADT [10]. European Association of Urology defines localized relapse as PSA > 2 ng/ml on three consecutive rises 1 week apart, with two 50% increases over nadir, while the patient is on ADT [11].

Figure 1. Prostate-specific antigen doubling time and risk for metastatic disease. Men with nonmetastatic castration-resistant prostate cancer with a prostate-specific antigen doubling time of <8–10 months are at a significant risk for metastatic disease and prostate cancer specific death.

PSADT: Prostate-specific antigen doubling time.

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The heterogeneity of nmCRPC is evident in the diversity of clinical courses for men in this disease state, ranging from indolent disease that may never present a health challenge, to aggressive disease which rapidly metastasizes and is characterized by consequent morbidity and mortality [12]. The identification of patients destined to do poorly has therefore been a priority. A cohort of 201 patients in the control arm of a randomized controlled trial to examine the effects of zoledronic acid on time to first bone metastasis was analyzed. In 2 years, they observed that 33% of patients had developed bone metastases and that baseline PSA and PSA velocity independently predicted overall survival and metastasis-free survival (MFS) [13]. Indeed, high-risk nmCRPC can be readily identified through multiple clinical and laboratory factors. PSA kinetics, generally expressed as PSA doubling time (PSADT), and absolute PSA level are factors that predict bone metastases or death [14,15]. Smith and colleagues observed that men with nmCRPC with a PSA doubling time (PSADT) of <8–10 months were at a significant risk for metastatic disease and prostate cancer specific death (Figure 1) [15].

Treatment gap in nmCRPC

High-risk nmCRPC leads to a lethal disease with potentially significant morbidity following disease progression. Development of bone metastases can be associated with acute complications including skeletal-related events, such as painful or pathologic lesions, fractures or spinal cord compression requiring emergent surgical decompression or radiation therapy [16–18]. There are also many chronic consequences of bone metastases including symptoms of pain, functional disability and decline in emotional well-being [16,19–21]. Increased morbidity associated with the development of metastasis also leads to worsening financial toxicity, because of the added costs associated with the direct receipt of health care and increased resource utilization [11,22].

Because metastases are a known major cause of morbidity and mortality in men with prostate cancer [23], and there were, until recently, no approved therapies for patients with nmCRPC, the prevention of metastases represents an important clinical priority.

Androgen signaling inhibitors

Androgen signaling inhibitors (ASIs) target the androgen-signaling pathway through a variety of mechanisms. In the CRPC setting, androgen receptor (AR) gene amplification and subsequent overexpression can perpetuate signaling despite low levels of ligand (testosterone) [24]. Androgen synthesis inhibitors, such as abiraterone acetate in combination with prednisone, reduce the production of testosterone thereby reducing the ligand for AR signaling [25]. Apalutamide (APA) and enzalutamide inhibit the AR and prohibit AR signaling [26,27].

ASIs improve clinical outcomes for men with metastatic CRPC [28,29]. However, the best treatment of CRPC patients who do not yet have evidence of metastases on imaging (nmCRPC) until recently has been less clear. Therefore, investigators recognized an acute need for the development of novel therapies in the nmCRPC setting [9].

Apalutamide

APA is an orally administered, next generation nonsteroidal ASI [30]. APA functions as an AR inhibitor that prevents AR nuclear translocation. Inhibits DNA binding, and impedes AR-mediated transcription [30]. In a Phase II study in men with nmCRPC, APA had substantial clinical response, resulting in a $\geq 50\%$ PSA decline at 12 weeks in 89% of patients with high-risk nmCRPC [31].

SPARTAN study

SPARTAN, a randomized Phase III, placebo-controlled study, evaluating the safety and efficacy of APA + ADT among men with nmCRPC and a rapidly rising PSA was launched [31]. Patients with a PSADT <10 months were eligible for this study.

In the study, patients were randomized in a 2:1 ratio to receive APA + ADT or matched placebo + ADT, administered orally on a continuous daily dosing regimen. Patients were stratified by PSADT (>6 mo vs ≤ 6 mo), bone-sparing agent use (yes vs no), and nodal status (N0 vs N1). In SPARTAN, patients with pelvic lymph nodes below the iliac bifurcation that were smaller than 2 cm were eligible. Androgen-deprivation therapy was continued throughout the study. Patients were allowed to have previously received therapy with a first-generation anti-androgens.

Patients continued therapy until protocol-defined development of metastasis, adverse events or withdrawal of consent. Disease assessments were performed every 16 weeks, and all imaging was assessed prospectively by blinded independent central review. PSA values were maintained blinded while on study. After developing metastases, patients were treated at their treating physician's discretion, with an option to receive study-provided abiraterone acetate plus prednisone. Study blind was not broken at the time of progression.

