Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology May 2022

Factors That Guide Selection Among Androgen Receptor Inhibitors in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

Moderator

Matthew B. Rettig, MD
Professor of Medicine and Urology
Medical Director, Prostate Cancer Program
Institute of Urologic Oncology
David Geffen School of Medicine at UCLA
Los Angeles, California
Chief, Division of Hematology-Oncology
VA Greater Los Angeles Healthcare System
Los Angeles, California

Discussants

Himisha Beltran, MD
Associate Professor of Medicine
Dana Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

William K. Oh, MD
Clinical Professor of Medicine
Division of Hematology and Medical Oncology
Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai
New York, New York

Abstract: Prostate cancer is the most common cancer affecting men in the United States. A significant proportion of men have nonmetastatic castration-resistant prostate cancer (CRPC), in which biochemical progression is evidenced by rising levels of prostate-specific antigen without radiographic progression in the setting of castrate levels of testosterone. Historically, the preferred treatment for these patients has been observation and continued treatment with androgen deprivation therapy (ADT). The standard of care has recently evolved to include the addition of androgen receptor (AR) inhibitors to ADT. The US Food and Drug Administration has approved 3 next-generation AR inhibitors for nonmetastatic CRPC: apalutamide, enzalutamide, and darolutamide. These agents were approved based on data from phase 3 randomized trials. There is now a significant amount of data from these trials. All 3 agents improve metastasis-free survival and overall survival. Selection of treatment can be guided by factors such as the patient's overall health and frailty, potential drug-drug interactions, and the safety profile associated with each agent.

Recent Clinical Trial Data of Androgen Receptor Inhibitors in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

Himisha Beltran, MD

Associate Professor of Medicine
Dana Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

Castration-resistant prostate cancer (CRPC) refers to prostate cancer that progresses during treatment with androgen deprivation therapy (ADT). Gonadal androgen suppression with testosterone-lowering therapy has been the backbone of systemic therapy for prostate cancer for nearly 80 years. ADT is used in combination with radiation for men with intermediate- and high-risk localized disease, intermittently for biochemically recurrent disease, and continuously for patients with metastatic disease, often in combination with other agents.

For patients with recurrent or metastatic prostate cancer, ADT is not considered a curative therapy, and tumors may become resistant to treatment. Mechanisms of resistance generally occur via reactivation of androgen receptor (AR) signaling.

CRPC is formally defined as a rising level of prostate-specific antigen (PSA) in the setting of castrate levels of testosterone (<50 ng/dL).[1] A rising PSA is defined as a level that is more than 2 ng/mL higher than the nadir and 25% or more over the nadir, which is confirmed by a second test at least 3 weeks after the first one.

In men with biochemically recurrent disease who develop rising PSA during treatment with ADT, scans are performed to evaluate for radiographic progression. Conventionally, these imaging tests have been conducted with computed tomography (CT) and bone scans. If no metastases are apparent on radiologic imaging, the designation is M0, or nonmetastatic, CRPC.

The natural history of nonmetastatic CRPC is variable, and approximately one-third of patients will develop visible metastases within 2 years.[2-4] Men with a PSA doubling time of less than 10 months are at very high risk for developing metastases.

Historically, management has consisted of watchful waiting. The rising PSA is monitored while ADT is continued without any other therapeutic intervention until metastasis becomes apparent on imaging. This paradigm has now changed in recent years, with the advent of earlier interventions specifically for patients at high risk for developing metastatic disease.

Current Treatment Paradigm

CRPC is primarily driven by reactivated AR signaling. Based on this underlying mechanism, several potent AR pathway inhibitors have entered the clinic and are now used in various scenarios, including nonmetastatic and

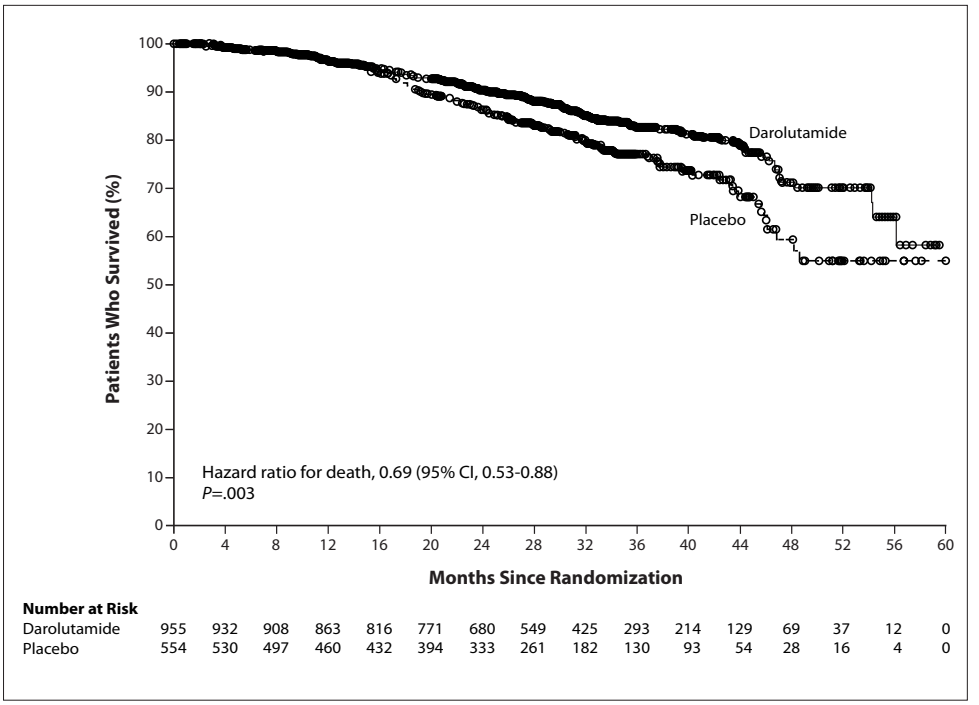


Figure 1. Overall survival in a long-term analysis of the phase 3 ARAMIS trial, which compared darolutamide vs placebo in patients with nonmetastatic, castration-resistant prostate cancer. Adapted from Fizazi K et al. *N Engl J Med*. 2020;383(11):1040-1049.[11]

metastatic CRPC.

For nonmetastatic CRPC, guidelines from the National Comprehensive Cancer Network (NCCN) recommend the addition of a potent AR antagonist to ADT in patients with rising PSA and a doubling time of 10 months or less.[5] For patients with longer PSA doubling times, the NCCN guidelines state that it remains acceptable to continue monitoring while continuing ADT. Three next-generation AR inhibitors are approved in this setting: apalutamide, enzalutamide, and darolutamide.

Efficacy of AR Pathway Inhibitors

The NCCN recommendations regarding the use of these AR inhibitors in nonmetastatic CRPC are based on data from three phase 3 clinical trials.[6-8] The study designs for each of these trials were very similar in that they enrolled men with nonmetastatic CRPC who showed evidence of rising PSA with no visible metastases on conventional imaging with CT and bone scans. All patients were at high risk for progression, with a baseline PSA of 2 ng/mL or higher and a PSA doubling time of 10 months or less. In each of these trials, the AR inhibitor was compared against placebo.

Each of the studies met their primary endpoint of an improvement in metastasis-free survival, which formed the basis of the approval of apalutamide, enzalutamide, and darolutamide by the US Food and Drug Administration (FDA). In addition, the 3 studies have since demonstrated an overall survival benefit for each of these agents, with approximately 1 year of life gained (Figure 1).[9-11] Importantly, these studies showed that the addition of an AR antagonist preserved quality of life. Therefore, early intervention with the addition of an AR inhibitor to ADT for patients with nonmetastatic CRPC at high risk for progression is the standard of care, with improvements in clinically meaningful endpoints of metastasis-free survival, overall survival, and quality of life.

It is important to note that in all 3 trials, conventional imaging with CT or a bone scan was used to confirm the absence of metastasis. In recent years, prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT scans have become more available and are considered a more sensitive technique for detecting prostate cancer metastasis.[12] This imaging modality detects PSMA expressed on the cell surface of prostate cancer cells. It is likely that many of the patients in these trials would have been positive for metastasis if assessed by a PSMA PET/CT scan.

