New Androgen Receptor Axis-Targeted Agents in the Treatment of Nonmetastatic Castration-Resistant Prostate Cancer: From Bench to Clinical Trials

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Bone metastasis is a common sign of disease progression in nonmetastatic castration-resistant prostate cancer (nmCRPC). It has been known to be associated with significant morbidity and mortality. Delaying or preventing development of distant metastasis is the ideal goal of treatment. There had been no standard treatment options available for patients with nmCRPC before 2018. Recent approval of new androgen receptor axis-targeted agents in the management of nmCRPC has led to rapid evolution and is worthy of detailed investigation. (Korean J Urol Oncol 2020;18:99-108)

Key Words: Castration-resistant prostate neoplasms • Neoplasm metastasis • Androgen receptor antagonists

INTRODUCTION

Nonmetastatic castration-resistant prostate cancer (nmCRPC) is defined by a progressively rising prostate-specific antigen (PSA) level despite a castrate level of testosterone, without definite radiologic evidence of metastatic disease on conventional imaging modalities.^{1,2} These patients represent a heterogeneous population with regard to risk of progression to metastatic disease, which some cancers progress aggressively while others show an indolent course.³ Prior to 2018, there was no approved treatment recommendation for nmCRPC patients. Men with nmCRPC were basically managed with continuous androgen deprivation therapy to main-

tain castrate serum level of testosterone. The following attempts have been considered for patients with nmCRPC such as clinical trial or observation until the occurrence of metastasis or secondary hormone therapy. The secondary hormone therapy included an addition of first-generation antiandrogen, antiandrogen withdrawal or using other second-line hormonal agents such as estrogen or ketoconazole, none of which has shown any proven survival benefit.⁴ Over the past year, novel second-generation androgen receptor axis-targeted agents (ARTAs) have led to a new paradigm shift in managing patient with nmCRPC. The management of nmCRPC has, therefore, become a major challenge. This review will discuss the recent advances and future direction for the management of nmCRPC using new ARTAs.

U.S. FOOD AND DRUG ADMINISTRATION APPROVAL OF NEW ARTAS

1. Abiraterone Acetate

Abiraterone acetate (AA) is an irreversible, highly se-

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lective inhibitor of cytochrome P450 17A1 that deplete the production of adrenal and intratumoral androgens.⁵ AA was first described in 1993, and the efficacy of AA with prednisone was established in 3 randomized placebo-controlled trials. The U.S. Food and Drug Administration (FDA) initially approved AA with prednisone 10 mg in April 2011 for patients with metastatic CRPC (mCRPC) who had received previously received docetaxel chemotherapy (COU-AA-301 trial) and expanded the indication in December 2012 for men with chemotherapy-naïve mCRPC (COU-AA-302 trial).^{6,7} The COU-AA-301 and COU-AA-302 phase 3 trials showed an improvement in overall survival (OS) with AA by 3.9 months (14.8 months vs. 10.9 months) and 4.4 months (34.7 months vs. 30.3 months) compared to the placebo. In February 2018, the FDA has approved AA with prednisone 5 mg for patients with high-risk, metastatic castration-sensitive prostate cancer (mCSPC) (LATTITUDE trial).⁸

2. Enzalutamide

Enzalutamide is a second-generation, nonsteroidal androgen receptor (AR) antagonist with greater affinity than the conventional first-generation AR antagonists, and patented in 2006.⁹ Enzalutamide competitively inhibits androgen binding to AR, AR nuclear translocation, and interaction with DNA. The FDA-approved enzalutamide for the treatment of mCRPC patients with previous docetaxel-based chemotherapy (AFFIRM trial) in August 2012 and men with chemotherapy-naïve mCRPC (PREVAIL trial) in September 2014, respectively.^{10,11} The AFFIRM and PREVAIL phase 3 trials demonstrated a further gain in OS with enzalutamide by 3.8 months (18.4 months vs. 13.6 months) and 2.2 months (32.4 months vs. 30.2 months) compared to the placebo. In July 2018, the FDA has approved a new indication of enzalutamide for the treatment of men with nmCRPC (PROSPER trial).¹²

