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Genitourinary Cancers (S Gupta, Section Editor)

Management of Nonmetastatic Castration-Resistant Prostate Cancer: Recent Advances and Future Direction

John Esther, MD[1]
Benjamin L. Maughan, MD, PharmD[1]
Neysi Anderson, BS[1]
Neeraj Agarwal, MD[1,2,*]
Andrew W. Hahn, MD[1,3,*]

Address
[1]Division of Medical Oncology, Department of Internal Medicine, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA
[*,2]GU Medical Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, USA
Email: neeraj.agarwal@hci.utah.edu
[*,3]Huntsman Cancer Institute, University of Utah Hospital, 2000 Circle of Hope, Ste. 2123, Salt Lake City, UT, 84112, USA
Email: andrew.hahn@hsc.utah.edu

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Opinion statement

Nonmetastatic castration-resistant prostate cancer (nmCRPC) comprises a relatively narrow niche of advanced prostate cancer, but the treatment landscape for men with nmCRPC has drastically changed over the past year. Prior to the SPARTAN and PROSPER trials, men with nmCRPC were commonly treated with first-generation androgen receptor antagonists, such as bicalutamide or flutamide, or with estrogens or ketoconazole, none of which were associated with any proven survival benefit. The SPARTAN trial evaluated apalutamide versus placebo for men with nmCRPC and found that apalutamide significantly improved metastasis-free survival (MFS), the primary endpoint of this trial. Similarly, the PROSPER trial showed that enzalutamide significantly improved MFS compared with placebo for men with nmCRPC. In both trials, the data for overall survival was immature at the time of analysis. The SPARTAN and PROSPER trials led to the approval of apalutamide and enzalutamide, respectively, for men with nmCRPC. More recently, the phase 3 trial ARAMIS showed that darolutamide, a novel androgen receptor antagonist, also improves MFS

compared with placebo for men with nmCRPC, and this trial is expected to garner regulatory approval for darolutamide in the nmCRPC setting. Novel imaging modalities are becoming more prevalent for the diagnostic evaluation of men with prostate cancer and are more sensitive than conventional bone or CT scans for detection of oligometastatic disease that previously was undetected. These modalities are likely to reduce the incidence and prevalence of nmCRPC in the near future. Ultimately, the treatment options for men with nmCRPC have significantly improved over the past 2 years.

Introduction

Localized prostate cancer is often cured by definitive therapy (DT), either with radical prostatectomy (RP), radiation therapy (RT), or both. However, it is estimated that between 27 and 53% of all patients that undergo DT will develop biochemical recurrence at some point during their life [1]. Patients with biochemical recurrence will often receive locally directed salvage therapy. Many of these men still go on to have rising prostate-specific antigen (PSA) levels and will start androgen deprivation therapy with a gonadotropin-releasing hormone (GNRH) agonist or antagonist. However, failure of androgen deprivation therapy (ADT) is almost universal. A progressively rising PSA level on continuous ADT with a castrate level of testosterone and absence of metastatic disease on imaging studies results in the disease state known as nonmetastatic castration-resistant prostate cancer (nmCRPC) [1]. For men with nmCRPC, the goal of treatment is to delay the time to metastasis, since bony metastases are associated with pain, pathologic fracture, and spinal cord compression [2, 3]. The risk of developing metastases is associated with baseline PSA levels and PSA doubling time [4–6].

Prior to 2018, there was no consensus recommendation for the ideal treatment of nmCRPC. The treatment options for men with nmCRPC were observation, first-generation androgen receptor (AR) antagonists, such as bicalutamide or flutamide, or with estrogens or ketoconazole, none of which were associated with a survival benefit [7–9]. Several early phase 3 trials evaluated additional treatment options for nmCRPC, and zoledronic acid, sodium clodronate, and atrasentan were all found to not improve survival in men with nmCRPC [4, 10, 11]. Denosumab was the first drug to improve median MFS, but it did not improve OS and ultimately did not receive FDA approval due to marginal improvement in MFS and poor toxicity profile (Table 1) [6, 12, 13]. Over the last decade, the development and introduction of novel second-generation AR antagonists led to the SPARTAN and PROSPER trials, which changed the treatment landscape for nmCRPC.

