

Recent Updates in the Treatment of Nonmetastatic Castration-Resistant Prostate Cancer

In this **CancerNetwork® OncView™** program, faculty panelist Aaron Berger, MD, explains the treatment options in this disease space and discusses a recent drug approval.



Aaron Berger, MD
Associated Urological Specialists
Chicago, IL

Scan QR code for the complete video series.



In a recent *OncView™* discussion, Aaron Berger, MD, vice president and chief medical officer at Associated Urological Specialists in Chicago, Illinois, shared clinical experiences and perspectives regarding treatments of patients with nonmetastatic castration-resistant prostate cancer (nmCRPC).

Clinicians need to be aware of all the treatment options available in this space, as many FDA-approved indications have emerged in the past few years, Berger said.

“There’ve been several new options for nonmetastatic castration-resistant prostate cancer to come to market,” he noted. “The first was enzalutamide [Xtandi] followed shortly thereafter by apalutamide [Erleada], and then most recently darolutamide [Nubeqa]. We’ve used all of them in our advanced prostate cancer clinic, and it’s certainly an improvement over the previous options [such] as first-generation antiandrogen therapies.”

Berger detailed his strategies for therapy selection in this patient population, including insights in baseline patient characteristics, clinical trial data, and toxicity profiles of each novel agent that guide his decisions.

Disease Monitoring in nmCRPC

Berger said his first consideration in a patient with nmCRPC is whether they need additional systemic therapy. Age, comorbidities, prostate-specific antigen (PSA) doubling time, and medication adherence are some of the factors that may incline a clinician to treat a patient with a newer antiandrogen medication.

“Some of these patients have a lot of other [medical] issues,” Berger said. “If they’re not excited about another medication or are worried about [adverse] effects, we may just observe them, especially if their [PSA is] rising somewhat slowly.”

Ultimately, the treatment goals in this setting are to prevent progression of disease from nonmetastatic to metastatic, as survival rates dramatically decrease in later stages of the disease. “Typically, we will check PSA and testosterone levels every 3 months,” Berger said. He noted that testosterone less than 50 ng/mL and a PSA doubling of 10 months or less was the threshold for administering medication to patients in clinical trials.

“That’s not in the labeling for all these medications. You certainly can use the medication if their doubling time is 11 months or 12 months, but

normally it's [with a PSA doubling time of] 10 months or less we're really focused on," he said.

For imaging in a patient with a significant PSA rise, Berger said he references the RADAR III guidelines, which recommend next-generation imaging techniques for detecting previously metastases (Table¹).

"We would certainly consider doing conventional imaging initially, such as a CT scan or bone scan, and if it's negative then we would likely continue observation," Berger said. "I typically wouldn't wait until PSA is 5, 10, or 20 ng/mL and just keep doing conventional imaging—we would likely move on to doing next-generation imaging studies earlier." Some other factors that might motivate imaging sooner include pain in the back, hips, or legs; urinary symptoms; or obstructions in the kidneys.

Therapy Selection

Regarding the 3 available next-generation androgen receptor inhibitors that are available to treat patients in this setting, Berger said their mechanisms of action

are similar but varying molecular sizes account for the biggest differences reflected in slightly different toxicity profiles.

"Darolutamide typically has less in the way of central nervous system effects—such as fatigue, light headedness, or dizziness—than what we sometimes may see [with the other agents]," Berger said. "But mechanistically, they work very similar."

Regarding metastasis-free and overall survival (OS) rates, pivotal clinical trials that led to the approval of these agents reflect similar results. "The design of the studies are very similar and the results of the studies are very similar," Berger said. "Sometimes there's a reason why you may not use one versus the other, such as if a patient does have significant fatigue or has any other central nervous system issues [such as] gait abnormalities. Potentially, the darolutamide may be a better choice than enzalutamide or the apalutamide. But in my experience, they're all tolerated pretty well."

Berger then explored data from the phase 3 PROSPER (NCT02003924), ARAMIS (NCT02200614), and SPAR-

TAN (NCT01946204) trials that led to the approvals of enzalutamide, darolutamide, and apalutamide, respectively.

"All 3 trials had very similar patient populations with a PSA doubling times of 10 months or less. All the patients had rising PSA that was confirmed on more than 1 occasion and castrate levels of testosterone less than 50 ng/mL," Berger said. "They were all looking at metastasis-free survival as the primary end point."

At the initial readout of the SPARTAN trial, metastasis-free survival (MFS) was statistically significantly improved with apalutamide versus the placebo group (HR, 0.28; 95% CI, 0.23-0.36; *P* < .001).² Similarly, MFS in PROSPER showed a 71% reduction in the risk of metastasis or death with enzalutamide compared with placebo (HR, 0.29; 95% CI, 0.24-0.35; *P* < .001).³ In ARAMIS, patients treated with darolutamide derived a significant treatment benefit versus those treated in the placebo group (HR, 0.41; 95% CI, 0.34-0.50; *P* < .001).⁴

