Case Study Series

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Cases in the Management of Nonmetastatic Castration-Resistant Prostate Cancer: Darolutamide Added to Leuprolide in a 73-Year-Old Patient

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Case 2 of a 3-Part Series

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Cases in the Management of Nonmetastatic Castration-Resistant Prostate Cancer: Darolutamide Added to Leuprolide in a 73-Year-Old Patient

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Patient Case

A 73-year-old man was diagnosed with prostate cancer based on a prostate-specific antigen (PSA) level of 6.5 ng/mL. The initial diagnosis was stage 3 disease (T3, N0, M0), with a Gleason score of 3+4=7. The patient was diagnosed with favorable intermediate-risk prostate cancer. Initial imaging studies, with both computed tomography (CT) and bone scans, revealed no metastatic disease.

After counseling, the patient elected to receive definitive external beam radiation therapy (EBRT) as his primary treatment. The patient also received a single dose of leuprolide as neoadjuvant therapy prior to EBRT. Following treatment with leuprolide, the patient's chief complaint was erectile dysfunction, as well as recurrent hot flashes. Both issues resolved after completion of EBRT, when his testosterone level recovered to a normal level.

We monitored the patient's progress with blood work every 6 months. Typically, when the testosterone recovers after treatment with leuprolide, the PSA will rise slightly. We consider treatment to be effective when the PSA level is below 2 ng/mL.

The patient's PSA level rose quickly from 0.14 ng/mL to 8 ng/mL. This rapid rise occurred within 8 months of completion of his radiation therapy, and it prompted a new round of imaging. Both CT and bone scans continued to show no evidence of metastatic disease.

These results led to another discussion with the patient. The patient was hesitant to resume treatment with leuprolide, but ultimately elected to do so. The PSA dropped to as low as 1.2 ng/mL quickly after initiation of leuprolide. However, 3 months after that, the PSA rose to 2 ng/mL. It was checked again within 6 weeks and rose again to 4.1 ng/mL. Another round of imaging showed no visible metastatic disease. An ^{18}F-fluciclovine positron emission tomography scan was also negative for distant disease.

The suboptimal efficacy of leuprolide led to the decision to add an androgen receptor (AR) inhibitor to treatment. We selected darolutamide. Although there are several options in this space, we opted for darolutamide for several reasons. Chief among them was the patient's preexistent hypertension (which he did not want to exacerbate), his desire to avoid any dose of glucocorticoids, and his career as a musician, for which he wanted to remain as mentally sharp as possible. We had concerns that other therapies might exacerbate his hypertension or lead to mental slowing.

The patient has now been receiving darolutamide for 24 months. His PSA level decreased nearly immediately. The PSA has been under 1 ng/mL since the first 2 cycles of darolutamide. He did not experience the mental slowing that he had feared when we discussed similar agents.

We did ultimately test the patient for mismatch repair mutations. He tested positive for various mutations, such as ataxia-telangiectasia mutated (ATM) and checkpoint

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

Table 1. Key Points of the Case

Initial Clinical Presentation	
• 73-year-old man • PSA level: 6.5 ng/mL • Gleason pattern: 3+4=7 (grade group 2) • T3, N0, M0 (stage 3) tumor • Diagnosed with favorable intermediate-risk prostate cancer • Initial staging imaging (CT scan and bone scan) showed no metastatic disease	
Initial Treatment	**Follow-Up PSA Levels**
• Neoadjuvant ADT (leuprolide) as a single dose • Definitive EBRT	• After 2 months: 0.14 ng/mL • After 10 months: 8 ng/mL
	Adverse Events
	• Erectile dysfunction • Hot flashes • Both resolved after completion of EBRT
	Imaging Studies
	• At PSA recurrence: CT scan and bone scan showed no evidence of metastasis
Second-Line Systemic Therapy	**Follow-Up PSA Levels**
• Leuprolide	• After 2 months: 1.2 ng/mL • After 3 months: 2 ng/mL • After 4.5 months: 4.1 ng/mL
	Imaging Studies
	• CT scan and bone scan showed no evidence of metastasis
Third-Line Systemic Therapy	**Follow-Up PSA Levels**
• Darolutamide + leuprolide	• After 6 weeks: 0.8 ng/mL

ADT, androgen deprivation therapy; CT, computed tomography; EBRT, external beam radiation therapy

serine-threonine kinase 2 (CHEK2), perhaps explaining why his disease was relatively resistant to treatment with single-agent leuprolide.