This review will provide an in-depth discussion of the SPARTAN and PROSPER trials. We will then discuss the utility of using metastasis-free survival (MFS) as an endpoint in nmCRPC and how novel imaging modalities will further change the treatment landscape of nmCRPC. Finally, we will discuss the future direction of treatment, particularly addressing the ARAMIS trial and the use of darolutamide for nmCRPC.

Enzalutamide for nmCRPC

Development of enzalutamide

Enzalutamide is a second-generation nonsteroidal antiandrogen (NSAA) and was first identified in 2006 [14]. Enzalutamide and other second generations differ from their predecessors by binding and antagonizing the AR with higher affinity, reducing nuclear translocation of the AR complex, and impairing DNA binding [14]. Additionally, they are not partial agonists, as seen with bicalutamide in the setting of AR overexpression [14]. In 2012, enzalutamide became the first second-generation AR antagonist to be approved for metastatic castration-resistant prostate cancer (mCRPC) after prior chemotherapy

Table 1. Efficacy and safety of completed and ongoing trials for nonmetastatic castration-resistant prostate cancer

Reported trials for nmCRPC

Trial name	*n*	Median PSA 2× time at baseline	MFS (drug vs. placebo)	Tx discontinuation due to AEs	Most common AEs
SPARTAN	1207	4.4 m	40.5 m vs 16.2 m, (HR 0.28)	10.6% vs 7.0%	Fatigue, HTN, rash, diarrhea, nausea, weight loss, arthralgia, and falls
PROSPER	1401	3.7 m	36.6 m vs 14.7 m, (HR 0.30)	9.3% vs 6.0%	Fatigue, hot flush, HTN, nausea, falls, diarrhea, dizziness, decreased appetite, constipation, and headache
Denosumab	1432	N/A	29.5 m vs 25.2 m, (HR 0.85)	11% vs 10%	Back pain, constipation, arthralgias, diarrhea, and UTIs

Ongoing trials for nmCRPC

Trial name	*n*	Anticipated completion	Primary endpoint	Secondary endpoints
ARAMIS	1509	June 30, 2020	MFS	1. Overall survival 2. Time to first symptomatic skeletal event 3. Time to initiation of first cytotoxic chemotherapy for prostate cancer 4. Time to pain progression 5. Safety and tolerability of ODM-201

nmCRPC nonmetastatic castration-resistant prostate cancer, *n* total number, *PSA* prostate-specific antigen, *MFS* metastasis-free survival, *HR* hazard ratio, *tx* treatment, *AE* adverse events, *m* months, *NR* not reached, *HTN* hypertension, *UTIs* urinary tract infections

following the AFFIRM trial. In the AFFIRM trial, enzalutamide improved overall survival (OS) compared with placebo (18.4 months (m) vs. 13.6 m, hazard ratio (HR) 0.63, $P < 0.001$), as well as improving all secondary endpoints [15]. In 2014, the PREVAIL trial demonstrated that enzalutamide was also effective prior to chemotherapy, with a 29% reduction in the risk of death (HR 0.71, 95% CI 0.60–0.84; $P < 0.001$) and 81% reduction in the risk of 12-month radiographic progression-free survival (rPFS) compared with placebo (HR 0.19, 95% CI 0.15–0.23, $P < 0.001$), as well as benefit in all secondary endpoints [16]. The AFFIRM and PREVAIL trials led to the approval of enzalutamide for all patients with mCRPC. Then, in 2016, the STRIVE trial showed that enzalutamide was superior to bicalutamide in both nonmetastatic and metastatic CRPC subgroups. In men with nmCRPC, enzalutamide resulted in a 76% reduction in risk of progression of disease or death compared with bicalutamide (HR 0.24, 95% CI 0.18–0.32, $P < 0.001$) 17.

PROSPER trial

The PROSPER trial was a landmark phase 3 trial that examined the use of enzalutamide in high-risk patients with nmCRPC [18••]. Men with radiographically confirmed nmCRPC were randomized in a 2:1 ratio to enzalutamide (160 mg po qday) vs. placebo. Patients were required to be on ADT with castration levels of testosterone (less than or equal to 1.73 nmol per liter),

ECOG performance status of 0–1, at least 3 rising PSA levels at greater than 1 week intervals, have a PSA doubling time of 10 months or less, and a baseline PSA level equal to or greater than 2 ng/ml [18••]. Patients were divided into subgroups based on PSA doubling times (< 6 m or ≥ 6 m) and whether they were on anti-osteoclastic agents. The primary endpoint was MFS or time of death of any cause [18••]. Secondary endpoints were OS, time to PSA progression, PSA response rates defined as a decrease of greater than 50% from baseline PSA, time to first chemotherapy, quality of life improvement, and safety [18••]. Total enrollment was ultimately 1401 men with 933 in the enzalutamide arm versus 468 in the placebo group [18••].