"In subsequent analyses, it is now

TABLE 1. RADAR III Next-Generation Imaging Recommendations¹

Prostate cancer disease state			
Newly diagnosed	Biochemically recurrent	M0 CRPC	M1 CRPC
Imaging recommendations			
If conventional imaging is equivocal or negative with continued suspicion for metastatic disease, consider next-generation imaging	Consider next-generation imaging for PSA ≥ 0.05 ng/mL PSA ≤ 0.05 ng/mL can be considered based on specific performances of various next-generation imaging techniques	Only consider next-generation imaging in the setting of a PSA doubling time of 6 months or less when M1 therapies would be appropriate	Utilize conventional scans and consider next-generation imaging only if conventional scans are negative and the clinician suspects disease progression

CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen; RADAR, Radiographic Assessment for Detection of Advanced Recurrence.

borne out that they all do result in improvements in overall survival,” Berger said. OS results with next-generation agents versus placebo were statistically significant for SPARTAN (HR, 0.78; 95% CI, 0.64-0.96; $P = .016$),⁵ PROSPER (HR, 0.73; 95% CI, 0.61-0.89; $P = .001$),⁶ and ARAMIS (HR, 0.69; 95% CI, 0.53-0.88; $P = .003$).⁷

Adverse Effects of Therapy

When discussing toxicity, Berger detailed each in the context of which adverse effects were commonly associated with each agent.

“We typically see with enzalutamide fatigue or asthenia. These patients are all on androgen deprivation therapy at baseline [and] they have low testosterone at baseline, which can certainly decrease their overall energy level to start with,” Berger said. “Adding the enzalutamide in some patients does zap their energy substantially to the point where some don’t really feel like they have any motivation and don’t want to get out of bed.”

For these patients, Berger said a slight dose reduction can have a profound effect on their energy levels. For example, reducing the dosage by 25% or switching a patient from a 4-pill dose to a 3-pill dose may help a patient’s experience without significant effects on their overall disease outcomes.

With apalutamide, full body rash 2 to 3 months into treatment may occur but often can be managed with oral antihistamines or topical corticosteroids. Rarely, patients have a severe full body rash that requires discontinuation of therapy.

“There’s also a slightly higher risk with apalutamide of hypothyroidism, but this is not typically something we screen for routinely,” Berger said. “It’s mainly for those patients who have a history of hypothyroidism and are on medications already for thyroid replacement that we’ll check a thyroid panel along with their PSA and testosterone.”

Regarding darolutamide, Berger said its toxicity profile is likely the most favorable of the 3 available agents with its lower rate of fatigue, with most symptoms occurring during treatment.⁸ “The bottom line is to know what to potentially expect and let the patients know what to be on the lookout for,” he said.

Comorbidities

Berger said comorbid conditions, such as obesity or diabetes, may inform the decision to administer an androgen inhibitor but they do not necessarily preclude a patient from treatment.

“If they don’t have significant cardiovascular issues and haven’t had a heart attacks, stroke, or congestive heart failure issues, I’m not going to withhold a second-generation androgen inhibitor just because they’re a bit overweight,” Berger said.

In fact, the relatively manageable safety profile of these agents means that treatment can be given without many dose adjustments even to patients with renal insufficiencies, he said.

Neurologic issues that may be present, such as unsteadiness, dizziness, or a history of falls should be taken into consideration, Berger said. “Then the data would indicate that darolutamide may be a better option [because] there wasn’t an increased risk from falls and fractures in the ARAMIS trial.”

Future Treatment Landscape in nmCRPC

Regarding unmet needs in the treatment space, Berger said that guidance for prescribers on drug-drug interactions is lacking. “There are a lot of medications patients are on, whether it’s antihypertensives, diabetes medications, or cardiovascular medications, especially the anticoagulants that may have some interactions with these medications. And the guidance, as far as what we can glean from the studies, is not always clear

about what’s safe and what may not be safe,” he said.

Another consideration is whether nmCRPC will continue to be a disease state in the future, as next-generation imaging techniques become more prevalent in the treatment landscape and reveal metastasis in patients who would have been formerly considered nonmetastatic.

“When you have a scan that can pick up an area of metastasis at [PSA of] 0.2 to 0.3 ng/mL, it may turn out that these patients are metastatic. All of these studies were done with conventional imaging,” Berger said. “The big question as far as this entire disease state is, will it still be a disease state 5 years from now?”

Overall, Berger said clinicians shouldn’t shy away from prescribing these medications to their patients, given their tolerability and ease of administration. “I would not be afraid of these medications because you can easily add them into your clinical practice without a lot of trepidation,” he said. ■

REFERENCES

1. Crawford ED, Koo PJ, Shore N, et al. A clinician’s guide to next generation imaging in patients with advanced prostate cancer (RADAR III). *J Urol*. 2019;201(4):682-692. doi:10.1016/j.juro.2018.05.164
2. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418. doi:10.1056/NEJMoa1715546
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. doi:10.1056/NEJMoa1800536
4. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2019;380(13):1235-1246. doi:10.1056/NEJMoa1815671
5. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. *Eur Urol*. 2021;79(1):150-158. doi:10.1016/j.eururo.2020.08.011
6. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2020;382(23):2197-2206. doi:10.1056/NEJMoa2003892
7. Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med*. 2020;383(11):1040-1049. doi:10.1056/NEJMoa2001342
8. Gratzke CJ, Fizazi K, Shore ND, et al. Time course profile of adverse events of interest and serious adverse events with darolutamide in the ARAMIS trial. *Ann Oncol*. 2021;32(suppl 5):S626-S677. doi:10.1016/j.annonc/annonc702.