

Using darolutamide in advanced prostate cancer: How I Do It

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Darolutamide is a nonsteroidal androgen inhibitor FDA approved for the treatment of castration-resistant non-metastatic prostate cancer (nmCRPC). After decades of offering androgen deprivation therapy (ADT) alone or first-generation androgen receptor blockers for patients whose PSA was rising despite castrate levels of testosterone, there are now three different treatment

options to add to ADT. These include apalutamide approved in February 2018, enzalutamide FDA approved in June 2018, and darolutamide approved July 2019. Each of these androgen receptor pathway blockers, when added to ADT or surgical orchiectomy, prolongs metastasis-free-survival (MFS) and median survival (MS). This paper focuses on the use of the newest approved agent in this class, darolutamide.

Key Words: darolutamide, prostate cancer, non-metastatic, castrate-resistant, antiandrogen

Introduction

Darolutamide is a third generation non-steroidal androgen receptor inhibitor (ARI) approved by the FDA in 2019 for use in patients with non-metastatic castrate resistant prostate cancer (M0CRPC/nmCRPC).¹ Upon approval of apalutamide and enzalutamide in 2018 for use in patients with nmCRPC, urologists have

had the ability to intensify treatment by including any of these agents to traditional androgen deprivation therapy (ADT) in patients with high risk nmCRPC. Each of these treatment options have known side effect profiles, drug interactions, and contraindications thus complicating the decision to which agent to use when intensifying treatment. Darolutamide offers a unique profile of limited adverse events (AEs), fewer drug interactions, and fewer contraindications compared to other medications in this class, Table 1.

Darolutamide, originally known as ODM-201, inhibits androgen binding to androgen receptor (AR) and androgen-induced translocation of the AR to the nucleus in AR overexpressing cells commonly referred

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TABLE 1. Adverse events (AE) of Interest based on clinical trial data

AE of interest	Apalutamide vs. placebo ^{11,14}	Enzalutamide vs. placebo ^{12,15}	Darolutamide vs. placebo ^{13,16}
Fatigue	30.4% vs. 21.1%	33% vs. 14%	12.1% vs. 8.7%
Hypertension	24.8% vs. 19.8%	12% vs. 5%	6.6% vs. 5.2%
Rash	23.8% vs. 5.5%		2.9% vs. 0.9%
Falls	15.6% vs. 9%	11% vs. 4%	4.2% vs. 4.7%
Fracture		17.6% vs. 5.4%	5.5% vs. 3.6%
Seizure	0.2% vs. 0%	0.3% vs. 0%	0.2% vs. 0.2%

to as androgen receptor inhibition (ARI).² Antagonist properties remain against clinically relevant AR mutations such as AR (F876L) which confer resistance to enzalutamide and apalutamide. Darolutamide has a chemically different structure from apalutamide and enzalutamide, with a flexible polar structure which decreases central nervous system (CNS) penetration, suggesting lower CNS effects. Mouse studies showed CNS penetrance with brain/plasma ratio 62% with apalutamide, 27% with enzalutamide, and up to 3.9% with darolutamide.²

ARADES was a phase 1-2 open-label trial of combining ADT and darolutamide in 124 men with metastatic CRPC (mCRPC), identified the most common treatment-emergent adverse events fatigue (12%), hot flush (5%), and decreased appetite (4%).³ There were no grade 4-5 adverse events. Prostate-specific antigen (PSA) response (50% or more PSA decline) was seen in 86% of chemotherapy-naïve patients. The tolerance and efficacy led to the international phase 3 Aramis study.

Overview of nmCRPC

Non-metastatic castrate resistant prostate cancer (nmCRPC) also referred to as M0CRPC, is defined as a rising PSA level above nadir, in the setting of a castrate testosterone level (< 50 ng/dL), and negative conventional imaging⁴ in a patient who is generally otherwise asymptomatic, with the exception of the side effects associated with castrate T levels. Men who have been previously treated for local disease with high risk nmCRPC, defined as PSA doubling time < 10 months, absolute PSA \geq 2.0 ng/dL are at higher risk of the development of metastasis, leading to morbidity and mortality.⁵

Based on CDC data, an estimated 3 million men were diagnosed with prostate cancer 2003-2017, with 88% of those cancers localized⁶ and 248,530 men

will be diagnosed with prostate cancer in the United States in 2021.⁷ Up to 20%-30% of men treated for localized prostate cancer will experience biochemical recurrence.⁸ For men ineligible for additional local therapy, ADT remains a reasonable treatment option to slow the progression of disease.