At the trial's conclusion, median MFS was 14.7 m in the placebo group compared with 36.6 m (as shown in Table 1) in the enzalutamide group denoting a 71% reduced risk of radiographic progression or death with enzalutamide (HR 0.29, 95% CI 0.24–0.35, $P < 0.001$) [18••]. Enzalutamide also improved all evaluable secondary endpoints. Median time to PSA progression was 37.2 m in the enzalutamide group compared with 3.9 m in the placebo group (HR 0.07, 95% CI 0.05–0.08, $P < 0.001$), and median time to use of first antineoplastic agent was 39.6 m in the enzalutamide arm compared with 17.7 m in the placebo arm (HR 0.21, 95% CI 0.17–0.26, $P < 0.001$) [18••]. Confirmed PSA response rates of greater than or equal to 50% were noted in 76% of patients in the enzalutamide group compared with 2% in the placebo group [18••]. Median OS was not yet reached at the time of publication and median time to deterioration of the Functional Assessment of Cancer Therapy-Prostate Score (FACT-P), assessing for decrease in quality of life was the same in both groups [18••].

In regard to safety, enzalutamide's toxicity profile was similar to previous experiences with the drug in the mCRPC setting. Additionally, men who received enzalutamide had similar quality of life as those men who received placebo. Therapy discontinuation due to an adverse event was similar in the two arms (9% with enzalutamide vs. 6% with placebo) [18••]. Severe adverse events, defined as grade 3 or higher, occurred in 24% of patients treated with enzalutamide compared with 18% with placebo [18••]. The most frequent adverse events were hypertension (12% with enzalutamide vs. 5% with placebo), major adverse cardiovascular events (5% with enzalutamide vs. 3% with placebo), falls and nonpathologic fractures (17% with enzalutamide vs. 8% with placebo), and mental impairment disorders (5% with enzalutamide vs. 2% with placebo) [18••].

Apalutamide for nmCRPC

Development of apalutamide

Apalutamide is another second-generation AR antagonist that is molecularly and mechanistically similar to enzalutamide, as it antagonizes the ligand-binding domain of the AR with potent affinity, prevents AR nuclear translocation, and does not have agonistic effects in the presence of AR overexpression [19]. However, it is of note that apalutamide may have more robust in vivo activity and be maximally effective at lower plasma steady states, which could translate to a safer side effect profile when dosing [19]. In 2016, a phase 2 clinical trial evaluated apalutamide in a small cohort of patients with high-risk nmCRPC, and apalutamide demonstrated promising PSA responses, time to

PSA progression, and good tolerability, ushering further investigation of its use in nmCRPC with the larger SPARTAN trial [20].

SPARTAN trial

The SPARTAN trial was a phase 3 trial that compared apalutamide with placebo (both cohorts being on ADT) in the setting of high-risk nmCRPC [21••]. One thousand two hundred seven men were randomized in 2:1 ratio to apalutamide vs. placebo from October 2013 to December 2016 [21••]. Patients were then further stratified by PSA doubling times (< or ≥ 6 m), use of bone-sparing agents, and whether they had local or regional nodal disease (N0 or N1) [21••]. Like the PROSPER trial, eligible patients had to be deemed high-risk, which was defined as having a PSA doubling time of ≤ 10 m while on ADT [21••]. Patients were also required to not have distant metastases but could still be deemed eligible if classified to have N1 disease on imaging, defined as nodal disease that measured less than 2 cm in the short access that was below the aortic bifurcation [21••]. Ultimately, 806 patients were enrolled in the apalutamide arm and 401 in the placebo group [21••]. Baseline characteristics were similar between the two groups including median age of 74 years, use of bone-sparing agents (10.2% vs. 9.6%), evidence of regional N1 disease (16.5% vs. 16.2%), and median PSA doubling times (4.4 months vs. 4.5 months) [21••]. The primary endpoint was MFS or death, whichever came first, with secondary endpoints being PFS, time to metastasis, time to symptomatic progression, OS, and time to initiation of cytotoxic chemotherapy [21••]. Exploratory endpoints included median second progression-free survival, median time to PSA progression, and percent of patients with PSA response [21••].