3. Apalutamide

Apalutamide is another second-generation, nonsteroidal antiandrogen that binds with high affinity to the ligand-binding domain of AR and inhibits AR translocation to the nucleus, DNA binding capacity, and AR-mediated transcription, which are similar to enzalutamide.¹³ The potential advantages of apalutamide compared to enzalutamide has

shown on its preclinical development include a maximal antitumor effect at a lower dose, and greater efficacy at lower steady-state plasma- and brain-levels, possibly indicating a higher therapeutic index and lower risk of seizure.¹³ Apalutamide was initially described in 2007, and was the first medication to be approved specifically for the treatment of nmCRPC in February 2018 (SPARTAN trial).¹⁴ The FDA has recently approved apalutamide for the management of patients with mCSPC in September 2019 (TITAN trial).¹⁵

4. Darolutamide

Darolutamide is a novel, nonsteroidal AR antagonist with a unique molecular structure that is different from other second-generation AR antagonists.¹⁶ It also competitively inhibits androgen binding to AR, AR nuclear translocation, and AR-mediated transcription. In preclinical study, darolutamide and its metabolite bound to both wild-type and mutant AR, thus retain its full antagonist activity even in AR mutations which have known to cause resistance to first- and second-generation AR antagonists.¹⁶ It has shown negligible blood-brain barrier penetration and low binding affinity for γ -aminobutyric acid type A receptor, which suggests less central nervous system-related adverse events (AEs) such as fatigue, dizziness, cognitive impairment, and seizure.¹⁷ Darolutamide was described in 2011, and this drug was approved for the treatment of men with nmCRPC in July 2019 (ARAMIS trial).¹⁸

Drug approval with novel ARTAs has moved toward earlier stages of prostate cancer from the postchemotherapy mCRPC, chemotherapy-naïve mCRPC, to the high-risk nmCRPC and, in the case of AA, to high-risk mCSPC. A summary of the new ARTAs is presented (Table 1).

EMERGING OF NEW ARTAS IN THE FIELD OF nmCRPC

Patients with nmCRPC are at high risk of developing metastasis or death from prostate cancer, with one-third of patients progressing to metastatic disease, one-fifth dying, and up to 42% experiencing one of these 2 events within 2 years of diagnosis for nmCRPC. Baseline PSA and PSA rise kinetics are known to independent predictors for the risk of metastasis.¹⁹ But, until recently, there was no optimal

Table 1. Drug summary

Drug name	Abiraterone acetate	Enzalutamide	Apalutamide	Darolutamide
Formula	C ₂₆ H ₃₃ NO ₂	C ₂₁ H ₁₆ F ₄ N ₄ O ₂ S	C ₂₁ H ₁₅ F ₄ N ₅ O ₂ S	C ₁₉ H ₁₉ ClN ₆ O ₂
Molecular structure
Molecular weight	391.55 g/mol	464.44 g/mol	477.43 g/mol	398.85 g/mol
Daily oral dose	1,000 mg	160 mg	240 mg	1,200 mg
Pivotal phase 3 trial(s)				
Postchemotherapy mCRPC	*COU-AA 301 (2011) ⁶	AFFIRM (2012) ¹⁰		
Chemotherapy-naïve mCRPC	*COU-AA 302 (2012) ⁷	PREVAIL (2014) ¹¹		
nmCRPC		PROSPER (2018) ¹²	*SPARTAN (2018) ¹⁴	ARAMIS (2019) ¹⁸
High-risk mCSPC	*LATTITUDE (2018) ⁸		TITAN (2019) ¹⁵	

mCRPC: metastatic castration-resistant prostate cancer, nmCRPC: nonmetastatic castration-resistant prostate cancer, mCSPC: metastatic castration-sensitive prostate cancer.
*The first U.S. Food and Drug Administration-approved drug in the different disease setting.

treatment for these patients. It has been demonstrated that new ARTAs improve OS in patients with chemotherapy-naïve mCRPC and in postchemotherapy mCRPC.²⁰ Based on the success of new ARTAs in the treatment of mCRPC, several clinical trials were conducted for the treatment of high risk, nmCRPC patients. Before entering into the main body of the text, 2 questions should be kept in mind for the application of new ARTAs in the nmCRPC setting.

