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Comment to Smith MR, Hussain M, Saad F et al. (2022, N Engl J Med) Darolutamide and survival in metastatic, hormone-sensitive prostate cancer

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Dear Editors,

We congratulate the investigators of the ARASENS trial demonstrating that darolutamide plus androgen-deprivation therapy (ADT) and docetaxel reduced the risk of death by 32.5% compared to ADT plus docetaxel [1].

Interestingly, treatment-related side effects were similar between the treatment arms, which could be explained by the fact that compared with other androgen receptor signaling inhibitors (ARSIs), darolutamide has a negligible ability to cross the blood–brain barrier and is consequently associated with fewer central side effects than other ARSIs [2].

Furthermore, at least in preclinical models, darolutamide exerts increased anti-tumor activity compared with other ARSIs [3]. Thus, we agree with the ARASENS study protocol of darolutamide plus ADT as an additional control arm.

The overall survival benefit of darolutamide was consistent across all subgroups, yet in the ARASENS study we missed a subgroup analysis on high vs. low risk/volume extent of disease. Of note, patients with a lower extent of disease (Gleason score <8, M1a) were considerably underrepresented in the trial, but it would be of utmost importance to assess the oncological benefit in those patients with low extent of disease in light of the risk–benefit constellation.

Importantly, compared to PEACE-1 combining docetaxel plus abiraterone/prednisolone in patients with de novo mHSPC, ARASENS included patients with recurrent M1 disease, thus expanding the patient spectrum for triple therapy [4].

In summary, despite the impressive survival results of ARASENS (and PEACE-1), one should keep in mind that most substances show unique efficacy claiming for clinical and molecular biomarkers to select those patients who will benefit best from combination therapies.

Conflict of interest I. Heidegger and A. Pircher declare that they have no competing interests.

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