In men treated with ADT, 10%-20% develop castration resistance within 5 years.⁹ In the United States, the incidence of nmCRPC is estimated to be over 100,000 men, with estimated 34% progressing to mCRPC in 1 year, and 80% within 3 years.¹⁰ The vast majority (86%) of men with mCRPC progressed from nmCRPC with 16% progressing from metastatic hormone-sensitive prostate cancer (mHSPC).¹⁰

The sequelae of progression to mCRPC include declining quality of life, symptoms due to cancer progression, adverse events and decreased overall survival. Preventing or delaying progression from nmCRPC to mCRPC stands to be an important strategy to improve quality and quantity of survival.

Clinical trials data in nmCRPC

Given the poor prognosis of mCRPC, adding an ARI to traditional ADT in nmCRPC was evaluated in three randomized placebo-controlled trials: SPARTAN (apalutamide) 2018,¹¹ PROSPER (enzalutamide) 2018,¹² and ARAMIS (darolutamide) 2019 summarized in Table 2.¹³ In each trial, patients with high risk nmCRPC were randomized to ADT/placebo or ADT/ARI, stratified according to PSA doubling time and the use of bone-modifying agents. Inclusion criteria included conventional imaging without systemic metastasis, with high risk disease defined as PSA doubling time \leq 10 months, absolute PSA \geq 2.0 ng/dL. Localized lymphadenopathy below the aortic bifurcation was permitted up to 2 cm in ARAMIS and SPARTAN, and up to 1.5 cm in PROSPER. Metastasis-free survival, defined

TABLE 2. Discontinuation rates vs. placebo based on clinical trials

	Apalutamide vs. placebo ^{11,14}	Enzalutamide vs. placebo ^{12,15}	Darolutamide vs. placebo ^{13,16}
Discontinuation rate vs. placebo	15% vs. 7.3%	17% vs. 9%	8.9% vs. 8.7%

as distant metastasis or death from any cause, was the primary endpoint of each trial. Secondary endpoints included overall survival, time to first chemotherapy, time to pain progression, and adverse events. ARAMIS included patients with seizure-predisposing conditions whereas these patients were excluded in PROSPER and SPARTAN due to the risk of seizure.

Primary analysis in each trial showed statistically significant improvement of metastasis free survival (MFS). MFS is the length of time from start of treatment for the cancer that a patient is still alive and the cancer has not spread to other parts of the body. In the context of a clinical trial, measuring the MFS is one way to see how well a new treatment works. With the combination of ADT and apalutamide (HR 0.28, 95% CI 0.23-0.35) with MFS 40.5 months versus 16.2 months,¹¹ enzalutamide (HR 0.29, 95% CI 0.24-0.35) with MFS 36.6 months versus 14.7 months,¹² and darolutamide (HR 0.41, 95% CI 0.34-0.50) with MFS 40.4 months versus 18.4 months.¹³

While delaying metastasis leads to clinical benefit such as delayed symptoms from cancer and or treatment, many providers shared concern over selecting for more aggressive cancer transformation upon progression, without impacting overall survival. However, overall survival was significantly prolonged in men treated with apalutamide (73.9 months, 95% CI 61.2-NR) versus placebo (59.9 months, 95% CI 52.8 months-NR), corresponding to a 21.6% reduction in the risk of death.¹⁴ Overall survival was prolonged in men treated with enzalutamide (67 months, 95% CI 64-NR) versus placebo (56.3 months 95% CI 54.4 versus 63 months), corresponding to a 27% reduction in the risk of death.¹⁵ Overall survival was prolonged in men treated with darolutamide versus placebo but in both cohorts median survival was not reached. Three year survival was significantly higher in men treated with darolutamide (83%, 95% CI 80-86 months) versus placebo (77%, 95% CI 72-81 months), corresponding to a 31% reduction in risk of death, Table 2.¹⁶ These trials demonstrate that clinicians' now have options in the nmCRPC patient instead of just waiting for the patient to develop symptoms or imaging findings consistent with metastatic disease. This strategy that not only delays progression but lengthens overall survival.