The SPARTAN Trial

SPARTAN was an international, randomized, double-blind, placebo-controlled phase 3 trial designed to evaluate the efficacy and safety of apalutamide in men with nonmetastatic CRPC.[6] This large study was conducted at 332 sites throughout North America, Europe, and

the Asia-Pacific region. All patients had histologically or cytologically confirmed prostate adenocarcinoma and had developed CRPC that was at high risk for disease progression and metastasis, based on a PSA doubling time of 10 months or less during continuous treatment with ADT. Patients had nonmetastatic disease based on the absence of visible metastasis on bone scans and CT scans of the pelvis, abdomen, chest, and head. Patients with local or regional nodal disease were largely excluded from enrollment. Enrollment did include patients with malignant pelvic lymph nodes located below the aortic bifurcation and measuring less than 2 cm in the short axis (N1). The SPARTAN trial excluded patients with a history of seizures or conditions that might predispose to seizures.[6]

Between October 2013 and December 2016, the trial randomly assigned 1207 patients in a 2-to-1 ratio to treatment with apalutamide at 240 mg/day (n=806) or matched placebo (n=401). Both were added to ADT, which was continued throughout the treatment period. Stratification factors included doubling time (>6 months vs ≤6 months), use of bone-sparing agents (yes vs no), and classification of local or regional nodal disease (N0 vs N1) at baseline. Treatment continued until disease progression, intolerable adverse events, or withdrawal of consent.[6]

At baseline, the patients' median age was 74 years in both arms (ranges, 48-94 in the apalutamide arm and 52-97 in the placebo arm). The median PSA doubling time was 4.40 months in the apalutamide arm vs 4.50 months in the placebo arm. A very short PSA doubling time of 6 months or less was reported in 71.5% vs 70.8%, respectively. Approximately 10% of patients were receiving a bone-sparing agent at baseline. N1 disease was reported in 16.5% of the apalutamide arm and 16.2% of the placebo arm.[6]

After a median follow-up of 20.3 months, the primary endpoint of metastasis-free survival was a median of 40.5 months with apalutamide vs 16.2 months with placebo, for a hazard ratio (HR) for metastasis or death of 0.28 (95% CI, 0.23-0.35; *P*<.001). These data plus the safety data led the study's independent data and safety monitoring committee to unanimously recommend that the study be unblinded and that treatment with apalutamide be offered to patients in the placebo arm.[6]

Several secondary endpoints also showed benefit with apalutamide vs placebo. The time to second progression-free survival was prolonged with apalutamide vs placebo (HR, 0.49; 95% CI, 0.36-0.66). The median time to PSA progression was not reached in the apalutamide arm vs 3.7 months in the placebo arm (HR, 0.06; 95% CI, 0.05-0.08). At the 12-week time point, the median PSA was 89.7% lower in the apalutamide arm, and had risen by 40.2% in the placebo arm.[6]

Overall survival was reported at the final analysis of the SPARTAN trial, at a median follow-up of 50.4 months. At that time, the median overall survival was 73.9 months with apalutamide vs 59.9 months with placebo (HR, 0.78; 95% CI, 0.64-0.96; *P*=.016).[9]

Treatment was discontinued by 10.6% of patients in the apalutamide arm vs 7% of those in the placebo arm. Grade 3/4 adverse events were reported in 45.1% vs 34.2%, respectively. Treatment-related adverse events of any grade that occurred at a higher rate in the apalutamide arm vs the placebo arm included fatigue (30.4% vs 21.1%), rash (23.8% vs 5.5%), falls (15.6% vs 9.0%), fractures (11.7% vs 6.5%), hypothyroidism (8.1% vs 2.0%), and seizures (0.2% vs 0%).[6]

A serious adverse event was reported in 24.8% of the apalutamide arm vs 23.1% of the placebo arm. In the apalutamide arm, 10 patients died from adverse events. Prostate cancer and sepsis caused the death of 2 patients. Acute myocardial infarction, cardiorespiratory arrest, cerebral hemorrhage, myocardial infarction, multiple organ dysfunction, and pneumonia each led to the death of 1 patient. One patient in the placebo arm died from an adverse event.[6]

Based on the results of this study, in February 2018, apalutamide received FDA approval for the treatment of men with nonmetastatic CRPC.[13]

The PROSPER Trial

PROSPER was an international, double-blind, randomized, placebo-controlled phase 3 trial conducted at more than 300 sites throughout 32 countries.[7] The study investigated the efficacy and safety of enzalutamide for the treatment of nonmetastatic CRPC. The trial enrolled patients with pathologically confirmed prostate adenocarcinoma. The patients had a minimum of 3 rising PSA measurements taken at least 1 week apart, a baseline PSA level of 2 ng/mL or higher, and a PSA doubling time of 10 months or less. Patients had nonmetastatic disease according to either CT or magnetic resonance imaging (MRI) and a whole-body bone scan. The trial excluded patients with suspected brain metastases, active leptomeningeal disease, or a history of seizures or a condition that might predispose to seizures.[7]

From November 2013 to June 2017, the trial randomly assigned 1401 patients in a 2-to-1 ratio to receive enzalutamide at 160 mg/day (n=933) or placebo (n=468). Both were added to ADT. Stratification factors included PSA doubling time (<6 months vs ≥6 months) and previous or current use of a bone-targeting agent (yes vs no). Treatment was continued until disease progression or intolerable toxicity.[7]

At baseline, the patients' median age was 74 years (range, 50-95) in the enzalutamide arm and 73 years

(range, 53-92) in the placebo arm. The median PSA level was 11.1 ng/mL vs 10.2 ng/mL, respectively. The median PSA doubling time was 3.8 months vs 3.6 months, respectively, and 77% of patients in each arm had a PSA doubling time of less than 6 months. Approximately 10% of patients in each arm were receiving a bone-sparing agent at baseline.[7]

The primary endpoint, metastasis-free survival, was significantly prolonged in the enzalutamide arm. The median metastasis-free survival was 36.6 months in the enzalutamide arm (after a median follow-up of 18.5 months) vs 14.7 months in the placebo arm (after a median follow-up of 15.1 months). This difference translated to a 71% lower risk of radiographic progression or death with enzalutamide (HR, 0.29; 95% CI, 0.24-0.35; *P*<.001). Based on this primary analysis, the study was unblinded, and patients in the placebo group were given the opportunity to receive enzalutamide.[7]

Several secondary endpoints also showed benefit with enzalutamide vs placebo, including median time to PSA progression (37.2 months vs 3.9 months, respectively; HR, 0.07; 95% CI, 0.05-0.08; *P*<.001) and confirmed PSA response of 50% or higher (76% vs 2%, respectively). Another key secondary endpoint was the median time to first use of subsequent antineoplastic therapy, which was 39.6 months with enzalutamide vs 17.7 months with placebo (HR, 0.21; 95% CI, 0.17-0.26; *P*<.001).[7]

A prespecified third interim analysis of the PROSPER study, conducted after a median follow-up of 48 months, reported data for overall survival. The median overall survival was 67 months in the enzalutamide arm vs 56.3 months in the placebo arm. Enzalutamide was associated with a 27% lower risk of death compared with placebo (HR, 0.73; 95% CI, 0.61-0.89; *P*=.001).[10]

Grade 3 or higher adverse events occurred in 31% of the enzalutamide arm vs 23% of the placebo arm. A total of 9% of patients in the enzalutamide arm and 6% in the placebo arm discontinued treatment owing to an adverse event. Fatigue was the most frequently reported adverse event with enzalutamide (all grades, 33% vs 14% with placebo; grade ≥3, 3% vs 1% with placebo). Adverse events of special interest that were at least 2% more frequent with enzalutamide vs placebo included hypertension (12% vs 5%), major adverse cardiovascular events (5% vs 3%), and mental impairment disorders (5% vs 2%). An adverse event led to death in 32 patients (3%) in the enzalutamide arm and 3 patients (1%) in the placebo arm.[7]

Based on these data, the FDA approved enzalutamide for the treatment of men with nonmetastatic CRPC in July 2018.[14] This approval broadened the indicated patient population to include patients with nonmetastatic CRPC. The previous approval encompassed men with metastatic CRPC.[14]

The ARAMIS Trial

The multinational, randomized, double-blind, placebo-controlled phase 3 ARAMIS trial assessed the efficacy and safety of darolutamide for the treatment of nonmetastatic CRPC.[8] The trial enrolled CRPC patients with histologically or cytologically confirmed prostate adenocarcinoma. Eligibility included a baseline PSA level of 2 ng/mL or higher and a PSA doubling time of 10 months or less. Nonmetastatic status was confirmed by either CT or MRI of the pelvis, abdomen, and chest or a whole-body bone scan that showed no detectable metastases. The trial enrolled patients with pelvic lymph nodes smaller than 2 cm in diameter in the short axis below the aortic bifurcation. In contrast to the SPARTAN and PROSPER trials,[6,7] the ARAMIS trial did not exclude patients with a history of seizures or conditions predisposing to seizures.[8]

Between September 2014 and March 2018, the trial randomly assigned 1509 patients in a 2-to-1 ratio to receive either darolutamide at 600 mg twice daily (n=955) or placebo (n=554). Both treatments were added to ADT. Stratification factors included PSA doubling time (≤6 months vs >6 months) and the use of osteoclast-targeted therapy at randomization (yes vs no). Treatment was continued until disease progression, intolerable toxicity, or withdrawal of consent.[8]

The patients' median age at baseline was 74 years in each arm (range, 48-95 in the darolutamide arm and 50-92 in the placebo arm). The median PSA level was 9.0 ng/mL in the darolutamide arm and 9.7 ng/mL in the placebo arm. The median PSA doubling time was 4.4 months and 4.7 months, respectively. A median PSA doubling time of 6 months or less was reported in 70% of patients in the darolutamide arm and 67% in the placebo arm. Use of a bone-sparing agent at baseline was noted in 3% of the darolutamide arm and 6% of the placebo arm. Positive lymph nodes, as defined by the study protocol, were found in 17% of patients in the darolutamide arm and 29% of patients in the placebo arm.[8]

The primary endpoint, metastasis-free survival, was significantly prolonged in the darolutamide arm compared with the placebo arm. The median metastasis-free survival was 40.4 months with darolutamide vs 18.4 months with placebo (HR, 0.41; 95% CI, 0.34-0.50; *P*<.001).[8]

