# CLINICAL UPDATE

Current Developments in the Management of Prostate Cancer

## How Quality of Life Can Help Guide Selection of Androgen Receptor Inhibitors in Nonmetastatic Castration-Resistant Prostate Cancer

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**H&O** What are the treatment goals for men with nonmetastatic, castration-resistant prostate cancer (CRPC)?

**MS** Men with nonmetastatic, castration-resistant prostate cancer are at substantial risk for disease progression, including the development of metastatic disease and, ultimately, death from prostate cancer. The overarching goals of treatment in nonmetastatic CRPC are to delay or prevent the development of metastatic disease and improve overall survival. Most men with nonmetastatic CRPC do not have disease-related symptoms, and therefore the treatment goals also include maintenance of a high quality of life. These patients may have ongoing symptoms related to treatment with androgen deprivation therapy. The goal of maintaining quality of life has important implications when choosing among the available treatment options.

**H&O** What factors lead to deteriorating quality of life among patients with nonmetastatic CRPC?

**MS** There are 2 categories of concern. Men with nonmetastatic CRPC are at risk for deterioration in quality of life owing to cancer progression, which manifests as a progressive rise in levels of prostate-specific antigen, as well as accompanying development of metastatic disease and associated symptoms. In addition, men who have received treatment for nonmetastatic CRPC are at risk for treatment-related adverse events, which can impact quality of life.

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**H&O** Which androgen receptor inhibitors are approved for nonmetastatic CRPC?

**MS** The US Food and Drug Administration (FDA) has approved 3 androgen receptor inhibitors for nonmetastatic CRPC: apalutamide (Erleada, Janssen), enzalutamide (Xtandi, Astellas/Pfizer), and darolutamide (Nubeqa, Bayer). Each of these drugs has shown large, statistically significant improvements in metastasis-free survival, as well as consistent improvements in overall survival, in phase 3 trials. There are no large studies evaluating the comparative effectiveness of these 3 drugs.

**H&O** What did these pivotal trials show in terms of adverse events and quality of life?

**MS** The SPARTAN trial of apalutamide, the PROSPER

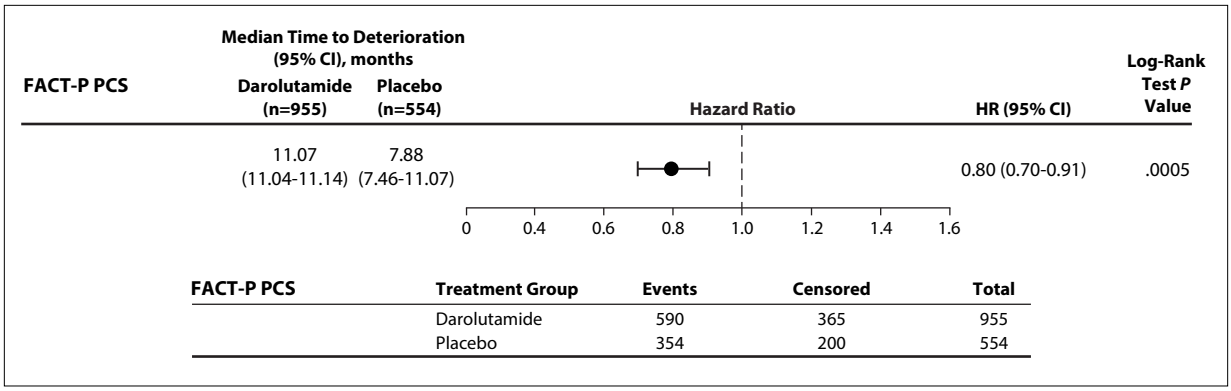



**Figure 1.** Cox regression analysis of time to deterioration in FACT-P PCS scores in an analysis of the phase 3 ARAMIS trial. FACT-P, Functional Assessment of Cancer Therapy–Prostate; HR, hazard ratio; NE, not estimable; PCS, prostate cancer subscale. Adapted from Smith MR et al. *Eur J Cancer*. 2021;154:138-146.

trial of enzalutamide, and the ARAMIS trial of darolutamide each carefully characterized adverse events and evaluated quality-of-life endpoints. In each of these trials, patient-reported quality of life was high at baseline and throughout the period of observation. Because patients with nonmetastatic CRPC have a low burden of cancer-related symptoms, we would not expect to see an improvement in quality of life. However, it was important for the trials to document that quality of life was maintained following treatment with these agents as compared with a placebo.

The pivotal studies showed differences in adverse events for the 3 treatments. Darolutamide appeared to have the best adverse event profile.