Using darolutamide

Our process of selecting men with high risk nmCRPC for treatment includes confirming that all eligible patients are evaluated for intensification of treatment, clarifying patient goals and preferences to allow for shared decision making, and considering the risks and benefits of each treatment option to guide the choice of treatment.

One office-based strategy for identifying patients eligible for medications such as darolutamide is selecting patients by navigation with an EMR. It should be noted that in the electronic health record (EHR) noting that at the present time there are no specific query rules as no nmCRPC diagnostic code exists. The following data is review for each patient:

1. Diagnosis Code Prostate Cancer C61, rising PSA post treatment R97.21, pelvic LN mets C77.5 allowed
2. Continuous ADT (or orchiectomy) with rising PSA and castrate testosterone
3. Negative standard imaging CT or MRI of the abdomen/pelvis and bone scan
4. PSA doubling time <= 10 months

Shared decision making and establishing patient goals

Shared decision making with a patient includes clarification of a patient's goals and preferences – do the costs associated with intensifying therapy (actual financial toxicity, side effects, quality of life) justify the benefit of delaying metastasis with potential longer life. As nmCRPC is a relatively asymptomatic disease state (except for side effects of castration), men are appropriately concerned about any additional treatment impacting their well-being, thus nuances of each option are weighed heavily when making treatment recommendations.

Discussion of a patient's goals, in both the medical and the non-medical spheres, includes topics such as cognitive, emotional, physical, financial, relational, and ongoing professional function. The clinician can then share with the patient the likely impact of adding

an ARI to the patient fulfilling his and the providers their goals. A thoughtful discussion elucidating expectations of a man's health can lead the decisions which align with the patient's priorities. Clarifying the side effects or inconvenience he is willing to experience for a survival benefit can drive the best fit.

Specific medication characteristics

NCCN Guidelines cite level 1 evidence supporting three different ARIs. In the decision on which to choose in the setting of high risk nmCRPC, patient characteristics, side effects and drug interactions often become deciding factors, assuming no insurance restrictions. Maintaining quality of life is often a priority for a patient, with acknowledgement that the nmCRPC disease state is characterized only by lab values, with no symptoms associated except for the potential anxiety of a rising PSA. Accordingly, patients and their providers frequently will choose an option with the least interference with their lifestyle and function.

Table 1 and Table 2 provide features of each specific medication from its respective clinical trial versus placebo.¹¹⁻¹⁶ These medications should not be directly compared as these medications were not tested head-to-head. A recent review of Drug-Drug Interactions focusing on darolutamide suggests a relatively low incidence of interactions with commonly prescribed medications.¹⁷ Some drugs to avoid concomitant use of darolutamide with combined P-gp and strong or moderate CYP3A4 inducers such as carbamazepine, dexamethasone, efavirenz, nafcillin, phenytoin, St John's Wort and others. Commonly used medications such as coumadin, losartan, omeprazole, oxycodone, lovastatin, tamsulosin, tolterodine and others have no significant interaction with darolutamide.¹⁷ Additional details on drug interactions can be found on line (<https://www.nubeqahcp.com/clinical-information>).

Prescribing darolutamide

Once the decision is made to start darolutamide in the setting of high risk nmCRPC, there should be a discussion with the patients concerning relevant side effects, quality of life issues and the potential for MFS/OS benefits. In our practice, darolutamide is frequently prescribed in this setting. Practical prescribing considerations include the following:

1. Access to this class of AR antagonist medications such as darolutamide usually requires authorization with insurance, with the dispensing by a specialty pharmacy as required by insurance. Stress to the

patient that they may receive specific phone calls relating to this process (a common source of delay in the age of "Robocalls"), out of pocket costs and or alternate drug requirement by insurance. Most manufacturers will work with patients and their insurance carrier to overcome many issues relating to co-pays and other considerations.

