

# Case Study Series

Clinical Advances in Hematology & Oncology

January 2022

## Cases in the Management of Nonmetastatic Castration-Resistant Prostate Cancer: Darolutamide as the First Androgen Receptor Inhibitor in a Fit, Older Man



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### Case 1 of a 3-Part Series

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# Cases in the Management of Nonmetastatic Castration-Resistant Prostate Cancer: Darolutamide as the First Androgen Receptor Inhibitor in a Fit, Older Man

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## Patient Case

A 71-year-old man presented to his urologist reporting hematuria during the previous month. A complete blood count was normal, as was a complete metabolic panel. A prostate-specific antigen (PSA) test showed an elevated level of 14.5 ng/mL, prompting the urologist to perform a core needle biopsy. Pathology testing confirmed a prostate adenocarcinoma with a Gleason pattern of 4+3=7 and a grade group of 3. Based on these findings, the patient was diagnosed with unfavorable intermediate-risk prostate cancer. Using the Memorial Sloan Kettering Cancer Center nomogram, the patient had a predicted probability of lymph node metastases of less than 2%.

The patient's urologist referred him to our medical center. We discussed the diagnosis and treatment options. After counseling, the patient elected to undergo a combination approach including definitive external beam radiation therapy (EBRT) with moderate hypofractionation (28 fractions at 2.5 Gy per fraction), followed by brachytherapy with a low-dose-rate implant. In addition, the patient initiated androgen deprivation therapy (ADT) with leuprolide. He continued therapy for 2 years. During this time, his PSA levels normalized, and serum testing showed castrate levels of testosterone (<50 ng/dL).

Following treatment, the patient underwent routine PSA testing every 6 months. During this time, his PSA levels remained below 1 ng/mL. As he was nearing 5 years

from completion of ADT, his urologist noted a rising PSA level. The PSA quickly escalated to 12.8 ng/mL in the fifth year. At that time, we ordered a computed tomography (CT) scan and a bone scan. Neither scan showed evidence of metastasis. A biopsy showed no local disease, leading his urologist to diagnose a biochemical recurrence.

The patient began treatment with leuprolide. He initially achieved a rapid PSA response (1.2 ng/mL). However, over the course of the following year, his PSA level rose quickly (10.6 ng/mL after 6 months and 23.4 ng/mL after 9 months), despite serum castrate levels of testosterone (30 ng/dL). At that time, the patient was reimaged with a fluciclovine positron emission tomography (PET)/CT, which showed no evidence of soft tissue or bone metastasis.

We diagnosed the patient with nonmetastatic castration-resistant prostate cancer (nmCRPC). He had a rapid PSA doubling time of approximately 3 months. At this point, the patient was 79 years old and had developed arthritis and osteoporosis. Otherwise, he was fairly healthy. He was receiving bone-sparing therapy with the bisphosphonate zoledronic acid.

We discussed the next line of treatment. Several options for therapy were discussed. Through shared decision making, and with particular concerns about side effects, we decided to start therapy with darolutamide. After 10 weeks of treatment, the patient reported mild fatigue, but no other side effects. A PSA test showed a

### On the Cover

Immunofluorescence micrograph of prostate cancer cells. The large cell nuclei, which contain DNA (dark blue), are typical of the rapid cell division that occurs in cancer. Proteins in the cytoplasm are green. One cell with red cytoplasm (above center) is undergoing mitotic cell division. The centrioles (yellow) and spindle fibers (light blue) needed for division can be seen.