Darolutamide also improved several secondary endpoints. The median time to pain progression was 40.3 months with darolutamide vs 25.4 months with placebo (HR, 0.65; 95% CI, 0.53-0.79; *P*<.001). The median time to first cytotoxic chemotherapy was not reached with darolutamide vs 38.2 months with placebo (HR, 0.43; 95% CI, 0.31-0.60; *P*<.001). The median time to first symptomatic skeletal event was not reached in both arms (HR, 0.43; 95% CI, 0.22-0.84; *P*=.01).[8]

At the prespecified final analysis, performed at a

median follow-up of 29.0 months, overall survival at 3 years was 83% with darolutamide vs 77% with placebo. The risk of death was 31% lower with darolutamide (HR, 0.69; 95% CI, 0.53-0.88; *P*=.003). The median overall survival was not reported.[11]

Grade 3/4 adverse events occurred in 24.7% of the darolutamide arm vs 19.5% of the placebo arm. Serious adverse events were reported in 24.8% vs 20.0%, respectively. The proportion of patients who discontinued treatment owing to an adverse event was similar in each arm (8.9% with darolutamide and 8.7% with placebo). Overall, adverse events occurred at a similar frequency in the darolutamide and placebo groups. As noted in the package insert, the only adverse events that occurred at a frequency of 2% or higher in the darolutamide arm vs the placebo arm were fatigue, pain in an extremity, and rash.[15] Fatigue was reported in 16% of the darolutamide arm (grade 3/4, 0.6%) vs 11% of the placebo arm (grade 3/4, 1.1%). Pain in an extremity occurred in 6% (grade 3/4, 0%) vs 3% (grade 3/4, 0.2%), respectively. Rash occurred in 3% (grade 3/4, 0.1%) vs 1% (grade 3/4, 0%). A grade 4 adverse event occurred in 37 patients (3.9%) in the darolutamide arm and 18 patients (3.2%) in the placebo arm.[8]

Key adverse events known to be associated with other AR inhibitors were not substantially more common with darolutamide vs placebo. Fractures occurred in 4.2% of the darolutamide arm vs 3.6% of the placebo arm, falls in 4.2% vs 4.7%, weight loss in 3.6% vs 2.2%, and seizures in 0.2% of each arm. There were slight differences in the incidences of other adverse events of interest, including hypertension (6.6% vs 5.2%), rash (2.9% vs 0.9%), dizziness (4.5% vs 4.0%), and cognitive disorder (0.4% vs 0.2%).[8]

Based on data from the ARAMIS trial, the FDA approved darolutamide for the treatment of men with nonmetastatic CRPC in July 2019.[16]

Safety and Quality-of-Life Considerations

Based on the efficacy shown in these studies, these potent AR inhibitors are being used earlier in the disease course, and patients are exposed to therapy for relatively long durations. It is therefore important to consider drug safety and tolerance, as well as quality of life. Apalutamide, enzalutamide, and darolutamide are similar in terms of their mechanism of action as an AR antagonist.[17] These second-generation AR antagonists bind the AR with higher affinity compared with first-generation agents, such as bicalutamide. They share common mechanisms of action, which include inhibition of ligand binding, AR translocation to the nucleus, and AR DNA binding, all of which are independent effects of these agents.

Table 1. Most Common Adverse Events Reported in the Apalutamide Arm of the Phase 3 SPARTAN Trial[a]

	Any Grade, n (%)	Grade 3 or 4, n (%)
Fatigue[b]	244 (30.4)	7 (0.9)
Hypertension	199 (24.8)	115 (14.3)
Rash[b]	191 (23.8)	42 (5.2)
Diarrhea	163 (20.3)	8 (1.0)
Nausea	145 (18.1)	0
Weight loss	129 (16.1)	9 (1.1)
Arthralgia	128 (15.9)	0
Falls[b]	125 (15.6)	14 (1.7)

[a]This category includes adverse events that occurred up to 28 days after the last dose of the trial regimen was administered.
[b]These adverse events were considered by the investigators to be related to the trial regimen.
Adapted from Smith MR et al. *N Engl J Med*. 2018;378(15):1408-1418.[6]

A recent pooled analysis of the three phase 3 trials of these agents demonstrated a significantly higher rate of adverse events with the AR inhibitors vs placebo.[18] Specifically, the AR inhibitors were associated with a higher likelihood of grade 3/4 adverse events (odds ratio [OR], 1.92; 95% CI, 1.30-2.85), serious adverse events (OR, 1.748; 95% CI, 1.19-2.54), adverse events leading to treatment discontinuation (OR, 1.62; 95% CI, 0.89-2.92), and adverse events leading to death (OR, 3.69; 95% CI, 0.79-17.30). Adverse events associated with all 3 of these agents included hypertension and cardiovascular events, which might be considered class effects of these drugs. Clinicians must consider these potential toxicities, especially when treating patients with comorbidities.

It is difficult to make comparisons across clinical trials, even of similar design. However, it is interesting to look at the reported rates of specific adverse events for each agent (Tables 1-3). More cases of fatigue and central nervous system (CNS)-related adverse events were reported with enzalutamide and apalutamide vs darolutamide.

FDA Warnings and Precautions

The FDA warnings and precautions for apalutamide and enzalutamide list seizures, as well as falls and fractures.[19,20] Notably, these events are not listed for darolutamide.[15] The differences in the safety profiles might be attributable to the different structures of the drugs. The distinct structure of darolutamide might explain its lower penetration of the blood-brain barrier. This characteristic may be especially important to consider when selecting treatment

Table 2. Most Common Adverse Events Reported in the Enzalutamide Arm of the Phase 3 PROSPER Trial

	All Grades, n (%)	Grade ≥3, n (%)
Fatigue	303 (33)	27 (3)
Hot flush	121 (13)	1 (<1)
Nausea	106 (11)	3 (<1)
Diarrhea	91 (10)	3 (<1)
Hypertension	111 (12)	43 (5)
Fall	106 (11)	12 (1)
Constipation	85 (9)	2 (<1)
Dizziness	91 (10)	4 (<1)
Arthralgia	78 (8)	1 (<1)
Asthenia	82 (9)	11 (1)
Decreased appetite	89 (10)	2 (<1)
Back pain	73 (8)	2 (<1)
Headache	85 (9)	2 (<1)
Hematuria	62 (7)	16 (2)
Urinary tract infection	38 (4)	7 (1)
Weight loss	55 (6)	2 (<1)
Urinary retention	20 (2)	4 (<1)

Adapted from Hussain M et al. *N Engl J Med*. 2018;378(26):2465-2474.[7]

Table 3. Most Common Adverse Events Reported in the Darolutamide Arm of the Phase 3 ARAMIS Trial

	Any Grade, n (%)	Grade 3 or 4, n (%)
Fatigue	115 (12.1)	4 (0.4)
Back pain	84 (8.8)	4 (0.4)
Arthralgia	77 (8.1)	3 (0.3)
Diarrhea	66 (6.9)	0
Hypertension	63 (6.6)	30 (3.1)
Constipation	60 (6.3)	0
Pain in an extremity	55 (5.8)	0
Anemia	53 (5.6)	8 (0.8)
Hot flush	50 (5.2)	0
Nausea	48 (5.0)	2 (0.2)
Urinary tract infection	47 (4.9)	6 (0.6)
Urinary retention	33 (3.5)	15 (1.6)

Adapted from Fizazi K et al. *N Engl J Med*. 2019;380(13):1235-1246.[8]

for elderly or frail patients, for whom CNS toxicities may be of particular concern. In an abstract presented at the 2019 American Society of Clinical Oncology Genitourinary Cancers Symposium, Zurth and colleagues reported preclinical data that examined in vivo tissue distribution data of labeled versions of each of these agents.[21] The analysis showed moderate blood-brain barrier penetration for both apalutamide and enzalutamide. Eight hours after dosing, brain concentrations of darolutamide were near the lower limit of quantification. These concentrations were approximately 26-fold lower than apalutamide and approximately 47-fold lower than enzalutamide.

Drug-Drug Interactions

The potential for drug-drug interactions is also an important consideration, particularly in older patients, who may be receiving other drugs. Each AR inhibitor has a different drug-drug interaction profile.[22] For example, enzalutamide is a moderate inducer of CYP2C9 and CYP2C19 and a strong inducer of CYP3A4. Apalutamide is a strong inducer of CYP3A4 and CYP2C19. For this reason, these 2 agents have the potential for CYP-mediated drug-drug interactions. In contrast, darolutamide is not a CYP inhibitor.