Do all asymptomatic, nmCRPC patients need to be treated? Men with nmCRPC consist of heterogeneous spectrum of the disease defined by a gradual rise in PSA and insensitive conventional imaging techniques. One of the strongest predictors of metastasis or death in men with nmCRPC is the PSA doubling time (PSADT).^{21,22} A phase 3 clinical trial examined the efficacy of denosumab in patients with nmCRPC at high-risk of metastases including baseline PSA $\geq$ 8 ng/mL or PSADT $\leq$ 10 months. It has shown that shorter PSADT was associated with faster development of bone metastasis. A total of 1,432 men with nmCRPC were assigned to receive monthly subcutaneous denosumab 120 mg or placebo. Denosumab increased median bone-metastasis-free survival for 4 months compared with placebo (29.5 months vs. 25.2 months; hazard ratio [HR], 0.85; $p=0.028$), but it did not improve OS (43.9 months vs. 44.8 months; HR, 1.01; $p=0.91$). There was an inflection point at a PSADT of around 8 months, where patient with shorter PSADT showed a dramatic increase in the risk of developing metastasis or death.²¹ An observational study of 441 men with nmCRPC also demonstrated that PSADT less than 9 months was closely associated with higher prostate cancer-specific mortality and all-cause mortality. The cutoff thresholds for risk stratification in men with nmCRPC have been proposed.²² These results confirmed the evidence linking PSA kinetics to development of metastasis or death in men with nmCRPC.

What is an adequate surrogate to predict on the survival in managing patients with nmCRPC? The well-known limitation of clinical trials in prostate cancer is that it requires a long-term follow-up period to assess the impact of the new therapeutic intervention. Metastasis-free survival (MFS) is defined as the time from beginning of treatment to the first detection of distant metastasis or death of any cause. The advantage of using a surrogate such as MFS rather than OS is the ability to observe the number of required events

earlier. Almost all of the patients who die from prostate cancer ultimately develop distant metastases to bone or other viscera prior to their death. The majority (86%) of incidence flow into mCRPC states was from the nmCRPC clinical state.²³ The Intermediate Clinical Endpoints in Cancer of the Prostate study, a meta-analysis of 28 randomized trials, showed that MFS is closely related with OS in clinically localized prostate cancer with an approximate 15% chance of dying prostate cancer over 10 years.²⁴ In addition, radiographic progression-free survival (PFS) was a highly predictive factor for OS in the mCRPC setting according to the COU-AA-302 and PREVAIL results.^{25,26} Thus, MFS can allow an expeditious surrogate endpoint for survival that is increasingly recognized in clinical trials from the FDA standpoint for regulatory approval.²⁷

CLINICAL TRIALS OF NEW ARTAS IN THE FIELD OF nmCRPC

1. Phase 2 Clinical Trials

1) STRIVE trial (enzalutamide vs. bicalutamide)

The STRIVE (Safety and Efficacy Study of Enzalutamide Versus Bicalutamide in Men with Prostate Cancer) trial enrolled the 396 patients with chemotherapy-naïve CRPC either metastatic ($n=257$, 65%) or nonmetastatic ($n=139$, 35%).²⁸ The patients were randomly assigned to receive enzalutamide 160 mg or bicalutamide 50 mg daily. The primary endpoint was PFS, defined as the time from initiation of treatment to a progression event including PSA progression or radiographic progression or death. The PFS was not yet reached with enzalutamide and 8.6 months with bicalutamide in men with nmCRPC (HR, 0.24; $p<0.001$). The secondary endpoints showed more beneficial in the enzalutamide group than in the bicalutamide group: time to PSA progression (not yet reached vs. 11.1 months; HR, 0.18; $p<0.001$), PSA decline of $\geq 50\%$ (91% vs. 42%, $p<0.001$), and radiographic PFS (not yet reached vs. not yet reached; HR, 0.24; $p<0.001$). Notably, in men treated with enzalutamide, more favorable results with regard to PFS and PSA progression were observed in the nmCRPC disease state than in the mCRPC: PFS (not yet reached in nmCRPC vs. 16.5 months in mCRPC), PSA progression (not yet reached vs. 24.9 months), and PSA decline of $\geq 50\%$ (91% vs. 76%). This was the first study to suggest a potential benefit

of new ARTAs in the nmCRPC setting.