2. Maintaining a castrate level of testosterone (ADT) most often with the use of an LHRH agonist typically administered every 3 months.
3. Monitoring while on darolutamide every 3 months includes PSA and total testosterone. No other routine labs are required (i.e., no renal function tests, liver function tests, thyroid monitoring). At each visit cognitive function, any falls, or other potential side effects with a review of any new medications.
4. Imaging should be considered with any change in symptoms or significant changes in lab values. There is no specific FDA labeling concerning imaging intervals.
5. Standard darolutamide dose is 300 mg tablet, 2 twice daily with food. Renal dosage with glomerular filtration 15-29 mL/min (not on hemodialysis) or hepatic dosage (Child Class B) is reduced to 300 mg, once daily with food.
6. Continued overall prostate cancer care included attention to bone health with calcium and vitamin D supplementation. Further support of bone health through supplemental medications is based on DEXA scan as clinically indicated. Weight bearing exercise is encouraged along with cardiac health optimization such as the "ABCDEs of Cardiac Health": Aspirin, Blood pressure, Cholesterol, Diet, Exercise.
7. Darolutamide is continued until radiographic progression, cancer-related symptoms, or request by the patient. Therapy should not be changed solely on the basis of PSA progression without change in symptoms or imaging changes. Survival benefit is noted in trials with continuation of medication with PSA only progression.

Other considerations using darolutamide

By the time a patient develops nmCRPC, he has oftentimes been under the care of the urologist for several years. After monitoring a rising PSA, despite castrate levels of testosterone, anxiety frequently parallels the rise. When an ARI is started, and the PSA declines patients are frequently relieved. As a clinician, the comments by patients such as "I can barely tell I'm taking this medication" tends to provide

equal encouragement. My clinical experience with other prostate cancer treatment options, which require either more frequent monitoring, dose adjustments, or toxicity management, makes darolutamide an optimal treatment choice for men with nmCRPC.

A major barrier in the United States is often the high cost of this class of drugs, with unaffordable out-of-pocket cost, which hinders access to a preferred medication. However, lower income patients often have access to assistance programs offering affordable out of pocket costs. Other patients may benefit from manufacturer sponsored support programs.

No current discussion of delineating non-metastatic from metastatic cancer is complete without mentioning next-generation imaging (NGI) such as PET-Flucyclovine, PET-Choline, or PET-PSMA. While the NCCN guidelines mention that during workup of nmCRPC with negative conventional imaging, NGI can be considered, the NCCN panel remains unsure of how to treat metastasis found on NGI which are not visualized on routine studies such as CT or bone scan.⁴ A retrospective analysis of patients with high risk nmCRPC (defined by negative conventional imaging) evaluated PSMA-PET in a cohort similar to SPARTAN, PROSPER, and ARAMIS. Of 200 patients with nmCRPC, PSMA-PET was positive for recurrent cancer in 196 of 200 patients (98%), with 55% of PET-PSMA scans revealing systemic metastasis.¹⁸ While these individuals may have micro-metastatic cancer by NGI, they were candidates for any of these trials, and would have realized a survival benefit with the addition of an ARI. Given the Level 1 treatment options available in this clinical setting, and the unknown benefit of potential focal therapy in lieu of an ARI, I have generally not pursued NGI in this group of patients unless the patient's goal is to delay additional systemic therapy with understanding of potentially foregoing survival-extending therapy.

Conclusions

Darolutamide is a third generation non-steroidal ARI indicated for the treatment of men with high risk nmCRPC. Darolutamide continues to be studied in additional prostate cancer settings alone and in combination with other agents and may have expanded indications in the future.¹⁹ In clinical trials of high risk nmCRPC it extended metastasis free survival by 22 months and reduced the risk of death by 31%. This oral agent is a reasonable treatment option for urologists to manage with few drug-drug interactions, low adverse event profile, and overall acceptable tolerability. □

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