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Re: Darolutamide in Nonmetastatic Castration-Resistant Prostate Cancer

Fizazi K, Shore N, Tammela TL, et al

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Experts' summary:
ARAMIS is an international, multicentre, randomized, double-blind, placebo-controlled phase 3 trial to evaluate darolutamide in nonmetastatic castration-resistant prostate cancer (nmCRPC) [1]. Darolutamide is a nonsteroidal antiandrogen that is a selective antagonist of the androgen receptor. M0 status in this trial was based on computed tomography (CT) and/or magnetic resonance imaging, and patients were required to have a prostate-specific antigen doubling time (PSA-DT) of ≤10 mo. Patients (n = 1509) were randomized in a 2:1 ratio to darolutamide (600 mg twice daily) or placebo, and treatment continued until progression. The primary endpoint of metastasis-free survival (MFS) favored darolutamide (hazard ratio [HR] 0.41; 40.4 vs 18.4 mo; $p < 0.001$). Darolutamide was also associated with a median progression-free survival (PFS) benefit (HR 0.38; 36.8 vs 14.8 mo; $p < 0.001$). A PSA response of ≥50% was observed more frequently in the darolutamide group (84% vs 8%). Other exploratory endpoints such as time to first cytotoxic chemotherapy and symptomatic skeletal events also favored darolutamide. Overall survival (OS) data are not yet mature. The safety data indicated no clinically relevant difference between darolutamide and placebo in the incidence of adverse events (AEs) during the treatment period. There was no difference in quality of life (QoL) between the groups.

Experts' comments:
ARAMIS [1] joins PROSPER [2] and SPARTAN [3] in reaching the primary endpoint of better MFS for patients with M0 CRPC in favor of the novel AR-targeted therapies darolutamide, enzalutamide, and apalutamide respectively. Extraordinarily, the design of the three studies is practically identical: men on androgen deprivation therapy (ADT) for PC whose disease has become castration resistant, with a PSADT of <10 mo and no evidence of metastases on conventional imaging, were randomized to placebo or intervention with the respective potent AR-targeted therapy. With a HR of ~0.4 in each study and an increase in PFS of >18 mo, both enzalutamide and apalutamide rapidly received US Food and Drug Administration, and darolutamide is expected to quickly follow suit. As expected, an OS benefit has not yet demonstrated in these studies, which does limit reimbursement in many jurisdictions.

What can we conclude about ARAMIS in the context of PROSPER and SPARTAN and the management of nmCRPC? Despite the positive endpoints, some questions arise.

First, what is the best approach to the intriguing disease state of nmCRPC? This state might be considered an iatrogenic condition, triggered by biochemical recurrence (BCR) following primary treatment of localized disease (~75% of patients in each study) in whom ADT is started in the absence of metastatic disease. Invariably, CRPC develops, and for those with fast rising PSA levels (PSADT <10 mo), there is a significant risk of progression to metastases within 18 mo [4]. Undoubtedly, too liberal use of ADT in the BCR setting contributes to the existence of nmCRPC, and clinicians should respect guidelines warning against ADT for asymptomatic men with BCR and no evidence of metastases.

Second, the stratification of nmCRPC into patients with short and longer PSA-DTs is an important and valid approach. These studies restricted enrollment to men with short PSA-DT, as these are a group with a higher risk of developing metastases within 18 mo. Yet, we are already being asked in industry consultations to consider whether we would extend the use of these agents to M0 CRPC patients with longer PSADT (personal observation, D.G.M.). It is very clear from previous data that there is a very sharp inflection point when the PSADT shortens to less than 10 mo [4], and it is therefore this group of men in whom we should consider therapy.

Third, as OS is not yet demonstrated in ARAMIS and its sister studies, we need to consider the value of endpoints such as MFS and, in particular, QoL. QoL is impacted by novel AR-targeted therapies, albeit in a predominantly tolerable fashion. It is, however, noteworthy that darolutamide appears to have a particularly favorable AE profile. Unlike enzalutamide and apalutamide, darolutamide does not cross the blood-brain barrier and therefore appears to avoid some of the treatment-specific AEs associated with enzalutamide and apalutamide.