2) IMAAGEN trial (abiraterone acetate)

The IMAAGEN (Impact of Abiraterone Acetate in Prostate-Specific Antigen) study recruited the high-risk, nmCRPC patients with baseline PSA ≥ 10 ng/mL or PSADT ≤ 10 months.²⁹ The 131 patients received once daily AA 1,000 mg plus prednisone 5 mg in customary 28-day treatment cycles. The primary endpoint was the proportion of men obtaining a PSA reduction of $\geq 50\%$ during cycles 1–6. Of total patients, 44 men (34%) remained on treatment, with a median follow-up of 40.0 months. One hundred 6 patients (86.9%) achieved a 50% reduction or greater in PSA by the end of cycle 6. The time to PSA progression and estimated radiographic PFS was 28.7 months and 41.4 months, respectively. However, this study has some limitations including no comparative arm, uncertain calculation of time to metastasis, and no available MFS data.

2. Phase 3 Clinical Trials

1) SPARTAN trial (apalutamide vs. placebo)

(1) Clinical efficacy

The SPARTAN (Selective Prostate Androgen Receptor Targeting with ARN-509) was a multicenter, double-blind, placebo-controlled, phase 3 trial of apalutamide in patients with high-risk nmCRPC who had rapidly rising PSA values with a PSADT ≤ 10 months.¹⁴ This trial was conducted at 332 sites in 26 countries. Sixteen percent of patients had N1 disease, defined as pelvic lymph nodes < 2 cm of diameter in the short axis below the aortic bifurcation, at study entry. A total of 1,207 patients were randomized in a 2:1 fashion to receive either apalutamide 240 mg/day (n=806) or placebo (n=401). The primary endpoint was MFS. Secondary endpoints were time to metastasis, PFS which defined as the time to the first detection of local or distant metastasis on imaging or death, time to symptomatic progression, OS, and time to the first use of cytotoxic chemotherapy.

With a median follow-up of 20.3 months, apalutamide significantly improved MFS compared to placebo (40.5 months vs. 16.2 months; HR, 0.28; $p < 0.001$), representing a 2-year delay in the development of distant metastasis. The favorable MFS of apalutamide was consistent across all subgroups. All secondary endpoints were in favor of apalu-

tamide: time to metastasis (40.5 months vs. 16.6 months; HR, 0.27; $p < 0.001$), PFS (40.5 months vs. 14.7 months; HR, 0.29; $p < 0.001$), and time to symptomatic progression (not yet reached vs. not yet reached; HR 0.45; $p < 0.001$). The time to PSA progression was not yet reached in the apalutamide group as compared to 3.7 months in the placebo group. (HR, 0.06). The apalutamide group showed an 89.7% decrease in median PSA value while placebo group showed a 40.2% increase at 3 months after randomization. Treatment discontinuation due to disease progression was 19.3% in the apalutamide arm and 52.8% in the placebo arm. The percentage of men receiving subsequent treatment for mCRPC was 52.5% in the apalutamide group and 77.8% in the placebo group. AA plus prednisone was the most common subsequent therapeutic drug. At the time of the analysis, the median PFS2 (PFS on subsequent treatment from randomization) was not yet reached in the apalutamide arm and 39.0 months in the placebo arm (HR, 0.49; $p < 0.001$), with a 51% risk reduction of subsequent treatment.

(2) Adverse events

Grade 3 or 4 AEs occurred in 45.1% of patients with apalutamide arm and 34.2% with placebo arm. The percentage of patients with serious AEs was similar in both groups (24.8% vs. 23.1%). The following AEs were higher in the apalutamide group than in the placebo group: 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. 0.0%). However, the majority of AEs were grade 2 or less. Treatment discontinuation due to AEs was more frequent in the enzalutamide group (10.6% vs. 7.0%).