In SPARTAN, patient demographics and disease characteristics were well balanced. The median baseline PSA doubling time was 4.4 months for patients receiving APA + ADT and 4.5 months for patients receiving placebo + ADT, 16.5% of patients receiving APA + ADT had node positive disease compared with 16.2% of patients receiving placebo + ADT, and 73.4% of patients receiving APA + ADT, compared with 72.3% of patients receiving placebo + ADT also previously received a first-generation anti-androgen.

In SPARTAN, APA + ADT treatment significantly improved MFS, time to metastasis, progression-free survival (PFS) and time to symptomatic progression, and it was associated with a favorable trend of improved overall survival [32]. APA + ADT treatment also significantly improved PFS on second therapy (PFS2). SPARTAN found that APA + ADT treatment significantly prolonged MFS by 2 years in men with nmCRPC and a rapidly rising PSA.

Metastasis-free survival

MFS in prostate cancer patients is a relatively new end point, which was successfully used as a regulatory end point in the SPARTAN trial. In the Intermediate Clinical Endpoints in Cancer of the Prostate (ICE CaP) study, Xie and colleagues identified 28 randomized trials of men with localized prostate cancer that was hormone untreated, with individual patient data available in a total of 28,905 patients [32]. Disease-free survival (DFS) and MFS were determined in 21,140 patients from 24 trials and 12,712 patients from 19 trials, respectively. These investigators identified MFS as a strong surrogate for overall survival for localized prostate cancer and is associated with a significant risk of death from prostate cancer [32]. MFS has not yet been validated as a surrogate for survival in patients with nmCRPC.

The primary end point for the SPARTAN study was MFS for which a single final analysis was planned by the study investigators. SPARTAN found that APA + ADT treatment significantly prolonged MFS by 2 years in men with nmCRPC and a PSADT of 10 months or less. The median MFS of 40.5 months in the APA group, compared with 16.2 months in the placebo + ADT group, represented a 72% risk reduction of distant progression or death, with a p-value of <0.001 (Figure 2). The treatment effect of APA + ADT on MFS was consistently favorable across all prespecified subgroups, including baseline PSA level, PSA DT and nodal status.

In SPARTAN, secondary end points were tested using a hierarchical adaptive group sequential procedure. A secondary end point had to be statistically significant to move on to testing of the next secondary end point on

Figure 2. Median metastasis-free survival in SPARTAN study. The median metastasis-free survival of 40.5 months in the Apalutamide group, compared with 16.2 months in the placebo group represents a 72% risk reduction of distant progression or death, with a p-value of <0.0001.

APA: Apalutamide; mo: Months; PBO: Placebo.

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the list. The results for the primary end point were supported by consistent improvement across all secondary end points: time to metastasis had a 73% risk reduction, PFS demonstrated a 71% risk reduction, and time to symptomatic progression had a 55% risk reduction. The improvement in time to symptomatic progression is an important outcome, not only because it is clearly of clinical significance to patients, but also because it represents an event following progression.

Exploratory end points included PFS2, time to PSA progression, PSA decline and patient-reported outcomes. Second PFS was defined as the time from randomization to investigator-assessed disease progression during the first subsequent treatment for metastatic castration-resistant disease or death from any cause. Of those patients who discontinued study treatment, nearly 80% of placebo + ADT patients went on to receive the US FDA approved (i.e., life prolonging) treatment for metastatic disease. Of these, 78% of placebo + ADT and 53% of APA + ADT patients had received FDA approved therapy for mCRPC. The investigators observed that APA + ADT used in the nmCRPC setting resulted in a 51% risk reduction of disease progression during the first subsequent treatment for metastatic CRPC. These data suggested that APA + ADT treatment in nmCRPC may provide clinical benefit compared with the prior standard of using approved treatments after progression to metastatic disease, although this study was not designed to specifically test this hypothesis.

Time to PSA progression was also significantly impacted by the use of APA + ADT, with a 94% risk reduction in PSA progression. PSA declined by 50% or more in 90% of patients treated with APA + ADT, and in 2% of patients treated with placebo + ADT. The first interim analysis of overall survival did not reach statistical significance, with 24% of required events.

Based on these aggregate data, including safety data, the independent data safety monitoring committee unanimously recommended unblinding the study and offering patients assigned to the placebo + ADT group the option to receive APA + ADT. At the time of the data safety monitoring committee's recommendation, 279 placebo + ADT patients and 314 APA + ADT patients had already discontinued study treatment, mostly due to having reached the MFS end point.