Credit: Nancy Kedersha / Science Source

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**Table 1.** Key Points of the Case

Initial Clinical Presentation	
<ul style="list-style-type: none"> <li>• 71-year-old man</li> <li>• PSA level: 14.5 ng/mL</li> <li>• Gleason pattern: 4+3=7 (grade group 3)</li> <li>• Diagnosed with unfavorable intermediate-risk prostate cancer</li> <li>• Predicted probability of lymph node metastasis &lt;2%</li> </ul>	
Initial Treatment	Follow-Up PSA Levels
<ul style="list-style-type: none"> <li>• Definitive EBRT</li> <li>• Brachytherapy with a low-dose-rate implant</li> <li>• ADT (leuprolide)</li> </ul>	<ul style="list-style-type: none"> <li>• Completion of initial treatment (2014): 2.7 ng/mL</li> <li>• 2015: 2.3 ng/mL</li> <li>• 2017: 2.9 ng/mL</li> <li>• 2018: 3.8 ng/mL</li> <li>• 2019: 12.8 ng/mL</li> </ul>
	Imaging Studies
	<ul style="list-style-type: none"> <li>• At PSA recurrence (2019): CT scan and bone scan showed no evidence of metastasis</li> </ul>
Second-Line Systemic Therapy	Follow-Up PSA Levels
<ul style="list-style-type: none"> <li>• Leuprolide</li> </ul>	<ul style="list-style-type: none"> <li>• After 1 month: 1.2 ng/mL</li> <li>• After 6 months: 10.6 ng/mL</li> <li>• After 9 months: 23.4 ng/mL</li> </ul>
	Imaging Studies
	<ul style="list-style-type: none"> <li>• Fluciclovine PET/CT showed no evidence of soft tissue or bone metastasis</li> </ul>
Third-Line Systemic Therapy	Follow-Up PSA Levels
<ul style="list-style-type: none"> <li>• Darolutamide</li> </ul>	<ul style="list-style-type: none"> <li>• After 6 weeks: 10.4 ng/mL</li> <li>• After 18 months: 0.7-0.8 ng/mL</li> </ul>

ADT, androgen deprivation therapy; CT, computed tomography; EBRT, external beam radiation therapy; PET, positron emission tomography; PSA, prostate-specific antigen.

rapid response after 6 weeks, with a decrease of more than 50% (10.4 ng/dL). After 18 months of therapy, the patient continues to respond to treatment. His PSA level is between 0.7 ng/mL and 0.8 ng/mL. He has experienced no significant adverse events.

### Rationale for Treatment Decisions

According to guidelines from the National Comprehensive Cancer Network (NCCN), patients with clinically localized disease are grouped according to an initial risk stratification.<sup>1</sup> Patients are categorized as having either very low, low, intermediate, high, or very high risk,

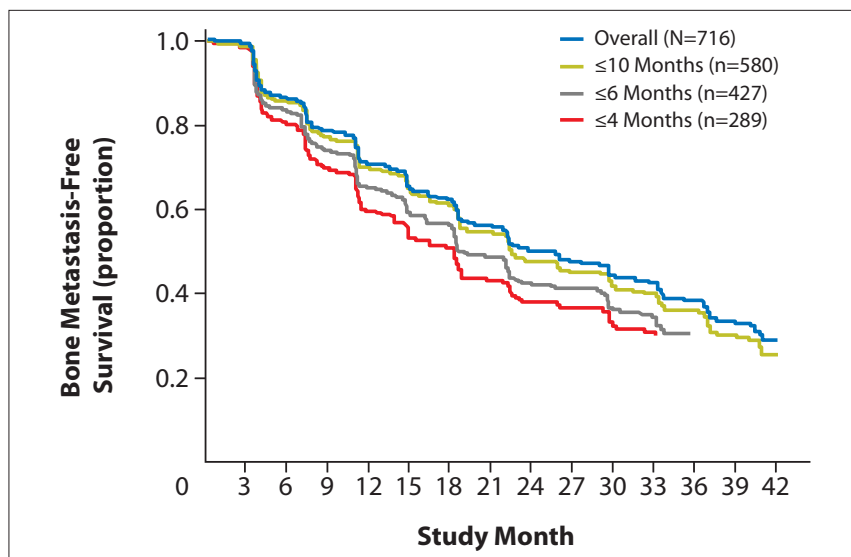
depending on their particular clinical and pathologic features. These risk groups help guide selection of the initial therapy. For the patient in this case, who had unfavorable, intermediate-risk disease, the choice of initial therapy was first guided by his expected survival (>10 years). The next delineation for treatment guidance was based on the predicted probability of lymph node metastasis. Based on the Memorial Sloan Kettering Cancer Center nomogram that uses pretreatment PSA, clinical stage, and Gleason sum, this patient's predicted risk of pelvic lymph node metastases was less than 2%.<sup>2</sup>