2) PROSPER trial (enzalutamide vs. placebo)

(1) Clinical efficacy

The PROSPER (Safety and Efficacy Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer) was a double-blind, placebo-controlled, phase 3 trial of enzalutamide and recruited patients with high-risk nmCRPC who are at high risk for progression based on a PSADT ≤ 10 months.¹² The trial was conducted more than 300 sites in 32 countries. A total of 1,401 patients were randomly assigned in a 2:1 ratio to receive either enzalutamide 160 mg (n=933) or placebo (n=468) once

daily. The primary endpoint was MFS. Secondary endpoints included time to PSA progression, PSA response rate (PSA decrease of $\geq 50\%$ from baseline), time to initiation of subsequent antineoplastic therapy, quality-of-life assessments, and OS.

Enzalutamide treatment significantly decreased the risk of distant metastasis or death compared to placebo (23% vs. 49%). The MFS was 36.6 months for men treated with enzalutamide and 14.7 months for men with placebo (HR, 0.29; $p < 0.001$), demonstrating a 71% risk reduction of radiographic progression or death. The MFS benefit of enzalutamide was consistent across all the prespecified subgroups. Patients receiving enzalutamide had longer time to PSA progression than the placebo group (37.2 months vs. 3.9 months; HR, 0.07; $p < 0.001$), more PSA response rate (76% vs. 2%), and delayed time to first use of an antineoplastic therapy (39.6 months vs. 17.7 months; HR, 0.21; $p < 0.001$). The proportion of patients experiencing radiographic progression or death in the enzalutamide arm was 50% less than that of the placebo arm (23% vs. 49%). Treatment discontinuation due to progressive disease was 14.8% in the enzalutamide group compared to 47.4% in the placebo group. The most common subsequent therapy was AA plus prednisone (37.7% vs. 36.4%).

(2) Adverse events

The AEs of enzalutamide were consistent with those reported in previous phase 3 clinical trials for patients with mCRPC.^{10,11} Grade 3 or 4 AEs were reported in 31.4% of patients in the enzalutamide group and 23.4% in the placebo group. A higher percentage of patients receiving enzalutamide had severe AEs than did those receiving placebo (24.3% vs. 18.3%). Fatigue was the most common AE in patients with enzalutamide (32.6% vs. 13.8%). Patients receiving enzalutamide had higher rate of falls or non-pathologic fractures compared to placebo group (17% vs. 8%). AEs of special interest occurred more frequently in the enzalutamide group than the placebo group including hypertension (12.3% vs. 5.4%), major cardiovascular events (5.2% vs. 2.8%), mental impairment disorders (5.2% vs. 1.9%), and convulsion (0.3% vs. 0.0%). Discontinuation of the treatment due to AEs were more common in the enzalutamide group (9.3% vs. 6.0%).

3) ARAMIS trial (darolutamide vs. placebo)

(1) Clinical efficacy

The ARAMIS (Androgen Receptor Antagonizing Agent for Metastasis-free Survival) was double-blind, placebo-controlled, phase 3 trial of darolutamide in men with nmCRPC and a PSADT ≤ 10 months.¹⁸ The trial was conducted at 409 sites in 36 countries. Similar to the SPARTAN trial, patients with pelvic lymph nodes which located below the aortic bifurcation and measuring < 2 cm in the short axis were allowed (21.6%). A total of 1,509 patients were randomized in a 2:1 ratio to receive either darolutamide 600 mg ($n=955$) or placebo ($n=554$) twice daily. Patients who have had previous seizure or conditions predisposing to seizure were not excluded from the study. The primary endpoint was MFS. Secondary endpoints included OS, time to pain progression, time to first symptomatic skeletal event, and time to first cytotoxic chemotherapy.