Rationale for Treatment Decisions

Intermediate-risk prostate cancer encompasses a highly heterogeneous population of patients with variable prognoses. These patients represent the largest risk group in prostate cancer.[1] They can be difficult to treat, as their risk of recurrence is typically wide.

For patients with favorable intermediate-risk prostate cancer, the main consideration when determining the treatment path is life expectancy. Guidelines from the National Comprehensive Cancer Network (NCCN) note that it may be difficult to estimate life expectancy for a given patient.[2] Life expectancy tools include tables from the Social Security Administration and the World Health Organization (WHO), as well as the Memorial Sloan Kettering Cancer Center male life expectancy tool. When using tables from the Social Security Administration or the WHO, the clinician's assessment of the patient's overall health should be incorporated into the life expectancy estimation. If the patient is in the best quartile of health, 50% is added. If the patient is in the worst quartile of health, 50% should be subtracted.

The addition of androgen deprivation therapy (ADT) to EBRT has become a standard treatment option for patients with intermediate-risk prostate cancer. However, ADT is associated with several adverse events, including an increased risk of cardiovascular disease, dyslipidemia, obesity, erectile dysfunction, and osteoporosis.[3] Therefore, the benefits and risks of adding ADT to EBRT should be carefully considered. The NCCN guidelines note that ADT may be administered with radiation therapy as neoadjuvant, concurrent, and/or adjuvant therapy.[2] Options for ADT in intermediate-risk disease include a single-agent luteinizing hormone-releasing hormone (LHRH) agonist (goserelin, histrelin, leuprolide, or triptorelin), an LHRH agonist plus a first-generation antiandrogen agent (nilutamide, flutamide, or bicalutamide), and an LHRH antagonist (degarelix or relugolix).

Addition of an AR Inhibitor in the Setting of Nonmetastatic CRPC

Patients who present with a biochemical recurrence (rising PSA level) in the setting of castrate levels of testosterone (<50 ng/dL) are diagnosed with castration-resistant prostate cancer (CRPC).[4] Men with evidence of CRPC undergo imaging scans (conventional CT and bone scans) to evaluate for radiographic progression. In the absence of metastases on radiologic imaging, a diagnosis of M0, or nonmetastatic, CRPC is made.

Following a diagnosis of nonmetastatic CRPC, an AR inhibitor may be added to ADT. Three AR inhibitors—apalutamide, enzalutamide, and darolutamide—have been evaluated in well-designed, randomized, placebo-controlled trials.[5-7] These trials were similar in design. They enrolled men with nonmetastatic CRPC who were at high risk for progression (per a baseline PSA of >2 ng/mL and a PSA doubling time of ≤10 months). The trials met their primary endpoint of metastasis-free survival. Long-term analyses also showed improvement in overall survival, a secondary endpoint.[8-10] Based on these studies, the US Food and Drug Administration (FDA)