At time of analysis, apalutamide significantly improved median MFS or time to death compared with placebo (40.5 m vs. 16.2 m, HR 0.28, 95% CI 0.23–0.35, $P < 0.001$) (Table 1) [21••]. Apalutamide also significantly improved most secondary endpoints reported. Median PFS was 40.5 m in the apalutamide arm compared with 14.7 m in the placebo group (HR 0.29, 95% CI 0.24–0.36, $P < 0.001$) [21••]. Median time to diagnosis of metastasis was 40.5 months in the apalutamide arm and 16.6 months in the placebo group (HR 0.27, 95% CI 0.22–0.34, $P < 0.001$) [21••]. The data for median OS, time to initiation of first chemotherapy, and median time to symptomatic progression was not yet mature at the time of analysis [21••]. Among exploratory endpoints, second progression-free survival and median time to PSA progression were not yet mature at the time of analysis, but PSA response (> 50% PSA decline from baseline) was noted to occur in 89.7% of patients receiving apalutamide and 2.2% with response in the placebo population (HR 40, 95% CI 21–77) [21••].

Apalutamide was also shown to be safe and well-tolerated in the SPARTAN trial. Apalutamide was discontinued due to adverse events in 10.6% of the patients receiving apalutamide and 7.0% of the placebo population, with grade 3–4 adverse events (AEs) occurring in 45.1% of apalutamide patients and 34.2% of patients given placebo [21••]. Serious adverse events occurred in 24.8% of apalutamide patients and 23.1% in patients receiving placebo; AEs resulting in death occurred in 10 patients in the apalutamide arm and only 1 in the placebo group [21••]. Common AEs of fatigue (30.4% vs. 21.1%), rash (23.8% vs. 5.5%), falls (15.6% vs. 9.0%), fracture (11.7% vs. 6.5%),

hypothyroidism (8.1% vs. 2.0%), and seizure (0.2% vs. 0%) occurred more frequently in patients receiving apalutamide compared with the placebo populations respectively [21••]. Additionally, a secondary analysis from SPARTAN showed that men who received apalutamide had similar health-related quality of life compared with men who received placebo only [22]. In the SPARTAN trial, two health-related quality of life questionnaires, Functional Assessment of Cancer Therapy-Prostate (FACT-P) and EQ-5D-3L, were surveyed longitudinally throughout treatment with either apalutamide or placebo, and group mean patient-reported scores changed similarly in both treatment arms over time [2].

Metastasis-free survival in nmCRPC

The Food and Drug Administration's (FDA) approval of apalutamide and enzalutamide for nmCRPC marked the first time that treatments for advanced prostate cancer were approved on the basis of MFS [23]. Many patients with nmCRPC will live for years before they develop mCRPC, and from the time of diagnosis with mCRPC, median OS is still approximately 3 years [16, 24]. Accordingly, median OS is an impractical primary endpoint for patients with nmCRPC, and established surrogate endpoints do not exist for OS in nmCRPC. MFS is defined as time from randomization to either imaging-detectable distant disease or death [21••]. MFS has established surrogacy for OS for adjuvant treatment of high-risk localized prostate cancer [25]. In a study of 19 clinical trials with 12,712 patients with high-risk localized prostate cancer, MFS was shown to be a strong surrogate for OS.

In contrast to adjuvant treatment of high-risk localized prostate cancer, MFS does not have established surrogacy for nmCRPC. An exploratory analysis from the SPARTAN trial showed an association between MFS and OS in men with nmCRPC. The authors showed that patients who developed metastases at 6, 9, and 12 months had significantly shorter median OS compared with those patients without metastases, and a significant positive correlation was observed (Spearman's correlation coefficient 0.62, $p < 0.0001$) [26•]. nmCRPC is not the only early-disease setting to utilize surrogate endpoints for OS. In clinical trials for adjuvant treatment of breast and colon cancer, surrogate endpoints, such as disease-free survival and recurrence-free survival, are commonly used [27, 28]. Moving forward, MFS will likely continue to be used as a primary endpoint for clinical trials in nmCRPC, yet more analyses using data from SPARTAN, PROSPER, and ARAMIS will need to clearly establish surrogacy for MFS in nmCRPC.