The median MFS with darolutamide was similar to those of 2 previous phase 3 randomized trials (SPARTAN, PROSPER) in patients with nmCRPC. The MFS was 40.4 months in the darolutamide group as compared to 18.4 months in the placebo group (HR, 0.41; $p < 0.001$), translating to a 59% risk reduction of metastasis or death. The MFS of darolutamide was consistently favorable among all subgroups. Darolutamide showed greater benefits than placebo for all secondary endpoints: OS (not yet reached vs. not yet reached; HR, 0.71; $p=0.045$), time to pain progression (40.3 months vs. 25.4 months; HR, 0.65; $p < 0.001$), time to cytotoxic chemotherapy (not yet reached vs. 38.2 months; HR, 0.43; $p < 0.001$), and time to symptomatic skeletal event (not yet reached vs. not yet reached; HR, 0.43; $p=0.01$). Other exploratory endpoints similarly favored darolutamide group including PFS (36.8 months vs. 14.8 months; HR, 0.38; $p < 0.001$) and time to PSA progression (33.2 months vs. 7.3 months; HR, 0.13; $p < 0.001$).

(2) Adverse events

Grade 3 or 4 AEs were observed in 24.7% of patients in the darolutamide arm and 19.5% in the placebo arm. The incidence of grade 5 AEs in both groups was comparable (3.9% vs. 3.2%). The incidence of AEs was generally similar in the darolutamide and placebo groups with the exception of fatigue (12.1% vs. 8.7%), but which was less common than in the SPARTAN or PROSPER trial. In addition, AEs of interest reported much lower incidence than

the previous 2 trials including hypertension (6.6%), falls (4.2%), dizziness (4.5%), and cognitive disorder (0.4%). Although patients with a history of seizure were allowed to recruit the trial, seizure occurred rarely and similar in either arm at 0.2%. AEs led to discontinuation of assigned regimen were similar in both groups (8.9% vs. 8.7%). A summary of pivotal nmCRPC phase 3 trials with new ARTAs is described (Table 2).

PROMISING IMPACT OF NEW IMAGING TECHNIQUES

The conventional imaging techniques for the evaluation of distant metastasis are computed tomography (CT) and

bone scan, but they have limited accuracy. CT has a poor performance in detection of metastatic lymph nodes in a meta-analysis (pooled sensitivity 42% and specificity 82%).³⁰ Similarly, other meta-analysis has shown that bone scan has a pooled sensitivity of 59% and specificity of 75% on a per-lesion basis for detection of bone metastasis.³¹

Positron emission tomography (PET) using ¹⁸F-fluorodeoxyglucose, the workhorse radiotracer in PET, has not found preference in prostate cancer because it shows poor glucose activity. Often, there is significant overlap in the uptake between malignancy and benign disease of the prostate. Furthermore, high urinary excretion of radiotracer may obscure pathologic uptake.³² Hence, last 2 decades have seen the development of new radioisotracers. Fatty

Table 2. Summary of new ARTAs trials in nmCRPC

Variable	SPARTAN ¹⁴			PROSPER ¹²			ARAMIS ¹⁸		
	Apalutamide (n=806)	Placebo (n=401)	HR	Enzalutamide (n=933)	Placebo (n=468)	HR	Darolutamide (n=955)	Placebo (n=554)	HR
Inclusion criteria	cN0-1M0 CRPC PSAD ≤10 months			cN0M0 CRPC PSAD ≤10 months, PSA ≥2 ng/mL			cN0-1M0 CRPC PSAD ≤10 months, PSA ≥2 ng/mL		
No. of patients		1,207			1,401			1,509	
Median duration of follow-up (mo)		20.3			18.5			17.9	
Median baseline PSA (ng/mL)	7.7	7.9		11.1	10.2		9.0	9.7	
Median baseline PSADT (mo)	4.4	4.5		3.8	3.6		4.4	4.7	
Stratification parameters									
Baseline PSADT ≤6 mo	71.5%	70.8%		76.6%	77.1%		69.8%	67.0%	
Use of bone sparing agent (yes)	10.2%	9.7%		11.2%	10.3%		3.2%	5.8%	
Presence of LNs on imaging (yes)	16.5%	16.2%		N/A	N/A		17.1%	28.5%	
Primary endpoint									
MFS (mo)	40.5	16.2	0.28	36.6	14.7	0.29	40.4	18.4	0.41
Secondary endpoints									
OS (mo): interim analysis	NYR	39.0	0.70	NYR	NYR	0.80	NYR	NYR	0.71
PFS (mo)	40.5	14.7	0.29	N/A	N/A		36.8	14.8	0.38
Time to PSA progression (mo)	NYR	3.7	0.06	37.2	3.9	0.07	33.2	7.3	0.13
Confirmed PSA response ≥50%	89.7%	2.2%		76.3%	2.3%		N/A	N/A	
Discontinued study treatment	39.1%	70.1%		32.0%	62.4%		35.5%	63.9%	
Treatment discontinuation due to progression	19.3%	52.8%		14.8%	47.4%		N/A	N/A	
AEs									
Any grade AEs	96.5%	93.2%		86.9%	77.4%		83.2%	76.9%	
Grade 3 or 4 AEs	45.1%	34.2%		31.4%	23.4%		24.7%	19.5%	
Treatment discontinuation due to AEs	10.6%	7.0%		9.3%	6.0%		8.9%	8.7%	
All cause of death	1.2%	0.3%		3.4%	0.9%		4.3%	3.4%	