Based on the NCCN algorithm, the recommended treatment for patients with these characteristics is EBRT plus brachytherapy, with or without 4 to 6 months of ADT.<sup>1</sup> Alternatively, patients may receive EBRT plus ADT. As seen with this patient, undetectable PSA or PSA nadir following this initial definitive therapy warrants follow-up testing every 6 to 12 months for the first 5 years, and then annually thereafter. When PSA recurrence occurs, imaging is used to rule out metastasis. In this patient, both the CT scan and bone scan showed no evidence of metastasis, and he began ADT.

After an initial rapid reduction in PSA level, this patient exhibited a rise in PSA despite concomitant serum testing that showed evidence of castrate levels of testosterone, defined as a biochemical recurrence. A 2003 analysis estimated that up to 20% to 30% of patients who undergo initial treatment for localized prostate cancer will experience a biochemical recurrence.<sup>3</sup> Although ADT remains the treatment of choice, approximately 10% to 20% of patients will develop castration resistance,<sup>4</sup> defined as a rising PSA level above the nadir in the setting of a castrate serum testosterone level (<50 ng/dL). When this occurs in the absence of visible disease spread, it is referred to as nmCRPC (or M0CRPC).

Approximately one-third of patients with nmCRPC develop metastatic disease within 1 year.<sup>5</sup> This rate increases to approximately 80% within 3 years. Shorter PSA doubling time (PSADT) has been associated with a reduced bone metastasis-free survival time among patients with nmCRPC, defining a subset at high risk for metastasis. For example, in a group of patients with nmCRPC in the placebo arm of a randomized trial, time to bone metastasis or death was approximately 3 months shorter among those with a PSADT of 10 months or less and 7 months shorter among those with a PSADT of 6 months or less compared with the overall cohort (Figure 1).<sup>6</sup> Preventing or delaying progression to metastatic CRPC is an important step to prolong patient survival and improve quality of life. According to the NCCN guidelines, there are 3 preferred treatment regimens in this situation: apalutamide, enzalutamide, and darolutamide.<sup>1</sup> These treatments have a category 1 recommendation

**Figure 1.** Proportion of patients with bone metastasis-free survival in the placebo group overall and according to the PSADT subgroup. PSADT, prostate-specific antigen doubling time. Adapted from Smith MR et al. *J Clin Oncol.* 2013;31(30):3800-3806.<sup>6</sup>



in the NCCN guidelines. They are androgen receptor inhibitors and act by competitively inhibiting androgen binding, androgen receptor nuclear translocation, and androgen receptor-mediated transcription.

#### ***Adding an Androgen Receptor Inhibitor to ADT in nmCRPC***

The addition of an androgen receptor inhibitor to ADT has been evaluated in 3 registrational, randomized, placebo-controlled trials. Apalutamide was evaluated in the SPARTAN trial, enzalutamide in the PROSPER trial, and darolutamide in the ARAMIS trial.<sup>7-9</sup> The studies were similarly designed, and all reported metastasis-free survival as a primary endpoint. The primary analyses from each study reported a significant benefit in metastasis-free survival with the combination of an androgen receptor inhibitor plus ADT. Importantly, this regimen also prolonged overall survival. Patients with nmCRPC therefore now have treatment options that will both delay progression to metastatic disease and prolong survival.