Quality-of-Life Data

The registrational trials for each of these agents showed that treatment maintained health-related quality of life and improved quality-of-life deterioration. In the ARAMIS trial, the median time to pain progression was 40.3 months with darolutamide vs 25.4 months with placebo (HR, 0.65; 95% CI, 0.53-0.79; *P*<.001).[8] The PROSPER trial found no difference in the median time to Functional Assessment of Cancer Therapy–Prostate (FACT-P) score degradation between enzalutamide and placebo (11.1 months in each arm; HR, 0.92; 95% CI, 0.79-1.08).[7] In the SPARTAN trial, the change in the total FACT-P score from baseline to 29 months was lower in the apalutamide arm (–0.99 ± 0.98) vs the placebo arm (–3.29 ± 1.97).[6]

Scanning Protocols

In the registrational trials for each of these agents, conventional imaging with CT and bone scans were used to determine the presence or absence of metastasis. Since the conduct of these studies, it has become apparent that

patients with nonmetastatic CRPC often do in fact have metastases detectable when they are examined using more sensitive scanning technologies, such as PSMA PET/CT.[23]

This finding has prompted the question of whether PSMA imaging should replace conventional imaging in a patient with a rising PSA. For most patients, results that are positive according to PSMA PET imaging but negative according to conventional scans would not change the management, and potent AR therapies should be added to ADT. Whether the addition of PSMA PET/CT imaging could improve outcomes by identifying the need for PET-directed salvage therapy or treatment of oligoprogressive disease should be evaluated in clinical trials. At present, the role for metastasis-directed therapy based on PSMA PET/CT is unclear, and I would not withhold an AR pathway inhibitor in this type of patient, given what we know from the practice-changing phase 3 trials. Nonmetastatic CRPC is an evolving disease space. In the future, a different term might be used to identify these patients.

Summary

Overall, the data from the practice-changing SPARTAN, PROSPER, and ARAMIS trials demonstrated that the addition of potent AR inhibitor therapy to ADT in men with high-risk nonmetastatic CRPC is associated with significantly prolonged metastasis-free survival and overall survival when compared with placebo plus ADT. AR inhibitors also improved several quality-of-life endpoints, including time to pain progression and time to next systemic therapy. Thus, early intervention with AR inhibitors should be considered as standard of care for patients with high-risk nonmetastatic CRPC. Implementation of this strategy must be guided by patient characteristics, such as disease state and comorbidities, and careful consideration of the benefits vs the toxicities.

Disclosure

Dr Beltran has served as a consultant/advisory board member for Janssen, Astellas, AstraZeneca, Merck, Pfizer, Foundation Medicine, Blue Earth Diagnostics, Amgen, Bayer, Oncorus, LOXO, and Daiichi Sankyo. She has received research funding (directed to her institution) from Janssen, AbbVie/Stemcentrx, Eli Lilly, Astellas, Millennium, and Bristol Myers Squibb.

References

1. Scher HI, Halabi S, Tannock I, et al; Prostate Cancer Clinical Trials Working Group. 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(7):1148-1159.
2. 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(13):2918-2925.
3. Smith MR, Cook R, Lee KA, Nelson JB. 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(10):2077-2085.
4. 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(30):3800-3806.
5. National Comprehensive Cancer Network. Prostate cancer. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Posted January 10, 2022. Accessed March 29, 2022.
6. Smith MR, Saad F, Chowdhury S, et al; SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.
7. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378(26):2465-2474.
8. Fizazi K, Shore N, Tammela TL, et al; ARAMIS Investigators. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235-1246.
9. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. *Eur Urol*. 2021;79(1):150-158.
10. Sternberg CN, Fizazi K, Saad F, et al; PROSPER Investigators. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2020;382(23):2197-2206.
11. Fizazi K, Shore N, Tammela TL, et al; ARAMIS Investigators. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med*. 2020;383(11):1040-1049.
12. Fankhauser CD, Poyet C, Kroeze SGC, et al. Current and potential future role of PSMA-PET in patients with castration-resistant prostate cancer. *World J Urol*. 2019;37(3):457-467.
13. FDA approves apalutamide for non-metastatic castration-resistant prostate cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-apalutamide-non-metastatic-castration-resistant-prostate-cancer. Posted May 3, 2018. Accessed March 29, 2022.
14. FDA approves enzalutamide for castration-resistant prostate cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-enzalutamide-castration-resistant-prostate-cancer. Posted July 2018. Accessed March 29, 2022
15. Nubeqa [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2021.
16. US Food and Drug Administration. FDA approves darolutamide for non-metastatic castration-resistant prostate cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-darolutamide-non-metastatic-castration-resistant-prostate-cancer. Posted July 31, 2019. Accessed March 29, 2022.
17. Rice MA, Malhotra SV, Stoyanova T. Second-generation antiandrogens: from discovery to standard of care in castration resistant prostate cancer. *Front Oncol*. 2019;9:801.
18. Maggi M, Salciccia S, Del Giudice F, et al. A systematic review and meta-analysis of randomized controlled trials with novel hormonal therapies for non-metastatic castration-resistant prostate cancer: an update from mature overall survival data. *Front Oncol*. 2021;11:700258.
19. Erleada [package insert]. Horsham, PA: Janssen Products LP; 2021.
20. Xtandi [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 2022.
21. Zurth C, Sandman S, Trummel D, et al. Higher blood–brain barrier penetration of [^{14}C]apalutamide and [^{14}C]enzalutamide compared to [^{14}C]darolutamide in rats using whole-body autoradiography [ASCO GU abstract 156]. *J Clin Oncol*. 2019;37(suppl 7).
22. Feng Z, Graff JN. Next-generation androgen receptor-signaling inhibitors for prostate cancer: considerations for older patients. *Drugs Aging*. 2021;38(2):111-123.
23. Fendler WP, Weber M, Iravani A, et al. Prostate-specific membrane antigen ligand positron emission tomography in men with nonmetastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2019;25(24):7448-7454.

How Patient Characteristics Can Guide Selection Among Androgen Receptor Inhibitors in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

Matthew B. Rettig, MD

Professor of Medicine and Urology
Medical Director, Prostate Cancer Program
Institute of Urologic Oncology
David Geffen School of Medicine at UCLA
Los Angeles, California
Chief, Division of Hematology-Oncology
VA Greater Los Angeles Healthcare System
Los Angeles, California

Characteristics of Patients With Nonmetastatic CRPC

Patients with nonmetastatic CRPC typically are receiving treatment with some type of ADT, usually a luteinizing hormone-releasing hormone (LHRH) analogue. The patient is considered to be in a castrate state when his level of serum testosterone is less than 50 ng/mL.[1] When PSA begins to rise, restaging scans are performed. For patients with nonmetastatic CRPC, conventional imaging will not show any visible distant metastatic disease.

Large, randomized, controlled phase 3 trials led to the regulatory approval of 3 different AR inhibitors for nonmetastatic CRPC: apalutamide, enzalutamide, and darolutamide.[2-4] The study inclusion criteria required that patients have a PSA doubling time of 10 months or less and a PSA of 2 ng/mL or higher. These criteria are important because the PSA doubling time and the absolute level of PSA are the only 2 factors known to predict for the time to onset of metastasis in the nonmetastatic CRPC population.[5-7] Of these, PSA doubling time is the more powerful predictor (Figure 2).[7] As an example, if a patient has a PSA doubling time of less than 3 months, the median time to metastasis is only approximately 9 months. Conversely, if the PSA doubling time is longer than 15 months, the time to metastasis is longer than 4 years. Therefore, the clinical trials that led to regulatory approval of apalutamide, enzalutamide, and darolutamide selected for patients with relatively aggressive nonmetastatic CRPC.

The trial designs were similar. Patients with nonmetastatic CRPC were randomly assigned to receive the active agent or a placebo.[2-4] Importantly, the trials used the same primary endpoint of metastases-free survival. Overall survival was a key secondary endpoint. All 3 studies showed that the AR inhibitors improved metastases-free survival and overall survival. Overall, the drugs appeared to have similar efficacy. It is difficult to make cross-trial comparisons, but the patient populations were largely the same.

Interestingly, the FDA-approved indications for all 3 agents do not mention PSA doubling time, despite the requirement in the enrollment criteria of the pivotal trials.[8-10] All of the drugs are approved for patients with nonmetastatic CRPC. However, clinicians should consider the PSA doubling time when selecting candidates for these treatments.

A key feature of nonmetastatic CRPC is that although the patients do not have distant metastases, they may show involvement of the pelvic lymph nodes. In the SPARTAN, PROSPER, and ARAMIS trials, patients could have lymph nodes with a dimension of up to 2 cm in the pelvis.[2,4] However, most patients did not have any local or regional lymph node involvement.