ARTAs: androgen receptor axis-targeted agents, nmCRPC: nonmetastatic castration-resistant prostate cancer, HR: hazard ratio, PSA: prostate-specific antigen, PSADT: PSA doubling time, LN: lymph node, MFS: metastasis-free survival, OS: overall survival, PFS: progression-free survival, AE: adverse event, NYR: not yet reached, N/A: not available.

acid oxidation, rather than glycolysis, is the dominant metabolic pathway in prostate cancer. In addition, during cell membrane turnover, carbon and choline uptake are increased in prostate cancer. Therefore, acetate and choline radiolabeled with C or F have been favored in prostate cancer.³³ The increase amino acid turnover in prostate cancer also promoted the use of ¹⁸F-fluciclovine, a synthetic leucine analogue.³⁴ Of late, much attention has been on developing radiotracer ligands targeted at the prostate-specific membrane antigen (PSMA), a cell surface protein whose expression is more specific to prostate than other tissue. PSMA expression shows a positive correlation with tumor aggressiveness, metastatic disease, and castrate resistance. The PSMA-ligand complex is readily internalized and released into the cytoplasm of prostate cancer cells, which makes PSMA an attractive target for diagnostic imaging.³⁵ Novel tracers for PET scans such as ¹¹C-choline, ¹⁸F-fluciclovine, ⁶⁸Ga-PSMA have shown improved sensitivity for detection of metastatic lesions in advanced prostate cancer.³⁶⁻³⁹ Newer and more sensitive imaging techniques are expected to improve the detection rate of metastasis, which will lead to less patient population that meets the definition of nmCRPC.

CONCLUSIONS

The advent of new, second-generation ARTAs has dramatically changed the management landscape for men with mCRPC. Conversely, there has been no consensus recommendation for the treatment of nmCRPC. Three recent phase 3 trials (SPARTAN, PROSPER, and ARAMIS) using of new ARTAs have demonstrated clear MFS benefit compared to the placebo as the primary endpoint. Nearly 60%-70% of risk reduction and 2 years delay in the development of metastases or death were reported. The secondary endpoints all met with the exception of OS that is not yet mature. Based on current available data, new ARTAs represent equivalent clinical efficacy for the treatment of patients with nmCRPC. The 2019 National Comprehensive Cancer Network guideline update included the category 1 option of apalutamide or darolutamide, or enzalutamide as a systemic therapy for nmCRPC patients with PSADT ≤ 10 months.⁴⁰ Although safety profiles showed that new ARTAs are generally well tolerated, AEs of interest such as fall, car-

diovascular, and central nervous system-related toxicity were more frequently found compared to the placebo. These AEs have negatively impacted the health-related quality of life. Therefore, surveillance without intervention may be considered, particularly for PSADT >10 months and/or when the patient is frail with limited life expectancy. Novel imaging modalities may contribute to discriminate between nmCRPC and mCRPC. Further studies are necessary to better understand for the patients who will most likely to benefit from earlier treatment with new ARTAs in nmCRPC.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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