Patient-reported outcomes

Patient-reported outcomes were also assessed. Patients were required to complete two self-administered quality of life (QoL) instruments: the Functional Assessment of Cancer Therapy–Prostate (FACT-P) and the Euro-QoL Group EQ-5D-3L [32]. FACT-P examines health-related QoL and prostate cancer-specific symptoms [33]. EQ-5D-3L assesses health status [34]. Assessments were collected at baseline, during the treatment phase, and 1-year post

Table 1. Treatment associated adverse events for apalutamide.

Adverse event	Number of patients (%)			
	Apalutamide (n = 803)		Placebo (n = 398)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any adverse event	775 (96.5)	362 (45.1)	371 (93.2)	136 (34.2)
Serious adverse event	199 (24.8)	–	92 (23.1)	–
Adverse event leading to discontinuation of the trial regimen	85 (10.6)	–	28 (7.0)	–
Adverse event associated with death	10 (1.2)	–	1 (0.3)	–
Adverse event that occurred in ≥15% of patients in either group:				
– Fatigue	244 (30.4)	7 (0.9)	84 (21.1)	1 (0.3)
– Hypertension	199 (24.8)	115 (14.3)	79 (19.8)	47 (11.8)
– Rash	191 (23.8)	42 (5.2)	22 (5.5)	1 (0.3)
– Diarrhea	163 (20.3)	8 (1.0)	60 (15.1)	2 (0.5)
– Nausea	145 (18.1)	0	63 (15.8)	0
– Weight loss	129 (16.1)	9 (1.1)	25 (6.3)	1 (0.3)
– Arthralgia	128 (15.9)	0	30 (7.5)	0
– Falls	125 (15.6)	14 (1.7)	36 (9.0)	3 (0.8)
Other adverse events of interest:				
– Fracture	94 (11.7)	22 (2.7)	26 (6.5)	3 (0.8)
– Dizziness	75 (9.3)	5 (0.6)	25 (6.3)	0
– Hypothyroidism	65 (8.1)	0	8 (2.0)	0
– Mental-impairment disorder	41 (5.1)	0	12 (3.0)	0
– Seizure	2 (0.2)	0	0	0

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treatment. Mean group patient-reported outcomes scores from baseline and throughout treatment were maintained for both the apalutamide treatment group and for patients receiving placebo [35]. Therefore, the investigators concluded that there was a similar tolerability between the two arms of the SPARTAN study.

Apalutamide toxicities

APA + ADT treatment is generally well tolerated. In the Phase II study, the most common TEAE in both arms was fatigue, which was generally grade 1 or 2. Among the 803 patients treated with apalutamide in SPARTAN, 97% of patients experienced any grade of adverse events; however 45% reported grade 3 or higher adverse events in the APA + ADT arm compared with 34% in placebo + ADT (see Table 1). Differences in grade 3 and 4 toxicities included fatigue in 0.9% of APA + ADT patients versus 0.3% in placebo + ADT patients; rash (5.2% vs 0.3%); weight loss (1.1 vs 0.3%); falls (1.7 vs 0.8%) and fractures (2.7 vs 0.8%). The overall seizure rate in the APA + ADT arm was 0.2%, with no grade 3 or higher events. Hypothyroidism was associated with APA + ADT therapy (8.1% vs 2%). For patients who experience rash, topical hydrocortisone cream can be applied for localized symptoms. If symptoms become more severe, then the patient may need discontinuation of the drug and oral steroid therapy [36].

Based on the totality of these data, APA + ADT was approved by the FDA for patients with nmCRPC on 14 February 2018 at a starting dose of 240 mg of apalutamide (four 60 mg tablets) daily [37].

Next steps in a rapidly changing field

In the era of advanced imaging, disease volume can be more precisely categorized. Specifically, increased accessibility to molecular or metabolic imaging modalities such as prostate specific membrane antigen (PSMA) positron-emission tomography (PET), Fluciclovine PET and NaF PET scans have led to a clinically meaningful stage shift [38,39]. Now clinicians are able to detect metastatic disease in patients who would be considered to have nmCRPC based on conventional imaging. Thus, many SPARTAN eligible patients would have had positive PSMA PET scans and they nevertheless benefited from early ASI therapy. Consequently, it is reasonable to treat patients with negative conventional imaging with APA + ADT, regardless of PSMA PET results. Prospective studies will need to examine the role of these therapies in the subset of patients with known metastatic disease based on advanced imaging.

Patients with oligometastatic disease, or few metastatic sites, based on advanced imaging are frequently candidates for localized treatment either surgically or through stereotactic body radiation therapy [40]. Whether APA + ADT should be used in conjunction with these locally directed therapies is not known.