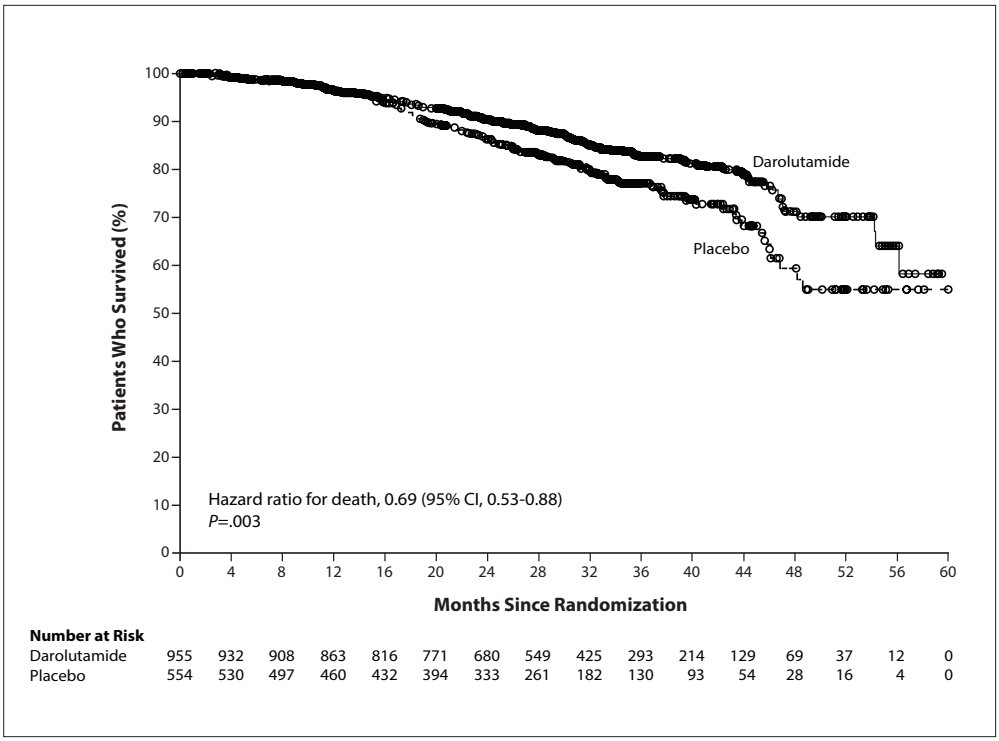

Figure 1. In a long-term analysis of the phase 3 ARAMIS trial, darolutamide improved overall survival compared with placebo in patients with nonmetastatic, castration-resistant prostate cancer. Adapted from Fizazi K et al. *N Engl J Med.* 2020;383(11):1040-1049.[10]

approved apalutamide, enzalutamide, and darolutamide for the treatment of nonmetastatic CRPC.[11-13] In the NCCN guidelines, these agents are listed as a preferred category 1 recommendation in this setting.[2]

The ARAMIS Trial of Darolutamide

The ARAMIS trial randomly assigned 1509 patients in a 2-to-1 ratio to treatment with either darolutamide at 600 mg twice daily or placebo, both added to ADT.[7] Treatment was continued until disease progression, intolerable toxicity, or withdrawal of consent. At the time of randomization, patients were stratified according to PSA doubling time and the use of osteoclast-targeted therapy. The median PSA doubling time was 4.4 months in the darolutamide arm and 4.7 months in the placebo arm. The trial permitted enrollment of patients with pelvic lymph nodes smaller than 2 cm in diameter in the short axis below the aortic bifurcation. This characteristic was reported in 17% of patients in the darolutamide arm and 29% of patients in the placebo arm.

The median metastasis-free survival was 40.4 months with darolutamide vs 18.4 months with placebo (hazard ratio [HR], 0.41; 95% CI, 0.34-0.50; *P*<.001).[7] Several secondary endpoints were also improved with darolutamide compared with placebo, including the median time to pain progression (HR, 0.65; 95% CI, 0.53-0.79; *P*<.001), the median time to first cytotoxic chemotherapy (HR, 0.43; 95% CI, 0.31-0.60; *P*<.001), and the median time to first symptomatic skeletal event (HR, 0.43; 95% CI, 0.22-0.84; *P*=.01).

A prespecified final analysis of 3-year overall survival, conducted at a median follow-up of 29.0 months, reported a 31% lower risk of death with darolutamide compared with placebo (HR, 0.69; 95% CI, 0.53-0.88; *P*=.003; Figure 1).[10] This long-term analysis also continued to show an improvement in the median time to first symptomatic skeletal event (HR, 0.48; 95% CI, 0.29-0.82; *P*=.005; Figure 2).

Serious adverse events were reported in 24.8% of the darolutamide arm and 20% of the placebo arm.[7] All-grade fatigue occurred in 12.1% of the darolutamide arm (grade 3/4, 0.4%) vs 8.7% of the placebo arm (grade 3/4, 0.9%). Notably, several adverse events reported with other AR inhibitors were not substantially higher with darolutamide vs placebo. These adverse events included fracture (4.2% vs 3.6%), falls (4.2% vs 4.7%), seizures (0.2% in each arm), and weight loss (3.6% vs 2.2%).