Because these patients do not have distant metastatic disease, their symptoms are limited. A local recurrence may cause some symptoms, but they typically do not impact the patient's quality of life. It is therefore critical to consider the side effect profiles of treatments for these patients. In addition, the treatments must have a proven impact on the biology of the disease. Apalutamide,

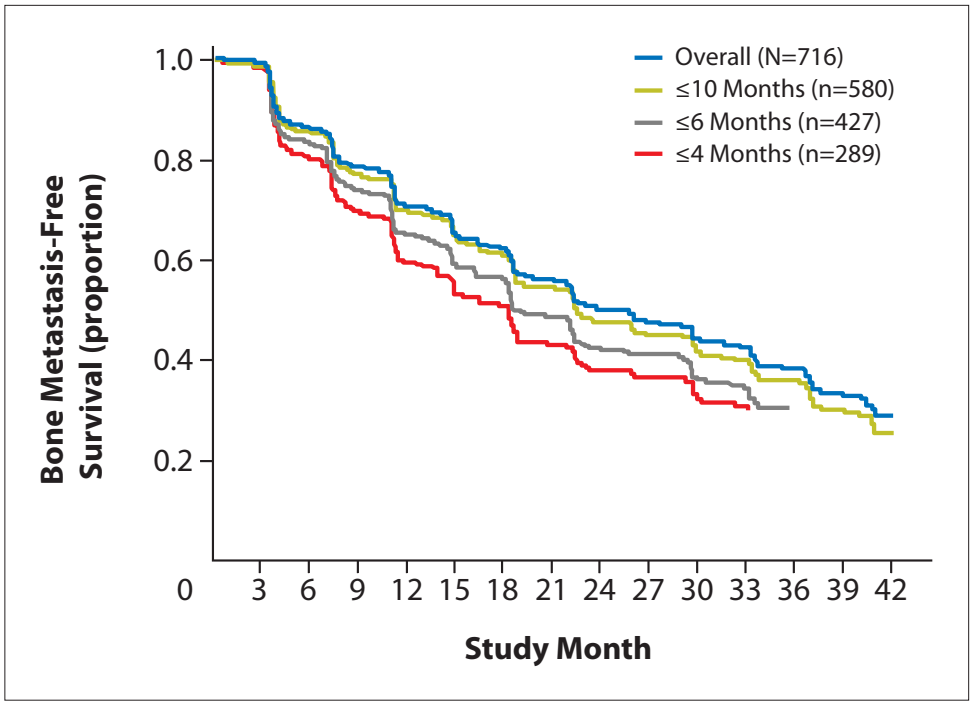


Figure 2. The correlation between prostate-specific antigen doubling time and bone metastases-free survival in the placebo arm of a study of patients with nonmetastatic castration-resistant prostate cancer. Adapted from Smith MR et al. *J Clin Oncol.* 2013;31(30):3800-3806.[7]

enzalutamide, and darolutamide meet this threshold, in that they prolong metastasis-free survival by approximately 2 years. Across the phase 3 studies, the median metastasis-free survival was approximately 16 to 18 months in the placebo arm, which was extended by approximately 22 to 24 months with each of the agents.[8-10] The treatments also improved overall survival despite a higher frequency of active second agents used in the placebo arms of each of the studies.

An older patient with multiple comorbidities and a long PSA doubling time might not be a candidate for treatment, but rather could be managed with watchful waiting. In contrast, if a patient has a short PSA doubling time and a particularly elevated PSA, then I would consider initiating one of these agents. A large percentage of patients with nonmetastatic CRPC meet these latter criteria.

Factors That Influence Selection of AR Inhibitors

The chemical structures of enzalutamide and apalutamide are similar.[8,9] In fact, these drugs are essentially analogues of each another. Apalutamide has just a few chemical differences from enzalutamide, but these are enough to render apalutamide slightly more polar, which suggests that it might enter the blood-brain barrier less rapidly. Regardless, these 2 agents have similar side effect profiles. Some of these side effects are especially relevant to the older nonmetastatic CRPC population, who may have osteoporosis related to chronic ADT. They are also subject to falls and fractures. Therefore, drugs that could increase the risk of complications related to the patient's age and his underlying treatments are important considerations. Both enzalutamide and apalutamide significantly increase risks of fractures and falls, as well as dizziness and cognitive impairment. Both of these agents have important side effects that need to be considered when selecting a drug for the nonmetastatic CRPC space.

Darolutamide has a different chemical structure.[10] It does not readily enter the blood-brain barrier. Preclinical studies show that the CNS plasma concentration of darolutamide is approximately 3% in mice and 8% in rats.[11,12] In the phase 3 ARAMIS trial, only 3 adverse events occurred with greater frequency (>2%) in the darolutamide arm than the placebo arm: lower extremity pain, rash, and fatigue.[4] When these side effects did occur, most were mild or moderate in severity. It is unsurprising that CNS toxicities, including mental and memory impairment, are not observed with any frequency with darolutamide. In addition, darolutamide does not significantly increase the incidence of falls or fractures. In a long-term analysis of the phase 3 ARAMIS trial, darolutamide extended the time to first symptomatic skeletal event compared with placebo (Figure 3).[13]

Darolutamide is administered twice daily, which is an important consideration in patients who have difficulty taking pills or with poor adherence to therapy.[10] In contrast, enzalutamide and apalutamide are administered once

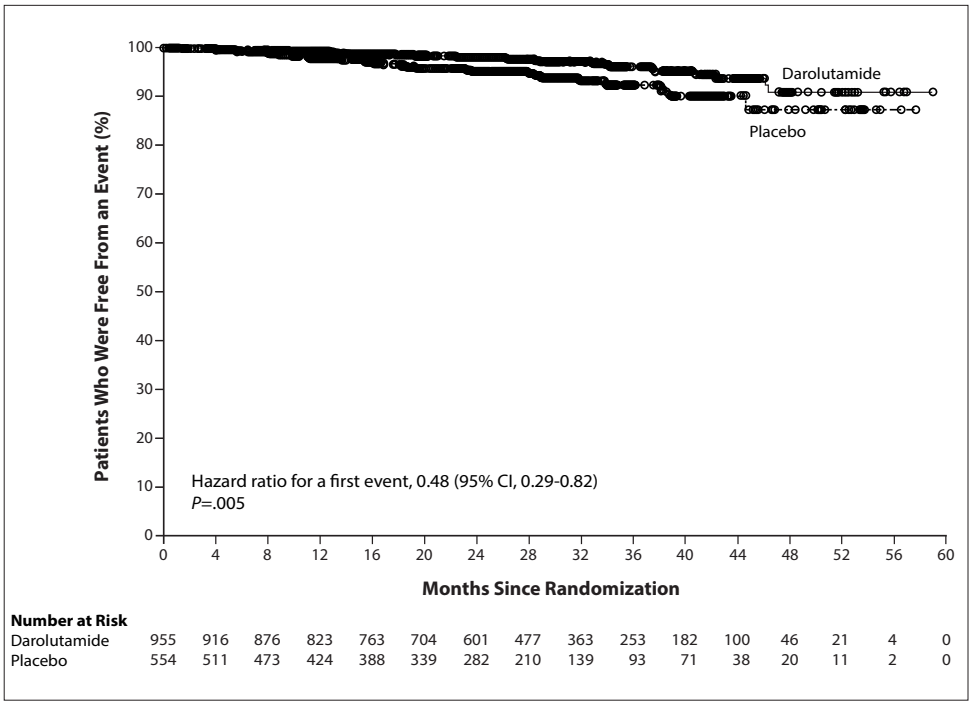


Figure 3. In a long-term analysis of the phase 3 ARAMIS trial, darolutamide extended the time to first symptomatic skeletal event compared with placebo. Adapted from Fizazi K et al. *N Engl J Med*. 2020;383(11):1040-1049.[13]

daily. The recommended dose for all 3 agents requires administration of 4 pills per day.[8-10]

In general, all 3 of these drugs are well tolerated. Apalutamide is associated with rash, and both enzalutamide and apalutamide can predispose to seizures.[8,9] In my practice, this association with seizures is one of the primary issues I consider when selecting treatment for patients. The clinical trials for enzalutamide and apalutamide excluded patients with any predisposing factors for seizures, such as a history of stroke, a recent transient ischemic attack, a history of seizures, or an anatomic or structural brain abnormality.[2,3] Conversely, the darolutamide study included such patients.[4] Some patients in the darolutamide arm had a history of seizures.[4] Despite this risk, there was no evidence that darolutamide increased rates of seizures. In contrast, enzalutamide and apalutamide cause seizures in approximately 0.5% of patients without predisposing factors.[2,3] The frequency of seizures with enzalutamide and apalutamide in patients without predisposing factors is unknown, because these patients were not enrolled in the respective trials.

It is also important to consider drug-drug interactions. Enzalutamide and apalutamide have several important drug interactions, notably with anticoagulants. It can be challenging to administer these agents to patients who are receiving anticoagulants, which cannot be stopped in most cases. For example, patients may have atrial fibrillation and cannot discontinue anticoagulant therapy. Darolutamide does not interact with anticoagulants. However, there is an important interaction between darolutamide and statins. Darolutamide can increase the serum concentrations of statins, which has the potential to increase statin toxicity, and clinicians should be alert for cases of hepatotoxicity or rhabdomyolysis.

Initiation of AR Inhibitors

There is a question of whether the AR inhibitors should be reserved for future use when the patient develops metastatic disease. However, the clear improvement in overall survival is much greater when used in patients with nonmetastatic disease. For example, in the metastatic CRPC setting, enzalutamide results in only a 2-month improvement in median overall survival.[14] By comparison, this survival benefit approaches a year in the nonmetastatic CRPC setting. In addition, the SPARTAN trial of apalutamide explored progression-free survival 2 (PFS2), which refers to the time from the initial randomization to the second disease progression (Figure 4).[2] In the placebo arm, when patients received another active agent, they did not "catch up" in the PFS2 outcome, again suggesting that earlier intervention is better than delaying the initiation of these agents or reserving them for a later, metastatic stage of the disease.