Novel imaging modalities and treatment for nmCRPC

nmCRPC comprises a relatively narrow niche in advanced prostate cancer, and the number of patients with nmCRPC will likely decrease as novel imaging modalities become more prevalent. To date, all stages of advanced prostate cancer are defined by conventional imaging, which includes computed tomography (CT) to assess for lymph node involvement or visceral disease and bone scans to assess for bony metastases. However, novel imaging modalities are becoming more common in advanced prostate cancer and include multiparametric magnetic resonance imaging (mpMRI), whole body MRI, and positron emission tomography (PET) with novel tracers. Conventional

imaging modalities have limited sensitivity to detect metastatic disease. In a meta-analysis of 24 studies, CT had a sensitivity of 0.42 for lymph node metastases [29]. Similarly, a meta-analysis of 27 studies showed that bone scintigraphy has a sensitivity of 0.79 for bone metastases at the patient level [30].

^{18}F-FDG PET is routinely used to assess many types of cancer; however, it performs poorly in advanced prostate cancer because prostate cancer cells have low avidity for glucose [31]. Novel tracers for PET scans, including ^{11}C-choline, NaF, F-18-fluciclovine, and ^{68}Ga-PSMA, have improved sensitivity for detecting metastatic lesions in patients with advanced prostate cancer. For example, in a meta-analysis of 16 studies evaluating ^{68}Ga-PSMA PET, 76% of men with biochemically recurrent prostate cancer had a lesion detected on ^{68}Ga-PSMA PET [32]. Similarly, in a systematic review including 4 studies, mpMRI had a sensitivity of 84% for detecting local recurrence [33]. As these novel imaging modalities improve the detection rate for local recurrence and pelvic lymph node metastases, less patients will meet the definition for nmCRPC. However, SPARTAN and PROSPER may provide guidance on how to treat these patients with conventional imaging-negative and novel imaging-positive metastatic disease, as these patients were not included in registration trials for currently approved treatments for metastatic disease [34]. Ultimately, as novel imaging modalities become more prevalent, clinical trials will need to guide treatment decisions for this new cohort of patients.

Future directions for nmCRPC

In addition to changes in nmCRPC due to novel imaging modalities, more therapeutic options are likely to join enzalutamide and apalutamide for men with nmCRPC, beginning with darolutamide. Darolutamide is a nonsteroidal AR antagonist with a unique molecular structure that differs from other AR antagonists [35]. Darolutamide is also distinct from other AR antagonists in that it retains antagonist activity in the setting of AR mutations [35]. Darolutamide was initially shown to be safe and has activity against prostate cancer in two early-phase clinical trials for men with mCRPC [36, 37]. Now, darolutamide is being evaluated in a phase 3 clinical trial for men with nmCRPC and ARAMIS. ARAMIS randomized more than 1500 men to either darolutamide or placebo. In a recent press release, Bayer announced that darolutamide met its primary endpoint by significantly improving MFS compared with placebo [38•]. More detailed results from ARAMIS are expected soon.

Conclusion

In conclusion, SPARTAN and PROSPER have drastically changed the treatment landscape for men with nmCRPC by demonstrating that enzalutamide and apalutamide significantly improve MFS compared with placebo. Currently, the data from these trials is not mature enough to answer whether these drugs improve OS in nmCRPC. While MFS has not been definitively established as a surrogate of OS in nmCRPC, initial studies suggest that MFS will have surrogacy for OS in this setting. Moving forward, darolutamide is likely to join enzalutamide and apalutamide as a therapeutic option for men with nmCRPC.

Finally, the number of patients with nmCRPC will likely decrease in the near future as novel imaging modalities for prostate cancer becomes more prevalent.

Compliance With Ethical Standards

Conflict of Interest

John Esther declares that he has no conflict of interest.

Benjamin L. Maughan has received compensation from Janssen Oncology, Exelixis, Peloton Therapeutics, and Tempus for participation on advisory boards.

Neysi Anderson declares that she has no conflict of interest.

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Andrew W. Hahn declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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This reference is for a press release that states that darolutamide met its primary endpoint of MFS in the phase 3 clinical trial ARAMIS. Darolutamide is a novel AR antagonist, and this result is expected to garner regulatory approval for darolutamide in the nmCRPC setting.