The SPARTAN Trial of Apalutamide

The SPARTAN trial enrolled 1207 patients with nonmetastatic CRPC who were considered at high risk for disease progression and the development of metastasis, based on a PSA doubling time of 10 months or less during continuous ADT.[5] Patients with malignant pelvic lymph nodes located below the aortic bifurcation and measuring less than 2 cm in the short axis (N1) were permitted to

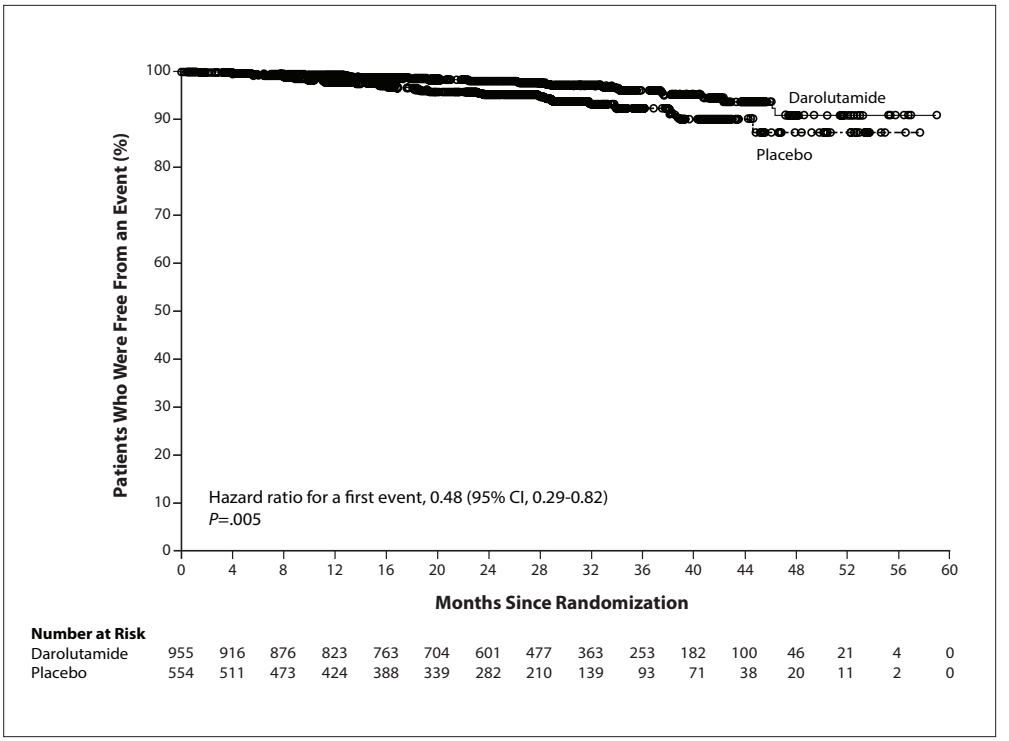

Figure 2.
Darolutamide extended the time to first symptomatic skeletal event compared with placebo in a long-term analysis of the phase 3 ARAMIS trial. Adapted from Fizazi K et al. *N Engl J Med.* 2020;383(11):1040-1049.[10]

enroll, and composed 16.5% of the apalutamide arm and 16.2% of the placebo arm. The patients were randomly assigned in a 2-to-1 ratio to receive either apalutamide at 240 mg/day or matched placebo, both added to continued ADT. Stratification factors included PSA doubling time, the use of bone-sparing agents, and classification of local or regional nodal disease. Treatment was continued until disease progression, intolerable adverse events, or withdrawal of consent.

The median metastasis-free survival was 40.5 months with apalutamide vs 16.2 months with placebo (HR, 0.28; 95% CI, 0.23-0.35; *P*<.001).[5] Several secondary endpoints were also improved with apalutamide compared with placebo, including the time to second progression-free survival (HR, 0.49; 95% CI, 0.36-0.66) and the median time to PSA progression (HR, 0.06; 95% CI, 0.05-0.08).

At the final analysis, the median overall survival was 73.9 months with apalutamide vs 59.9 months with placebo, resulting in a 22% decrease in the HR for death (HR, 0.78; 95% CI, 0.64-0.96; *P*=.016).[8]

Serious adverse events occurred in 24.8% of the apalutamide arm and 23.1% of the placebo arm.[5] Any-grade treatment-related adverse events that occurred more frequently with apalutamide than placebo included fatigue (30.4% vs 21.1%), rash (23.8% vs 5.5%), falls (15.6% vs 9.0%), fracture (11.7% vs 6.5%), hypothyroidism (8.1% vs 2.0%), and seizure (0.2% vs 0%).