Investigators are increasingly trying to elucidate mechanisms of resistance to ASIs. Molecular characterization of patients who progress while on ADT and ASI therapy is essential in order to develop therapeutic approaches to disrupt the development of resistance. AR anomalies, such as splice variants, alterations to the AR ligand binding domain, and amplifications are associated with resistance in mCRPC [41,42]. However, the significance of AR anomalies in the context of nmCRPC is not clearly understood. The SPARTAN investigators attempted to characterize frequencies of AR anomalies among study patients and assess the effects of anomalies on disease progression while on treatment [43]. Among study participants, blood samples were collected at baseline and at the end of the study. Next-generation sequencing was performed on 240 end of treatment specimens and 144 matched baseline samples. Compared with placebo + ADT, APA + ADT did not increase frequency of AR genomic alterations and no mechanisms of resistance were identified [43]. However, the presence of an AR anomaly was found to be associated with a shorter time to progression on hormone therapy among patients in the APA + ADT and placebo + ADT group [43]. Future studies should further elucidate drivers of ASI resistance among patients with nmCRPC. Furthermore, the development of treatment-associated small cell/neuroendocrine prostate cancer (t-SCNC) could be a reasonably frequent mechanism of resistance in patients with metastatic CRPC treated with ASIs [44,45]. Whether this mechanism exists in patients with nmCRPC who develop progressive disease following treatment with APA + ADT remains unknown.

PROSPER study

In June 2018, Hussain and colleagues published the PROSPER study that examined the efficacy of enzalutamide, in a double-blind, Phase III, placebo-controlled, randomized clinical trial for men with nmCRPC and a PSADT <10 months or less [46]. The primary end point was MFS and enzalutamide was found to significantly lower risk of metastasis or death compared with placebo [46]. Although enzalutamide was well-tolerated overall, the notable adverse events that occurred more frequently in the enzalutamide group included cardiovascular events, hypertension and cognitive toxicities [46]. Enzalutamide and apalutamide have not been compared head to head in a randomized clinical trial for men with nmCRPC.

Conclusion

NmCRPC is a lethal disease that previously lacked clear treatment options. Progression to bone metastases is associated with significant morbidity and high cost [16,19–22]. APA, a high affinity AR inhibitor, has substantial clinical activity in nmCRPC and should be considered a new standard of care for managing these patients [31,47]. APA + ADT is well tolerated and improves MFS, time to metastasis, PFS and time to symptomatic progression, and is associated with a favorable trend of improved overall survival [31]. Future research is needed to elucidate mechanisms of resistance to ASI therapy.

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Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusion.

Disclosure

The authors are fully responsible for all content and editorial decisions.

Executive summary

Nonmetastatic castration-resistant prostate cancer is a clinically heterogeneous disease and high-risk nmCRPC previously lacked treatment options

- Non-metastatic castration-resistant prostate cancer (nmCRPC) is defined as increasing prostate-specific antigen (PSA) in setting of castrate levels of serum testosterone with no evidence of metastases on conventional imaging.
- Heterogeneity of nmCRPC is evident in diversity of clinical course of men ranging from indolent to rapidly aggressive metastases development.
- PSA doubling time is a predictor of the development of bone metastases and death.
- Progression to bone metastases is associated with significant morbidity and high cost.

Apalutamide & nmCRPC

- Apalutamide (APA) is an orally administered, next generation nonsteroidal androgen signaling inhibitor.
- APA functions as an androgen receptor inhibitor that prevents androgen receptor nuclear translocation, inhibits DNA binding and impedes AR-mediated transcription.
- In Phase II study in men with nmCRPC, apalutamide had substantial clinical response including more than 50% PSA decline at 12 weeks in 89% of patients with high-risk nmCRPC.

SPARTAN study

- SPARTAN is a randomized Phase III, placebo-controlled study, evaluating the safety and efficacy of apalutamide and androgen deprivation therapy among men with nmCRPC and a rapidly rising PSA (PSADT <10 months were eligible or study).
- APA was found to be well-tolerated, improves metastasis-free survival, progression-free survival and time to symptomatic progression, and is associated with a favorable trend of improved overall survival.
- The most common treatment experienced adverse event was fatigue for both arms of the study.
- Based on the results from the SPARTAN study, this therapy was approved by the US FDA as a treatment for men with nmCRPC.

PROSPER study

- This study examined the efficacy of enzalutamide, in a double-blind, Phase III, placebo-controlled, randomized clinical trial for men with nmCRPC and a PSADT <10 months or less.
- Enzalutamide was well-tolerated overall.
- Enzalutamide and apalutamide have not been compared directly in a randomized clinical trial among men with nmCRPC.

Conclusion

- NmCRPC previously lacked clear treatment options.
- APA is well-tolerated treatment option for men with high-risk nmCRPC.

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