Novel Imaging Modalities

The use of novel imaging modalities, such as PSMA PET

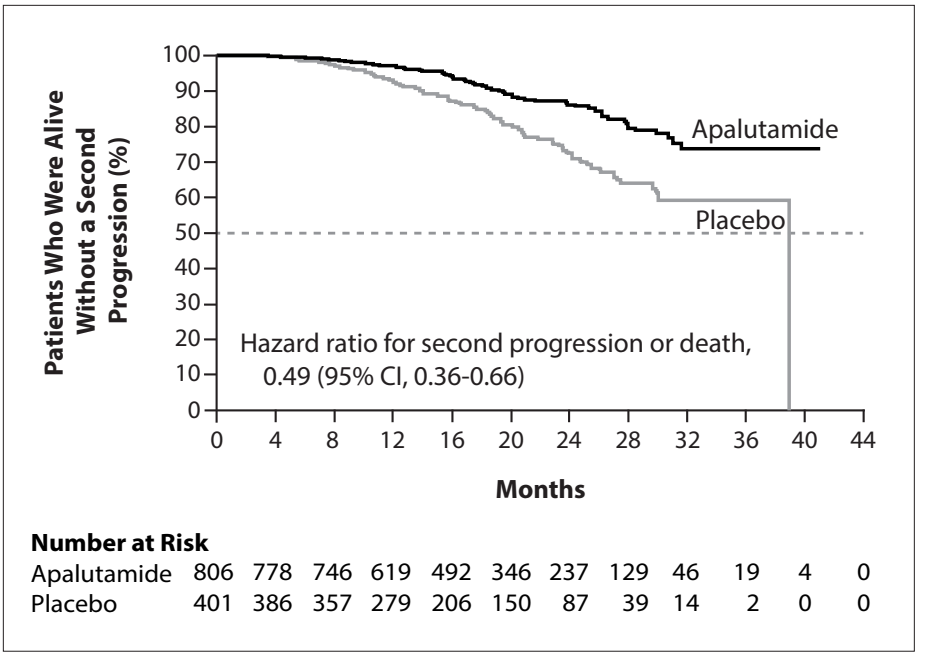


Figure 4. Second progression-free survival, which refers to the time from the initial randomization to the second disease progression, in the phase 3 SPARTAN trial of apalutamide. Adapted from Smith MR et al. *N Engl J Med*. 2018;378(15):1408-1418.[2]

scans, is allowing detection of occult metastatic disease that would be missed with conventional imaging.[15] I consider patients with negative results via conventional imaging to have nonmetastatic CRPC, even if a PSMA scan or a similar advanced imaging modality shows metastatic disease. I take this approach because the clinical trials used conventional imaging to define these patients. That said, I do not ignore signs of metastatic disease on advanced imaging. These patients might be candidates for metastasis-directed therapy. Emerging data suggest that treatment of oligoprogressive metastatic disease can prolong the efficacy of a therapy the patient is already receiving.

Conclusion

Nonmetastatic CRPC is a complicated disease state. Selection of treatment should reflect the characteristics of the individual patient, including his comorbidities and risks. The selected drug should minimize toxicity and drug-drug interactions, while maximizing quality of life.

Disclosure

Dr Rettig is a consultant for Amgen, Clovis, and Ambrx. He is a speaker for Janssen and Bayer. He has received research support from Novartis, Janssen, Exini, and Merck.

References

1. Scher HI, Halabi S, Tannock I, et al; Prostate Cancer Clinical Trials Working Group. 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(7):1148-1159.
2. Smith MR, Saad F, Chowdhury S, et al; SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.
3. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378(26):2465-2474.
4. Fizazi K, Shore N, Tammela TL, et al; ARAMIS Investigators. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235-1246.
5. 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(13):2918-2925.
6. Smith MR, Cook R, Lee KA, Nelson JB. 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(10):2077-2085.
7. 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(30):3800-3806.
8. Erleada [package insert]. Horsham, PA: Janssen Products LP; 2021.
9. Xtandi [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 2022.
10. Nubeqa [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2021.
11. Moilanen A, Riikonen R, Oksala R, et al. ODM-201–new generation antiandrogen with excellent antiandrogenic and antitumor activity in nonclinical models of CRPC [ECC abstract 2869]. *Eur J Cancer*. 2013;49(suppl 2).
12. Zurth C, Sandman S, Trummel D, et al. Higher blood–brain barrier penetration of [^{14}C]apalutamide and [^{14}C]enzalutamide compared to [^{14}C]darolutamide in rats using whole-body autoradiography [ASCO GU abstract 156]. *J Clin Oncol*. 2019;37(suppl 7).
13. Fizazi K, Shore N, Tammela TL, et al; ARAMIS Investigators. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med*. 2020;383(11):1040-1049.
14. Beer TM, Armstrong AJ, Rathkopf DE, et al; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
15. Fankhauser CD, Poyet C, Kroeze SGC, et al. Current and potential future role of PSMA-PET in patients with castration-resistant prostate cancer. *World J Urol*. 2019;37(3):457-467.

Clinical Observations Regarding the Use of Androgen Receptor Inhibitors in Patients With Nonmetastatic Castration-Resistant Prostate Cancer

William K. Oh, MD

Clinical Professor of Medicine
Division of Hematology and Medical Oncology
Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai
New York, New York

Initiation of AR-Targeted Therapy

Several issues must be addressed with patients when considering the initiation of treatment with enzalutamide, apalutamide, or darolutamide. Patients sometimes question the need for treatment with an AR inhibitor, particularly because they are generally asymptomatic at this point. They also have no visible metastatic disease on conventional imaging. It is therefore important to inform patients about the benefits of treatment, as well as the potential toxicity. Patients may already be experiencing adverse effects from their current treatment with LHRH agonists or antagonists. AR inhibitors might exacerbate some of these side effects, such as fatigue, muscle weakness, and cognitive issues. In addition, these agents are associated with other adverse events specific to their mechanisms of action.[1]

AR inhibitors are costly. Insurance companies have different procedures for ordering and shipping. Typically, the drugs are shipped directly to the patient. In our practice, the nurses or I discuss this process with the patient, to clarify the steps in place. We do everything possible to minimize the out-of-pocket costs for patients, given the significant financial issues.

Patient Monitoring

Patients must be monitored during treatment with an

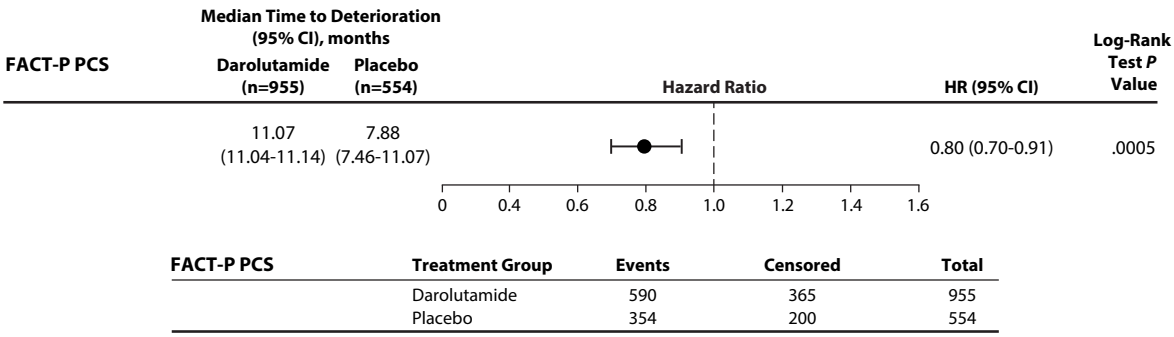
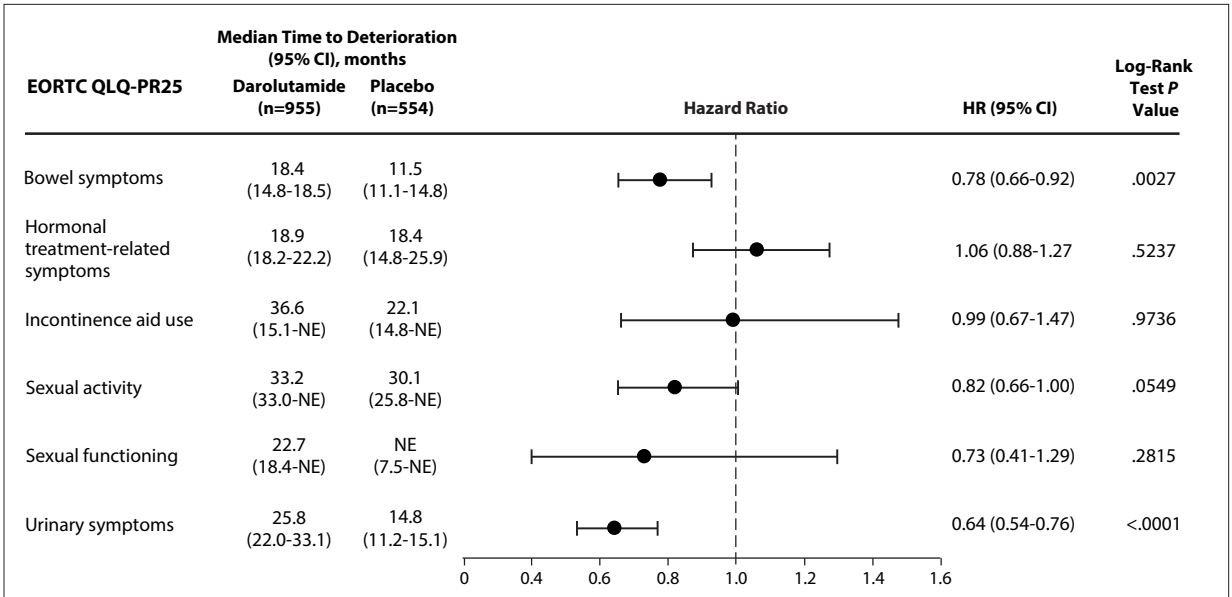