The PROSPER Trial of Enzalutamide

The PROSPER study randomly assigned 1401 patients with nonmetastatic CRPC in a 2-to-1 ratio to treatment with enzalutamide at 160 mg once daily or placebo, both added to ADT.[6] Treatment was continued until disease progression or intolerable toxicity. Stratification factors included PSA doubling time and previous or current use of a bone-targeting agent.

The median metastasis-free survival was 36.6 months with enzalutamide vs 14.7 months with placebo.[6] This difference equated to a 71% lower risk of radiographic progression or death (HR, 0.29; 95% CI, 0.24-0.35; *P*<.001). Several secondary endpoints were also improved with enzalutamide vs placebo, including the median time to PSA progression (HR, 0.07; 95% CI, 0.05-0.08; *P*<.001), confirmed PSA response of at least 50% (76% vs 2%, respectively), and the median time to first use of subsequent antineoplastic therapy (HR, 0.21; 95% CI, 0.17-0.26; *P*<.001).

In a prespecified third interim analysis, the median overall survival was 67 months with enzalutamide vs 56.3 months with placebo. Treatment with enzalutamide reduced the risk of death by 27% vs placebo (HR, 0.73; 95% CI, 0.61-0.89; *P*=.001).[9]

The most frequently reported adverse event with enzalutamide was fatigue.[6] All-grade fatigue occurred in 33% of the enzalutamide arm (grade ≥3, 3%) vs 14% of the placebo arm (grade ≥3, 1%). Several adverse events of

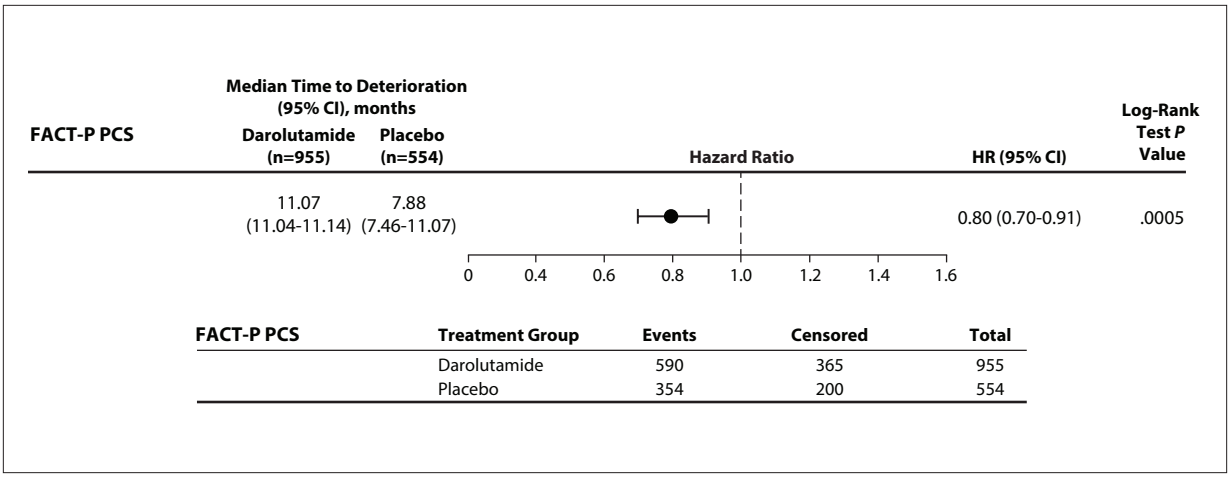

Figure 3. Time to deterioration in FACT-P PCS scores, as assessed by Cox regression analysis, in the phase 3 ARAMIS trial. FACT-P, Functional Assessment of Cancer Therapy–Prostate; HR, hazard ratio; NE, not estimable; PCS, prostate cancer subscale. Adapted from Smith MR et al. *Eur J Cancer.* 2021;154:138-146.[16]

special interest were found to be at least 2% more frequent in the enzalutamide arm vs the placebo arm, including hypertension (12% vs 5%), major adverse cardiovascular events (5% vs 3%), and mental impairment disorders (5% vs 2%).