Finally, what of the designation of these CRPC patients as having M0 PC, or "nonmetastatic" as industry seems to prefer. It has become blindingly obvious to those of us with extensive experience using positron emission tomography (PET) tracers such as prostate-specific membrane antigen (PSMA) that the sensitivity of conventional imaging for detection of PC metastases is highly limited, especially in the BCR state [5]. Indeed, emerging data suggest that of men who meet the inclusion criteria for these nmCRPC studies, the vast majority will actually have metastases as detected via PSMA PET/CT [6]. Therefore, to describe this population definitively as having "nonmetastatic" PC is disingenuous.

They should be described as having M0 PC according to conventional imaging. As these patients actually have mCRPC (according to novel imaging), it is unsurprising that they benefit from AR-targeted therapies.

In summary, ARAMIS joins PROSPER and SPARTAN in demonstrating an improvement in MFS using AR-targeted therapies in select men with M0 CRPC. A point of difference in this study, is that QoL appears to be better preserved.

Conflicts of interest: The authors have nothing to disclose.

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Re: Evaluation of Intense Androgen Deprivation Before Prostatectomy: A Randomized Phase II Trial of Enzalutamide and Leuprolide With or Without Abiraterone

McKay RR, Ye H, Xie W, et al

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Experts' summary:
McKay et al. [1] investigated the role of 6 mo of neoadjuvant leuprolide and enzalutamide with or without abiraterone in patients with high-risk localized prostate cancer before radical prostatectomy (RP). The primary endpoint was the proportion of patients with a pathological complete response (pCR) or minimal residual disease (MRD; defined as a residual tumor diameter <5 mm) at final pathology. Although no significant difference was found between the treatment arms, patients in the abiraterone + enzalutmide + leuprolide arm had a tendency towards more pCR or MRD (30% vs 16%). Furthermore, the authors found that patients with ERG positivity or PTEN loss were more resistant to neoadjuvant treatment in both arms.

Experts' comments:
The concept of treating prostate cancer with neoadjuvant hormonal therapy (NHT) before RP to improve local control of the tumor is not new. Numerous trials using luteinizing hormone–releasing hormone (LHRH) agonists have investigated the possible benefit of NHT. Despite a reduction in positive surgical margins, these trials found no benefit in terms of disease-free survival and overall survival [2]. However, most of these trials were underpowered to show differences in overall survival, had a lack of long-term follow-up, and included mainly patients with low- and intermediate-risk disease. Since the introduction of novel molecules targeting the androgen receptor axis, such as enzalutamide and abiraterone, trials using these drugs in the neoadjuvant setting in a high-risk population have been published [3,4]. These novel molecules were more effective in reducing tissue androgens than LHRH agonists were [3]. An exploratory pooled analysis of studies using abiraterone or enzalutamide showed that patients with pathologic downstaging or residual tumor <0.5 cm at final pathology developed no biochemical recurrence (BCR) during 3-yr follow-up [5]. As a consequence, pathological response may be a prognostic factor in predicting the risk of recurrence. However, 30% of patients still experienced BCR. Therefore, patient selection may be crucial in determining who might benefit most from NHT. The findings of McKay et al. provide good perspectives, as they observed that patients who were ERG-positive or PTEN-negative had a worse response on NHT.

Numerous trials using second-line antiandrogens are ongoing (one of which is at our center using neoadjuvant apalutamide; NCT03080116). However, as long as the benefit of NHT for hard clinical endpoints such as survival is not clear, it should be considered as experimental. Currently, a phase 3 trial with neoadjuvant apalutamide is starting and will address these hard clinical endpoints (NCT03767244).

Conflicts of interest: The authors have nothing to disclose.

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