Figure 5. Time to deterioration in FACT-P PCS scores in an analysis of the phase 3 ARAMIS trial, as assessed by Cox regression analysis. FACT-P, Functional Assessment of Cancer Therapy–Prostate; HR, hazard ratio; NE, not estimable; PCS, prostate cancer subscale. Adapted from Smith MR et al. *Eur J Cancer*. 2021;154:138-146.[5]



EORTC QLQ-PR25	Treatment Group	Events	Censored	Total
Bowel symptoms	Darolutamide	415	540	955
	Placebo	235	319	554
Hormonal treatment-related symptoms	Darolutamide	385	570	955
	Placebo	172	382	554
Incontinence aid use	Darolutamide	83	169	252
	Placebo	36	93	129
Sexual activity	Darolutamide	253	702	955
	Placebo	143	411	554
Sexual functioning	Darolutamide	29	71	100
	Placebo	22	48	70
Urinary symptoms	Darolutamide	321	634	955
	Placebo	215	339	554

Figure 6. Time to deterioration in EORTC QLQ-PR25 subscale scores in an analysis of the phase 3 ARAMIS trial, as assessed by Cox regression analysis. For the category of sexual function, the hazard ratio was not significant because of the low numbers of patients who were sexually active: 100 in the darolutamide arm and 70 in the placebo arm. EORTC QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module; HR, hazard ratio; NE, not estimable. Adapted from Smith MR et al. *Eur J Cancer*. 2021;154:138-146.[5]

AR-targeted therapy.[2-4] In my practice, I typically see patients a month after they initiate treatment, followed by regular visits scheduled at intervals of 1 to 3 months. The main aim of monitoring is to ensure that the patient is tolerating the therapy well. The frequency of monitoring will depend on how well the patient is tolerating treatment. Blood work should be performed on a regular basis. When treating with ADT, I usually use an LHRH agonist administered in-office every 3 months. If the patient is responding well to AR-targeted therapy, I maintain this schedule.

In general, patients with nonmetastatic CRPC require regular follow-up assessments. These patients may experience more rapid disease progression than patients who are hormone-sensitive and therefore must be monitored more frequently. At a minimum, patients with nonmetastatic CRPC should undergo assessment of PSA, complete blood counts, and chemistries every 3 months. Some patients may require more frequent monitoring, such as every 4 or 6 weeks, to track drug tolerability and response to treatment. The monitoring strategy for each of the AR inhibitors is largely similar.

It is important to encourage patients to contact their clinician if adverse events arise. Patients could develop symptoms within 1 week, or they may not have symptoms for 6 months. Patients should feel empowered to contact their treatment center if they notice an adverse event between visits.

Clinical Observations

Apalutamide, enzalutamide, and darolutamide are effective and well tolerated. These drugs had equivalent benefits in terms of metastasis-free survival and overall survival in the randomized phase 3 trials.[5-7] These drugs have never been directly compared in randomized, head-to-head clinical trials. Ongoing studies are evaluating long-term tolerability.

Each of these agents is a reasonable choice of therapy for patients with nonmetastatic CRPC. There are small differences that can guide selection. Potential drug-drug interactions can exclude a certain agent. Adverse events are another factor.

Fatigue is not uncommon among patients treated with apalutamide. Rash is a unique side effect of apalutamide.[2] The rash is usually mild. Typically, I withhold treatment until the rash improves and then begin again. When initiating treatment with apalutamide, I warn patients that they may develop a rash.

Enzalutamide is the oldest of these agents and has the broadest range of FDA approvals. Enzalutamide is approved in both the metastatic and nonmetastatic CRPC settings, as well as for metastatic hormone-sensitive disease. Many doctors may have extensive experience with enzalutamide. It is an effective drug. The biggest concern with enzalutamide is that patients can experience significant fatigue and muscle weakness.[3] The rates of severe fatigue and muscle weakness are not high, but these events can have a significant impact on patients when they do occur.

Compared with apalutamide and enzalutamide, darolutamide may have some structural benefits. In particular, the structure of darolutamide limits penetration of the blood-brain barrier. In my practice, patients tend to favor darolutamide over apalutamide and enzalutamide. In general, patients develop less fatigue and fewer cognitive complaints with darolutamide than with the other AR-targeted therapies.[4] In an analysis of the ARAMIS trial that focused on health-related quality of life, darolutamide significantly delayed time to deterioration of the FACT-P prostate cancer subscale scores (Figure 5).[8] An analysis of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module (EORTC QLQ-PR25) subscales showed that darolutamide delayed progression of urinary and bowel symptoms (Figure 6).[8]

In general, treatment with apalutamide, enzalutamide, or darolutamide leads to a slight increase in some of the symptoms patients are already experiencing with ADT. The increase may be less with darolutamide, although darolutamide is not better tolerated by all patients.

Dose Adjustments

An advantage of these medications is that they come in divided doses, so it is possible to adjust the dose when needed to manage adverse events. I often make dose adjustments for these treatments, more so for enzalutamide and apalutamide compared with darolutamide. The goal is to maximize the therapeutic benefit of an AR-targeted therapy by administering the prescribed dose. However, the full dose might not be tolerated by all patients. If a patient develops a specific symptom—such as severe fatigue, most commonly, or weakness—I will lower the dose of the drug. Among patients who are already experiencing some fatigue or weakness, I sometimes initiate the drug at a lower dose. If the patient is older and/or has some comorbidities, I may start treatment at half the recommended dose. For most patients, I initiate treatment at the full dose, and then decrease by 25% or 50% if tolerability issues arise.

In the pivotal phase 3 trials, the survival benefit of these drugs was based on administration of the full dose.[5-7] However, it is sometimes necessary to balance quality of life with duration of life. It is preferable for the patient to continue treatment at a lower dose rather than discontinue treatment altogether, in my opinion.

Measurement of PSA Levels

PSA can be used as a biomarker to assess whether treatment with enzalutamide, apalutamide, or darolutamide is having the desired effect on the cancer. However, it is important to not become too reliant on PSA. Levels of PSA respond in most patients who receive treatment for nonmetastatic CRPC. However, the cancer may start to progress again, most commonly when the PSA level begins to rise. A rising PSA level is not necessarily a reason to stop treatment. The aim of treatment with these drugs is not just to keep the PSA from rising, but more importantly to prevent metastases and cancer-related death. The endpoint of the pivotal studies was to prevent metastases as detected by a conventional scan. Therefore, I do not typically stop treatment unless the patient develops metastases, definite progression of the cancer, or symptoms. The decision to stop one treatment and start another is based on PSA levels, PSA doubling time, symptoms, and reimaging scans. Typically, I will stop an AR-targeted therapy in the setting of nonmetastatic disease when the patient develops metastases.

Evidence suggests that switching to another AR-targeted therapy has little to no value. The next treatment will depend on the patient's prior treatments. Options include chemotherapy, such as docetaxel, in patients who are naive to this treatment. Other choices

include sipuleucel-T, if the patient is asymptomatic, and radium-223. For patients with a homologous recombination repair deficiency mutation, a poly(ADP-ribose) polymerase inhibitor, such as olaparib, is a possibility.

Disclosure

Dr Oh is a consultant for GSK, Merck, Janssen, and Pfizer. He is an employee with stock options of Sema4 (Chief Medical Science Officer).

References

1. Rice MA, Malhotra SV, Stoyanova T. Second-generation antiandrogens: from discovery to standard of care in castration resistant prostate cancer. *Front Oncol*. 2019;9:801.
2. Erleada [package insert]. Horsham, PA: Janssen Products LP; 2021.
3. Xtandi [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 2022.
4. Nubeqa [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2021.
5. Smith MR, Saad F, Chowdhury S, et al; SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.
6. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378(26):2465-2474.
7. Fizazi K, Shore N, Tammela TL, et al; ARAMIS Investigators. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235-1246.
8. Smith MR, Shore N, Tammela TL, et al. Darolutamide and health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the phase III ARAMIS trial. *Eur J Cancer*. 2021;154:138-146.

Factors That Guide Selection Among Androgen Receptor Inhibitors in Patients With Nonmetastatic Castration-Resistant Prostate Cancer: Q&A

William K. Oh, MD, and Matthew B. Rettig, MD

William K. Oh, MD Patients sometimes ask me whether it is necessary for their treatment to include both an LHRH agonist and an AR-targeted therapy. There is the possibility that AR-targeted therapy alone might be able to improve quality of life, particularly for those patients with a rising PSA level and a normal testosterone level. Some studies have evaluated this idea, and more research is needed.

Matthew B. Rettig, MD What is your approach to the timing of scans?

William K. Oh, MD This area is poorly studied. Previously, I delayed scans until the patient's PSA rose. However, I have modified this practice because a subset of patients—likely less than 20%—may develop progressive disease in the absence of a rise in PSA. Some patients have poorly differentiated cancers, with high Gleason scores and potentially neuroendocrine differentiation. When a patient presents with a worrisome symptom—such as bone pain or weight loss—I will scan them. Even among patients without a rising PSA, I strongly consider some form of imaging on an annual basis. These patients can be receiving an AR-targeted therapy for years. Imaging can confirm that they have no metastases. For patients at higher risk for dedifferentiated cancer, I perform scanning at least once a year.