#### ***Use of Darolutamide in the Treatment of nmCRPC: Primary Analysis of the ARAMIS Study***

In 2019, darolutamide gained US Food and Drug Administration (FDA) approval for the treatment of patients with nmCRPC.<sup>10</sup> The approval was granted based on results from the randomized, double-blind, placebo-controlled phase 3 ARAMIS trial, which were published in 2019 by Fizazi and colleagues.<sup>9</sup> A total of 1509 patients were enrolled in the trial between September 2014 and March 2018. The patients had histologically or cytologically confirmed prostate adenocarcinoma and a diagnosis of castration-resistant disease. A baseline PSA level of 2 ng/mL or higher and a PSA doubling time of 10 months or less were also required, as was an Eastern Cooperative

Oncology Group (ECOG) performance status of 0 or 1. The trial permitted enrollment of patients with a history of seizures or conditions predisposing to seizures.

Patients were randomly assigned to receive either darolutamide at 600 mg twice daily (n=955) or matched placebo (n=554). Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. All patients continued to receive ADT throughout the study. At randomization, the patients were stratified according to their PSA doubling time ( $\leq 6$  months vs  $> 6$  months) and whether they were receiving osteoclast-targeted therapy at randomization (yes vs no).<sup>9</sup>

At baseline, patient demographics and characteristics were relatively similar between the 2 treatment arms. The median age of patients in both arms was 74 years. The study enrolled patients from North America (12.2%), the Asia-Pacific region (12.3%), and the rest of the world (primarily Europe; 75.5%). The patients' ECOG performance status was 0 in 69.0% and 1 in 31.0%. Most patients were not receiving a bone-sparing agent (95.8%), and most had received 2 or more prior hormonal therapies (76.0%).<sup>9</sup>

The median time from the initial diagnosis was 86.2 months (range, 2.6-337.5) in the darolutamide arm and 84.2 months (range, 0.5-344.7) in the placebo arm. In the darolutamide arm, the median serum PSA level was 9.0 ng/mL (range, 0.3-858.3), and the median PSA doubling time was 4.4 months (range, 0.7-11.0). In the placebo arm, the median serum PSA level was 9.7 ng/mL (range, 1.5-885.2), and the median PSA doubling time was 4.7 months (range, 0.7-13.2). The median serum testosterone level in both arms was 0.6 nmol/L (range, 0.2-25.9 in the darolutamide arm and 0.2-7.3 in the placebo arm).<sup>9</sup>

The primary endpoint of the ARAMIS study was metastasis-free survival, which was assessed by blinded central imaging review. Metastasis-free survival was

defined as the time from randomization to confirmed evidence of distant metastasis on imaging or death from any cause, whichever occurred first. During blinded central imaging review, some patients were retrospectively found to have had metastases at baseline; these patients were included in the primary analysis of metastasis-free survival. Lymph node involvement was identified during central imaging review in 17% of the darolutamide arm and 29% of the placebo arm.<sup>9</sup>

The primary data analysis occurred after a median follow-up of 17.9 months. At this time, the median metastasis-free survival was 40.4 months in the darolutamide arm vs 18.4 months in the placebo arm (hazard ratio [HR] for metastasis or death, 0.41; 95% CI, 0.34-0.50;  $P < .001$ ). This benefit in metastasis-free survival was observed with darolutamide across all prespecified subgroups, such as patients with PSA doubling times of 6 months or less at baseline (HR, 0.41; 95% CI, 0.33-0.52), patients with a PSA level higher than 20 ng/mL at baseline (HR, 0.39; 95% CI, 0.29-0.54), and patients with regional pathologic lymph nodes at baseline (HR, 0.28; 95% CI, 0.15-0.51).<sup>9</sup>

Darolutamide demonstrated improved outcomes compared with placebo across each of the secondary endpoints reported in the primary analysis. Median overall survival was not reached in either arm. The hazard ratio for death indicated a lower risk with darolutamide vs placebo (HR, 0.71; 95% CI, 0.50-0.99;  $P = .045$ ). The median time to pain progression, defined as either an increase of 2 points or more from baseline in the Brief Pain Inventory–Short Form (BPI-SF) questionnaire or initiation of opioid treatment for cancer pain, was longer with darolutamide compared with placebo (40.3 months vs 25.4 months; HR, 0.65; 95% CI, 0.53-0.79;  $P < .001$ ). The median time to first symptomatic skeletal event, defined as the use of external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention was not reached in either treatment arm, but showed a benefit with darolutamide (HR, 0.43; 95% CI, 0.22-0.84;  $P = .01$ ). The median time to first cytotoxic chemotherapy was not reached in the darolutamide arm vs 38.2 months in the placebo arm (HR, 0.43; 95% CI, 0.31-0.60;  $P < .001$ ).<sup>9</sup>

