

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

*J Clin Oncol* 2019;37:923–31

### 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 + enzalutamide + 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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## Re: Assessment of <sup>68</sup>Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial

Fendler WP, Calais J, Eiber M, et al

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### Experts' summary:

This prospective, multicentre, single-arm trial among 635 men with biochemically recurrent prostate cancer (PC) revealed high PC detection rates for positron emission tomography (PET) with the <sup>68</sup>Ga-labelled prostate-specific membrane antigen ligand PSMA-11. Using histopathology and a composite reference standard of follow-up imaging and prostate-specific antigen (PSA) measurements after focal salvage therapy, PSMA-PET had a positive predictive value of 84–92%. The overall PC detection rate in this cohort with median PSA of 2.1 ng/ml was 75%. Detection rates significantly increased with higher PSA levels. At PSA of <0.5 ng/ml ( $n = 136$ ), PC recurrence was visualized in 38% of men. Importantly, no serious adverse events were noted and inter-reader agreement was substantial.

### Experts' comments:

In this study randomly assigned blinded readers prospectively confirmed data from recent meta-analyses [1,2]. The study included a mix of patients, including hormone-sensitive and castration-resistant PCs. The high PC detection rates for men with low PSA levels highlight the potential for early detection and changes in clinical management. PET-directed focal therapy led to PSA declines of >50% in 31 of 39 men. However, it cannot be emphasized enough that it is still unclear if more sensitive imaging is really improving relevant oncological endpoints such as overall and metastasis-free survival [3]. Therefore, we have to reflect before initiation of PET imaging if the results are going to influence subsequent PC management decisions for individual patients [4]. For men with hormone-sensitive PC experiencing early relapse, a great concern is the omission of timely salvage radiotherapy for men without PET findings. The current study only reports PSA declines for patients with PET-positive findings, and it would have been of interest to see the response in patients

with PET-negative findings receiving salvage radiotherapy. Previous reports showed a high chance of a PSA decline among these men, suggesting poor sensitivity of PSMA-PET in detecting local recurrences at low PSA levels [5]. Improvement in outcome by adapting the radiotherapy field to imaging findings is likely, but prospectively unproven [3]. For men with high-risk M0 castration-resistant PC, by contrast, high rates of N1 and M1 PC detection with PSMA-PET imaging should not be a surprise and these men need systemic treatment [4,6]. Whether localized salvage therapy is useful in patients with short PSA doubling times remains questionable.

Taken together, data indicate that PSMA-PET is a great advance in imaging and most certainly will help in curing more men with advanced PC. This hypothesis must now be tested in prospective studies with adequate oncological endpoints. Identifying the optimal target populations for image-guided salvage approaches is the next step in therapy optimization.

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