### H&O Do these drugs differ in their penetration of the blood-brain barrier?

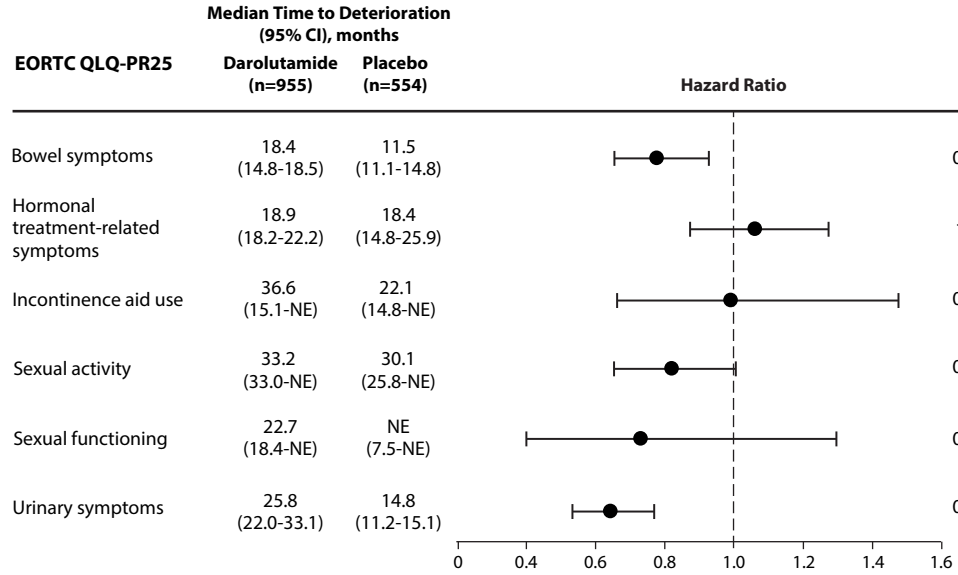
**MS** Darolutamide was developed as an agent with low penetration of the blood-brain barrier, which distinguishes it from the other drugs approved in this setting. Based on this difference in penetration of the blood-brain barrier, it was anticipated that darolutamide might have a lower rate of adverse events associated with the central nervous system, including risks for seizures and falls. Consistent with the known pharmacologic differences among the agents, their adverse event profiles differ. Darolutamide does not appear to increase the risk for falls, fractures, or seizures, in contrast to apalutamide and enzalutamide.

### H&O What were the findings of the recent quality-of-life analysis of the ARAMIS trial?

**MS** My colleagues and I recently published a quality-of-life analysis of the ARAMIS trial. The analysis showed that men with nonmetastatic CRPC were largely asymptomatic at baseline, and that treatment with darolutamide was associated with maintenance of patient-reported quality of life. The median time to deterioration as measured by the Functional Assessment of Cancer Therapy–Prostate (FACT-P) prostate cancer subscale was 11.1 months with darolutamide vs 7.9 months with placebo (hazard ratio [HR], 0.80; 95% CI, 0.70-0.91; *P*=.0005; Figure 1). As measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module (EORTC QLQ-PR25) subscales, the median time to deterioration of urinary symptoms was 25.8 months with darolutamide vs 14.8 months with placebo (HR, 0.64; 95% CI, 0.54-0.76; *P*<.0001; Figure 2). The median time to deterioration of bladder symptoms was 18.4 months vs 11.5 months, respectively (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.

### H&O Do the FDA warnings and precautions of androgen receptor inhibitors differ?

**MS** Based on the results of the pivotal phase 3 studies, the FDA warnings and precautions for the androgen receptor inhibitors approved for nonmetastatic CRPC differ. The labels for both enzalutamide and apalutamide include warnings about the risk for fractures, falls, and seizures. The warnings and precautions for apalutamide also include cerebrovascular and ischemic cardiovascular events. For enzalutamide, the warnings also list posterior reversible encephalopathy syndrome, hypersensitivity, and ischemic heart disease. In contrast, the FDA label for darolutamide does not include warnings and precautions for cerebrovascular or cardiovascular events, falls, fractures, or seizures. The differences in the label highlight some of the key distinctions in the observed safety profiles of these 3 agents.




| 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 2.** Cox regression analysis of time to deterioration in EORTC QLQ-PR25 subscale scores in an analysis of 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.

**H&O** Are there any drug-drug interactions between androgen receptor inhibitors and other drugs often used by these patients?

**MS** Many patients with nonmetastatic CRPC are receiving other medications for concurrent medical conditions, most commonly, hypertension, elevated cholesterol, and diabetes. There are important potential drug-drug interactions for the androgen receptor inhibitors. Among the 3 agents, darolutamide has the fewest drug-drug interactions, which in many ways offers the potential for greater safety when treating patients who are receiving other medications, while also requiring fewer changes to the existing treatment regimens.

**H&O** Are there any other recent studies of these agents?

**MS** My colleagues and I performed an extended follow-up analysis of the ARAMIS trial that focused on the tolerability of darolutamide. The results were presented at the 2021 American Society of Clinical Oncology annual meeting. In patients randomly assigned to the darolutamide arm, the median duration of treatment was 18.5 months during the double-blind period and 25.8 months during the double-blind plus open-label periods.

Among patients treated with darolutamide, the rates of discontinuation owing to adverse events were 8.9% during the double-blind portion and 10.5% during

the double-blind plus open-label portions. With longer follow-up, darolutamide remained well tolerated. Almost all patients were able to receive the full planned dose. This finding is important, as completion of treatment will maximize the benefit of this intervention. These data confirm the favorable benefit-risk considerations for darolutamide among patients with nonmetastatic CRPC.

***Disclosure***

*Dr Smith has served as an advisor or consultant for Amgen, Bayer HealthCare, Janssen, Eli Lilly and Company, and Pfizer.*

## Suggested Readings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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.