Progression-free survival (PFS) was an exploratory endpoint. The median PFS was 36.8 months with darolutamide vs 14.8 months with placebo (HR for disease progression or death, 0.38; 95% CI, 0.32-0.45;  $P < .001$ ). Other exploratory endpoints included median time to PSA progression (HR, 0.13; 95% CI, 0.11-0.16;  $P < .001$ ), median time to first prostate cancer–related invasive procedure (HR, 0.39; 95% CI, 0.25-0.61;  $P < .001$ ), and median time to initiation of subsequent antineoplastic

therapy (HR, 0.33; 95% CI, 0.23-0.47;  $P < .001$ ).<sup>9</sup>

Another exploratory endpoint, patient-reported quality of life, was similar between the 2 treatment arms. Differences in least-squares mean time-adjusted area under the curve scores showed a benefit with darolutamide. Statistically significant differences were noted for BPI-SF (pain severity and pain interference scores), Functional Assessment of Cancer Therapy–Prostate (FACT-P; Physical Well-Being, Emotional Well-Being, Prostate Cancer Subscale, General, FACT-P Total, and Trial Outcome Index), and the European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-PR25) urinary symptoms subscale, although these differences did not reach clinically meaningful thresholds.<sup>9</sup>

The most frequent any-grade adverse event was fatigue, which occurred in 12.1% of patients in the darolutamide arm and 8.7% of patients in the placebo arm. Most adverse events reported in the ARAMIS study were grade 1 or 2 (54.6% with darolutamide and 54.2% with placebo). Grade 3 or 4 adverse events were reported in 24.7% of the darolutamide arm and 19.5% of the placebo arm. Grade 5 adverse events occurred in 3.9% and 3.2% of patients, respectively. These deaths were considered treatment-related for 1 patient in the darolutamide arm and 2 patients in the placebo arm. Serious adverse events were reported in 24.8% vs 20.0%, respectively. Adverse events led to treatment discontinuation in 8.9% of patients in the darolutamide arm and 8.7% of those in the placebo arm.<sup>9</sup>

Certain adverse events of interest were selected for analysis because they are known to be associated with next-generation androgen receptor inhibitors. They included bone fracture, falls, and weight decrease. Most of these events occurred at a similar incidence between the darolutamide arm and the placebo arm. In addition, there was a similar incidence of seizures, dizziness, and cognitive impairment. The incidence of fatigue or asthenic conditions (including disturbances in consciousness, decreased strength and energy, malaise, lethargy, asthenia, and fatigue) was 15.8% in the darolutamide arm and 11.4% in the placebo arm.<sup>9</sup>

#### **ARAMIS Study: Final Analysis**

After the positive results in the primary endpoint of metastasis-free survival were reported in the primary analysis of the ARAMIS study, the trial was unblinded. Patients in the placebo arm were permitted to cross over to receive darolutamide as an open-label treatment. At the time of unblinding, all patients who were still receiving placebo ( $n = 170$ ) initiated darolutamide. A final analysis of the ARAMIS trial was published in 2020 by Fizazi and colleagues.<sup>11</sup> The median follow-up was 29.0 months.