Selecting an AR Inhibitor in Nonmetastatic CRPC

Until recently, the standard of care for patients with nonmetastatic CRPC was to continue ADT with close monitoring until the onset of metastatic CRPC. Owing to the natural progression of the disease, approximately one-third of these patients will develop bone metastases within 2 years.[14] The introduction of new treatment options with the potential to delay metastatic progression has the potential to improve patient outcomes. Metastasis-free survival predicts overall survival in nonmetastatic CRPC. Furthermore, delaying metastasis is an important strategy to prevent morbidities associated with prostate cancer, such as skeletal-related events, as well as to prolong quality of life.

Based on the reported improvements in metastasis-free survival and overall survival in patients with nonmetastatic CRPC, AR inhibitors were quickly incorporated into the standard of care for patients with nonmetastatic CRPC. Apalutamide, enzalutamide, and darolutamide have not been studied in head-to-head clinical trials. Considerations such as cost, physician experience, patient preference, and toxicities will impact selection.[15] The potential for drug-drug interactions is another important factor when deciding among these agents.

Data from the phase 3 trials suggest that enzalutamide and apalutamide can significantly increase the risks of fractures and falls, as well as dizziness and cognitive impairment.[5,6] In contrast, darolutamide does not appear to significantly increase rates of central nervous system toxicities, including mental and memory impairment, or of falls or fractures.[7] The FDA warnings and precautions for apalutamide and enzalutamide include seizures, falls, and fractures.[11,12] Seizures, falls, and fractures are not listed for darolutamide.[13] This different toxicity profile is attributed to a lower accumulation of darolutamide within the central nervous system. An analysis of the ARAMIS trial that focused on health-related quality of life found that darolutamide significantly delayed time to deterioration of the Functional Assessment of Cancer Therapy–Prostate (FACT-P) prostate cancer subscale scores (Figure 3).[16] Darolutamide was shown to delay progression of urinary and bowel symptoms in an analysis of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module (EORTC QLQ-PR25) subscales (Figure 4). There is some evidence that darolutamide may offer better tolerance and fewer drug-drug interactions. Further studies are needed.

Disclosure

Dr Landau is a compensated speaker for Pfizer, Janssen, Pharmacyclics, Sanofi Genzyme, Seagen, and Karyopharm.

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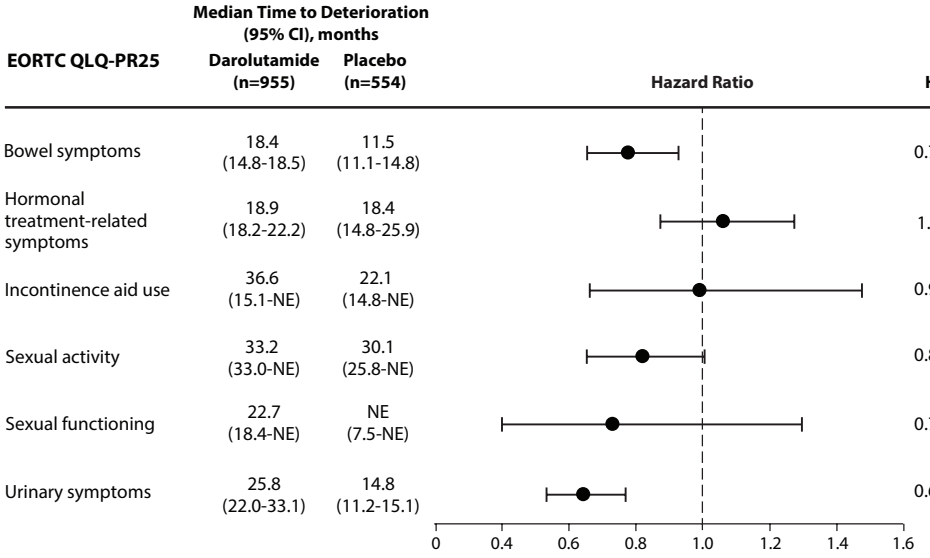

EORTC QLQ-PR25	Treatment Group	Events	Censored	Total
Bowel symptoms	Darolutamide	415	540	955
	Placebo	235	319	554
Hormonal treatment-related symptoms	Darolutamide	385	570	955
	Placebo	172	382	554
Incontinence aid use	Darolutamide	83	169	252
	Placebo	36	93	129
Sexual activity	Darolutamide	253	702	955
	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 4. Time to deterioration in EORTC QLQ-PR25 subscale scores, as assessed by Cox regression analysis, in the phase 3 ARAMIS trial. 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.[16]

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