Title
Re: Darolutamide and Survival in Metastatic, Hormone-sensitive Prostate Cancer

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Words of Wisdom

Re: Darolutamide and Survival in Metastatic, Hormone-sensitive Prostate Cancer

Smith MR, Hussain M, Saad F, et al.

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Experts' summary:
ARASENS was a randomized, double-blind, placebo-controlled, global phase 3 trial [1]. Patients with metastatic hormone-sensitive prostate cancer (mHSPC) were randomized to either darolutamide or placebo, in addition to docetaxel plus androgen deprivation therapy (ADT). The primary endpoint, overall survival (OS), was significantly better in the experimental arm (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.57–0.80; $p < 0.001$).

Experts' comments:
The addition of androgen receptor–targeted agents (ARTAs) to docetaxel and ADT for patients with mHSPC was recently supported by results from PEACE-1 [2], which included patients with de novo mHSPC, for whom addition of abiraterone resulted in a significant survival benefit (HR 0.75, 95.1% CI 0.59–0.95; $p = 0.017$).

When confronted with results claiming that routine use of a drug—that already has a role in a particular malignancy—at an earlier point in the therapeutic course confers a survival benefit, several questions come to mind. (1) Is earlier administration of an ARTA, in addition to docetaxel, superior to sequential treatment with docetaxel and then an ARTA? (2) Is there a reason to prefer darolutamide over abiraterone? Importantly, neither of these trials investigated the clinical efficacy of triplet combinations over an ARTA plus ADT. Here we highlight differences between these two studies.

First, data on parameters after progression are vital for interpretation of OS when there is a proposal to move active agents to an earlier line of therapy. OS benefits with abiraterone and darolutamide have previously been demonstrated in castrate-resistant settings. In PEACE-1, patients were exclusively enrolled in European countries, mostly in France, and subsequent therapy reflected high access to life-prolonging therapies, and 60% of patients initially assigned to the control arm with docetaxel and ADT eventually received an ARTA [2]. For ARASENS, it is unknown how many patients exactly received an ARTA on progression. The authors only reported total drug usage after progression, so we do not know the differences between those who got abiraterone, those who got enzalutamide, and those who got both. Thus, rates of subsequent ARTA receipt could be as low as 35% and as high as 57% [1]. Therefore, it cannot be excluded that the survival benefit in ARASENS was magnified by suboptimal postprogression treatment in the control arm.

Second, patient selection matters: the survival benefit in PEACE-1 was most notable in the group of patients with high-volume metastatic disease (defined according to the CHAARTED criteria), but this subgroup analysis was not available in ARASENS [1]. It is unclear whether disease volume modifies the effect size of darolutamide. Another trial, ENZAMET, also investigated the triplet strategy with enzalutamide [3]. In contrast to the results from PEACE-1, the survival benefit with enzalutamide evident in the overall population was smaller in the docetaxel subgroup and in the cohort with high-volume disease.

Is timing important? One study showed that abiraterone followed by enzalutamide resulted in modest activity, while the opposite sequence had lower response rates [4]. Assuming that this pattern is true for all second- and third-generation ARTA, we would favor abiraterone over darolutamide or enzalutamide in patients with high-volume disease.

Third, financial toxicity is now recognized as a major source of physical and psychological burdens for patients with cancer [5]. A 1-mo treatment course costs US$14 700 for darolutamide and US$200 for abiraterone acetate. This difference can be profound, as the median duration of treatment was 41 mo in ARASENS and 34.1 mo in PEACE-1, resulting in an overall cost difference approximating US $600 000 per patient.

Poorly reported and incomplete postprotocol treatment data, combined with the potential for financial toxicity, point in favor of the PEACE-1 strategy over ARASENS for patients with high-volume mHSPC. Given the lack of subgroup analyses for disease volume, the risk-benefit balance for darolutamide in patients with low-volume disease cannot be estimated. Shared decision-making should also consider differences in toxicity profile between drugs and patient comorbidities.

Conflicts of interest: Vinay Prasad has received research funding from Arnold Ventures; has received royalties from Johns Hopkins Press and

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Medscape; has received honoraria for grand rounds/lectures from universities, medical centers, nonprofit organizations, and professional societies; is a consultant for United Healthcare; has received speaking fees from Evicore; and has Patreon backers for the Plenary Session podcast. Timothée Olivier and Petros Tsantoulis have nothing to disclose.

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