At the final analysis, the risk of death was significantly



lower with darolutamide vs placebo (HR, 0.69; 95% CI, 0.53-0.88;  $P=.003$ ). The 3-year rate of overall survival was 83% (95% CI, 80%-86%) with darolutamide vs 77% (95% CI, 72%-81%) with placebo.<sup>11</sup>

The secondary endpoint of overall survival was statistically significant at the final analysis. Therefore, other secondary endpoints were also evaluated in the final analysis using a hierarchical sequence. Because no additional data had been collected, data from the primary analysis of the median time to pain progression were analyzed. This endpoint was 40.3 months with darolutamide vs 25.4 months with placebo (HR, 0.65; 95% CI, 0.53-0.79;  $P<.001$ ). The next secondary endpoint in the hierarchical analysis, time to first use of cytotoxic chemotherapy, was also significantly prolonged with darolutamide (HR, 0.58; 95% CI, 0.44-0.76;  $P<.001$ ). The time to first symptomatic skeletal event was then analyzed in the hierarchical analysis. Darolutamide was associated with a significantly longer time to first symptomatic skeletal event (HR, 0.48; 95% CI, 0.29-0.82;  $P=.005$ ).<sup>11</sup>

#### ***ARAMIS Study: Extended Follow-Up of Tolerability***

An extended follow-up of the ARAMIS study, which focused on the tolerability of darolutamide, was reported by Fizazi and colleagues at the 2021 American Society of Clinical Oncology annual meeting.<sup>12</sup> This analysis showed that patients remained on treatment longer in the darolutamide arm. The median duration of treatment with darolutamide was 18.5 months during the double-blind period and 25.8 months during the double-blind/open-label periods. In the placebo arm, the median duration of treatment was 11.6 months during the double-blind period and 11.0 months during the double-blind/open-label periods for patients who had crossed over.

Darolutamide remained well tolerated during both the double-blind and open-label treatment periods. Fewer patients treated with darolutamide discontinued therapy owing to disease progression compared with placebo (12.5% vs 25.3%). During the double-blind and double-blind/open-label periods, 98.8% of patients treated with darolutamide were able to receive their full planned dose. Most patients who required a dose modification were able to re-escalate to the full dose.<sup>12</sup>

This extended follow-up analysis identified a potential association between PSA response and overall survival. In a pharmacodynamic model, longer overall survival was associated with the maximum PSA decline (defined as a  $\geq 90\%$  decline from baseline) among the patients treated with darolutamide. A total of 95.1% of patients with a maximum PSA decline were alive after 2 years. A landmark sensitivity analysis at week 16 confirmed a positive association between the maximum PSA decline at week 16 and subsequent overall survival.<sup>12</sup>

#### ***ARAMIS Study: HRQoL Analysis***

In 2021, Smith and colleagues published an analysis of HRQoL in patients treated in the ARAMIS study.<sup>13</sup> Data from the primary analysis were used to compare changes in patient-reported HRQoL outcomes between darolutamide and placebo. Two validated questionnaires were used in this analysis.

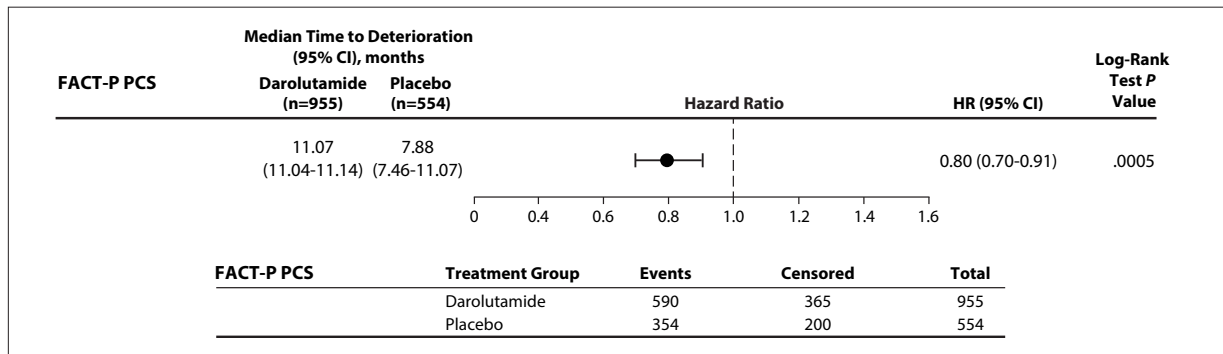
According to an analysis of the FACT-P Prostate Cancer Subscale, the median time to deterioration was 11.1 months with darolutamide vs 7.9 months with placebo (HR, 0.80; 95% CI, 0.70-0.91;  $P=.0005$ ; Figure 2).<sup>13</sup> The time to deterioration in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module (EORTC QLQ-PR25) subscales showed significant delays in progression of urinary and bowel symptoms with darolutamide vs placebo. For urinary symptoms, the median time to deterioration was 25.8 months in the darolutamide arm compared with 14.8 months in the placebo arm (HR, 0.64; 95% CI, 0.54-0.76;  $P<.0001$ ). For bowel symptoms, the median time to deterioration was 18.4 months in the darolutamide arm compared with 11.5 months in the placebo arm (HR, 0.78; 95% CI, 0.66-0.92;  $P=.0027$ ). At least some of the effect on urinary and bladder symptoms was thought to be related to the delay or prevention of disease progression. There was no significant difference in the time to deterioration of hormonal treatment-related symptoms between the treatment arms.<sup>13</sup>

