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Re: Optimizing Patient's Selection for Prostate Biopsy: A Single Institution Experience with Multi-parametric MRI and the 4Kscore Test for the Detection of Aggressive Prostate Cancer

Punnen S, Nahar B, Soodana Prakash N, et al

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Experts' summary:
This retrospective study included a consecutive cohort of patients for whom both multiparametric magnetic resonance imaging (mpMRI) and the 4Kscore test were carried out for prostate cancer (PC) diagnosis. Of the 300 patients identified, 149 (49%) were biopsied and 49 (33%) had significant PC (Gleason score $\geq$7). The diagnostic value of mpMRI and 4Kscore was examined. The authors found that the area under the receiver operating characteristic curve was superior when using 4Kscore and mpMRI together (0.82; 0.75 $\pm$ 0.89) compared using 4Kscore (0.70; 0.62 $\pm$ 0.79) or mpMRI (0.74; 0.66 $\pm$ 0.81) alone (p = 0.001). The likelihood of clinically significant PC was best predicted by combining mpMRI and 4Kscore. The 4Kscore test provided a more accurate level of risk within each mpMRI Prostate Imaging-Reporting and Data System (PI-RADS) category. The authors concluded that both mpMRI and 4Kscore have independent and additive prognostic value for predicting significant PC.

Experts' comments:
In the past, the main clinical dilemma facing a patient with elevated prostate-specific antigen (PSA) was whether to have a prostate biopsy. Today, the clinical dilemma has expanded from a simple yes/no biopsy decision to a more sophisticated question of whether to perform another test, where to aim the biopsy needle, and what technology to use.

Several PC biomarkers are now available for blood (phi, 4Kscore, IsoPSA), urine (PCA3, SelectMDx), and tissue (ConfirmMDx). For all of these biomarkers, an advantage over PSA has been demonstrated [1,2]. The biomarkers are noninvasive and the results are reproducible. However, unlike mpMRI, they can only assist in the question of whether or not to perform a biopsy. Furthermore, none of these have been tested in a randomized control trial.

We now have level 1 evidence from the PROMIS study showing that mpMRI used as a triage test before biopsy could both identify a quarter of men who might avoid biopsy and improve the detection of clinically significant PC [3]. The PRECISION trial went a step further and demonstrated that MRI-ultrasound fusion biopsies are superior to systemic biopsies [4]. Thus, prebiopsy mpMRI provides answers to all three questions: do we need a biopsy, where to aim, and how to carry out the biopsy. However, mpMRI is costly and unavailable in many centers, and results are subject to the operator's experience.

The current study is one of the first to look at a combination of biomarkers and mpMRI. The authors demonstrated that their combination can improve the accuracy of predicting significant PC. While performing the 4Kscore test and mpMRI before biopsy for all patients might be too expensive, several clinical scenarios may be cost-effective. For example, one approach could be to triage all patients using MRI, and then observe patients with normal MRI findings, biopsy all PI-RADS 4/5 lesions, and refer PI-RADS 3 lesions for further biomarker analyses. Another possibility would be to triage patients using biomarker analyses, observing men with normal values and referring patients with abnormal values for MRI before biopsy. All such strategies would need to be tested in well-designed studies.

Emerging from these studies is the fact that an abnormal PSA finding alone may not be enough to trigger a biopsy.

Conflicts of interest: The authors have nothing to disclose.

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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.