Matthew B. Rettig, MD I follow the same strategy, and my practice has evolved in a similar way. Previously, I was less inclined to obtain a restaging set of scans for a patient who was asymptomatic with a stable PSA. However, I now perform scans in such patients, even if there are no other signs of progression. I tend to scan patients on an annual basis.

William K. Oh, MD Do you prefer PSMA PET scans over conventional imaging with bone scans and CT?

Matthew B. Rettig, MD I perform PSMA PET scans. There are limited data regarding serial PSMA scans and their impact on outcomes. However, I like to perform these scans when the patient is at maximal response—even if he has never had a previous PSMA scan—to

establish a baseline for future reference. As the patient progresses, a repeat PSMA scan will be more likely to capture the earlier onset of metastatic and oligoprogressive disease.

There are patients with slow progression, as evidenced by 1 or 2 sites of metastasis. Rather than abandon therapy, I will perform a PSMA scan and consider metastatic-directed radiation, typically stereotactic body radiation therapy, which is safe and effective. I practice at 2 centers. At the University of California Los Angeles, it can be difficult to obtain insurance coverage for this type of scan. At my center affiliated with the US Veterans Affairs Department, this scan is covered. We are also able to obtain a concurrent FDG-PET for these patients.

William K. Oh, MD Medicare will not cover PSMA PET scans for patients with a PSA level of 0 ng/mL. If PSA and PSMA run together, an interesting question is whether the PSMA PET scan is the ideal way to look for poorly differentiated metastases. When the PSA is rising, the PSMA scan is ideal. Among patients who are receiving treatment with AR-targeted therapies, a PSMA PET scan is the best technique to look for oligometastatic lesions, which might require radiation. However, when the PSA is 0 ng/mL, is a PSMA PET scan the ideal way to evaluate for poorly differentiated non-PSA producing tumors?

Matthew B. Rettig, MD That is a great point. My strategy takes these factors into consideration. Approximately 10% to 20% of patients have metastatic progression in the absence of a PSMA-positive lesion. When performing a PSMA PET/CT, the CT component should detect these lesions, especially if they are clinically significant. If the PSMA PET/CT is negative, but I am still concerned about disease progression, I will perform some other form of imaging, whether it is a conventional CAT scan, a bone scan, or an FDG-PET scan.

Disclosures

Dr Oh is a consultant for GSK, Merck, Janssen, and Pfizer. He is an employee with stock options of Sema4 (Chief Medical Science Officer). Dr Rettig is a consultant for Amgen, Clovis, and Ambrx. He is a speaker for Janssen and Bayer. He has received research support from Novartis, Janssen, Exini, and Merck.

Slide Library

Nonmetastatic CRPC

- The natural history of nonmetastatic CRPC is variable
- Approximately one-third of patients will develop visible metastases within 2 years.[1-3] Men with a PSA doubling time of less than 10 months are at very high risk for developing metastases
- Historically, management consisted of watchful waiting. The rising PSA was monitored while ADT was continued without any other therapeutic intervention until metastasis became apparent on imaging
- This paradigm has changed in recent years, with the advent of earlier interventions specifically for patients at high risk for developing metastatic disease

ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen. 1. Smith MR et al. *J Clin Oncol*. 2005;23(13):2918-2925. 2. Smith MR et al. *Cancer*. 2011;117(10):2077-2085. 3. Smith MR et al. *J Clin Oncol*. 2013;31(30):3800-3806.

Treatment Considerations for Nonmetastatic CRPC

- Because these patients do not have distant metastatic disease, their symptoms are limited
- A local recurrence may cause some symptoms, but they typically do not impact the patient's quality of life
- It is critical to consider the side effect profile of treatments for these patients
- Treatments must have a proven impact on the biology of the disease

NCCN Recommendations for Nonmetastatic CRPC

- The NCCN recommends the addition of a potent AR antagonist to ADT in patients with a rising PSA and a doubling time of 10 months or less[1]
- For patients with longer PSA doubling times, the NCCN guidelines state that it remains acceptable to continue monitoring while continuing ADT
- Three next-generation AR inhibitors are FDA-approved in this setting: apalutamide, enzalutamide, and darolutamide

AR, androgen receptor; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network.
1. National Comprehensive Cancer Network. Prostate cancer. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Posted January 10, 2022. Accessed March 29, 2022.

Efficacy of AR Pathway Inhibitors

- The NCCN recommendations regarding the use of AR inhibitors in nonmetastatic CRPC are based on data from phase 3 clinical trials
- Each of the studies met their primary endpoint of an improvement in metastasis-free survival[1-3]
- Long-term analyses showed a benefit in overall survival, with approximately 1 year of life gained[4-6]
- The addition of an AR antagonist preserved quality of life
- Early intervention with the addition of an AR inhibitor to ADT at high risk for progression is the standard of care

1. Smith MR et al. *N Engl J Med*. 2018;378(15):1408-1418. 2. Hussain M et al. *N Engl J Med*. 2018;378(26):2465-2474. 3. Fizazi K et al. *N Engl J Med*. 2019;380(13):1235-1246. 4. Smith MR et al. *Eur Urol*. 2021;79(1):150-158. 5. Sternberg CN et al. *N Engl J Med*. 2020;382(23):2197-2206. 6. Fizazi K et al. *N Engl J Med*. 2020;383(11):1040-1049.

Adverse Events of AR Inhibitors

- Both enzalutamide and apalutamide significantly increase risks of fractures and falls, as well as dizziness and cognitive impairment[1,2]
- In the phase 3 ARAMIS trial, only 3 adverse events occurred with greater frequency (>2%) in the darolutamide arm vs the placebo arm: lower extremity pain, rash, and fatigue.[3] When these side effects did occur, most were mild or moderate in severity
- CNS toxicities, including mental and memory impairment, were not observed with any frequency with darolutamide
- Darolutamide did not significantly increase the incidence of falls or fractures

CNS, central nervous system. 1. Smith MR et al. *N Engl J Med*. 2018;378(15):1408-1418. 2. Hussain M et al. *N Engl J Med*. 2018;378(26):2465-2474. 3. Fizazi K et al. *N Engl J Med*. 2019;380(13):1235-1246.

Reports of Seizures in the Phase 3 Clinical Trials

- Enzalutamide and apalutamide caused seizures in approximately 0.5% of patients without predisposing factors[1,2]
- The clinical trials for enzalutamide and apalutamide excluded patients with any predisposing factors for seizures[1,2]
- The darolutamide study included such patients[3]
- There was no evidence that darolutamide increased the rates of seizures[3]

1. Smith MR et al. *N Engl J Med*. 2018;378(15):1408-1418. 2. Hussain M et al. *N Engl J Med*. 2018;378(26):2465-2474. 3. Fizazi K et al. *N Engl J Med*. 2019;380(13):1235-1246.

Blood-Brain Barrier Penetration

- The FDA warnings and precautions for apalutamide and enzalutamide include seizures, falls, and fractures. These events are not listed for darolutamide
- The distinct structure of darolutamide might explain its lower penetration of the blood-brain barrier
- A preclinical study showed moderate blood-brain barrier penetration for both apalutamide and enzalutamide.[1] Eight hours after dosing, brain concentrations of darolutamide were near the lower limit of quantification. These concentrations were approximately 26-fold lower than apalutamide and approximately 47-fold lower than enzalutamide

1. Zurth C et al. ASCO GU abstract 156. *J Clin Oncol*. 2019;37(suppl 7).

Drug-Drug Interactions

- Enzalutamide and apalutamide have several important drug interactions, notably with anticoagulants
- Darolutamide does not interact with anticoagulants
- Darolutamide can increase the serum concentrations of statins. Clinicians should be alert for cases of hepatotoxicity or rhabdomyolysis

Initiation of AR Inhibitors

- The improvement in overall survival is much greater when AR inhibitors are used in patients with nonmetastatic disease
- In the metastatic CRPC setting, enzalutamide results in a 2-month improvement in median overall survival.[1] By comparison, this survival benefit approaches a year in the nonmetastatic CRPC setting
- The SPARTAN trial of apalutamide explored PFS2.[2] In the placebo arm, when patients received another active agent, they did not "catch up" in the PFS2 outcome, suggesting that earlier intervention is better than delaying the initiation of these agents or reserving them for a later, metastatic stage of the disease

PFS2, second progression-free survival. 1. Beer TM et al. *N Engl J Med*. 2014;371(5):424-433. 2. Smith MR et al. *N Engl J Med*. 2018;378(15):1408-1418.

Dosing of AR Inhibitors

- The recommended dose for apalutamide, enzalutamide, and darolutamide requires administration of 4 pills per day. It is therefore possible to adjust the dose to manage adverse events
- If a patient develops a specific symptom—such as fatigue, most commonly, or weakness—it is possible to lower the dosage by 25% or 50%
- It can be helpful to initiate treatment at half the recommended dose in patients who are older and those who present with fatigue, weakness, or comorbidities

For a free electronic download of these slides, please direct your browser to the following web address:

http://www.hematologyandoncology.net