#### ***Selecting an Androgen Receptor Inhibitor in Patients With nmCRPC***

The 3 approved androgen receptor inhibitors—apalutamide, enzalutamide, and darolutamide—have not been directly compared in a randomized, controlled trial. Most men with nmCRPC do not have disease-related symptoms. Treatment goals for this patient population focus on quality of life.

The registrational trials for each of the androgen receptor inhibitors evaluated patient-reported quality of life. Rates were high at baseline and throughout the study period, reflecting the overall low burden of cancer-related symptoms among the populations. Analyses of the toxicity profiles in these trials showed some differences among the agents. In particular, darolutamide did not appear to be associated with an increased risk for falls, fractures, or seizures, unlike apalutamide and enzalutamide.<sup>7-9</sup> Two of these adverse events—falls and seizures—are linked to negative effects on the central nervous system (CNS), such as cognitive impairment.

The low frequency of CNS-related symptoms reported with darolutamide may be attributable to the drug's minimal degree of blood-brain penetration. In a pharmacokinetic rat model, quantitative whole-body



**Figure 2.** FACT-P PCS scores in the phase 3 ARAMIS trial. 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.<sup>13</sup>

autoradiography showed that both enzalutamide and apalutamide maintained persistent concentrations in the brain 8 hours postdose, with similar brain-to-blood concentration ratios (0.807 for enzalutamide and 0.847 for apalutamide). By comparison, the 8 hours postdose concentration of darolutamide was near the limit of detection and showed a brain-to-blood concentration ratio of 0.079.<sup>14</sup>

The adverse event profiles from the pivotal phase 3 studies led to differences in the FDA-label warnings and precautions for each of the androgen receptor inhibitors. The labels for both enzalutamide and apalutamide include warnings about the risk for fractures, falls, and seizures.<sup>15,16</sup> Warnings and precautions for apalutamide also list cerebrovascular and ischemic cardiovascular events.<sup>15</sup> Enzalutamide warnings and precautions list posterior reversible encephalopathy syndrome, hypersensitivity, and ischemic heart disease.<sup>16</sup> In contrast, the FDA label for darolutamide does not include warnings and precautions for cerebrovascular or cardiovascular events, falls, fractures, or seizures.<sup>10</sup> Instead, the only warning and precaution listed in the darolutamide label is regarding embryo-fetal toxicity, which is also included for apalutamide and enzalutamide. The differences in the labels highlight some of the key distinctions in the observed safety profiles of these agents.

### Disclosure

Dr Lowentritt is a meeting participant/lecturer for Bayer, Clovis Oncology, Genomic Health, Inc, Merck, Pfizer Inc, and Blue Earth Diagnostics Ltd. He is a consultant/advisor for UroGen Pharma. He is a consultant/advisor and meeting participant/lecturer and has performed scientific studies/trials for Janssen Scientific Affairs. He is a consultant/advisor and meeting participant/lecturer for Astellas. He has performed scientific studies/trials for Myovant Sciences. He is a consultant/advisor and has performed scientific studies/trials for Dendreon Pharmaceuticals, LLC.

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