Darolutamide in Metastatic Prostate Cancer

TO THE EDITOR: The results of the ARASENS trial (March 24 issue)[1] represent the beginning of the third revolution in the treatment of metastatic hormone-sensitive prostate cancer (mHSPC). In this trial, Smith and colleagues found that overall survival was significantly longer with the combination of darolutamide, androgen-deprivation therapy, and docetaxel than with placebo plus androgen-deprivation therapy and docetaxel. However, the trial results raise some crucial questions. One of the most important is the identification of patients who would most benefit from such triplet therapy. In the PEACE-1 trial,[2] investigators found that the greatest benefit from triplet therapy with abiraterone plus androgen-deprivation therapy and docetaxel occurred in patients with high-volume mHSPC. Outcome findings according to the tumor volume were not provided in the ARASENS trial. These data would be helpful in understanding whether triplet therapy can be avoided in patients with low-volume disease. In addition, the ARASENS trial did not evaluate whether triplet therapy results in better outcomes than darolutamide plus androgen-deprivation therapy. It is important to understand in which patients chemotherapy can be avoided.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the ARASENS trial, 85 patients (13.0%) in the darolutamide group had hypertension as compared with 59 (9.1%) in the placebo group. Fatigue, increased weight, and myalgias were also more common with darolutamide. Because androgen-receptor inhibition can cause redirection of steroidogenic pathway metabolites, we hypothesize that the use of darolutamide may result in initial mineralocorticoid excess or hyperaldosteronism, with volume expansion and hypertension.[1] The subsequent aldosterone escape can manifest as changes in mental status (i.e., fatigue, which could reflect changes in the serum sodium level),[2] weight gain, and myalgias. Therefore, it would be informative if the authors could present a subgroup analysis of volume-status assessments, plasma potassium and sodium levels, and urinary sodium levels in the subgroup of patients with fatigue, hypertension, weight gain, or myalgias.

In addition, the ARASENS trial was not powered for an evaluation of safety. Given the deleterious effect of hyperaldosteronism on the myocardium[3] in the context of major adverse cardiovascular events associated with androgen-deprivation therapy,[4] long-term cardiovascular monitoring is warranted. Since differences in trial design preclude a head-to-head efficacy comparison of the available androgen-receptor inhibitors, standardized reporting of cardiovascular events with darolutamide becomes paramount in shared decision making.

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THE AUTHOR REPLIES: In response to the comments by Turco and colleagues: we agree that the combination of darolutamide with androgen-deprivation therapy and docetaxel should be used in patients who are most likely to benefit. In our trial, patients were stratified according to the extent of metastatic disease and alkaline phosphatase levels because these are known prognostic factors and were considered to be appropriate for generating data to guide decision making. In prespecified analyses of survival in our trial, we saw consistently improved survival outcomes across these subgroups. We did not perform subgroup comparisons on the basis of high-volume or low-volume disease because these criteria were controversial at the time that the trial was designed. The efficacy of darolutamide and androgen-deprivation therapy without docetaxel is being addressed in the ongoing ARANOTE (ClinicalTrials.gov number, NCT04736199) and ARASEC (NCT05059236) trials.

We acknowledge the point raised by Bowling and Dimitrakoff regarding the apparent higher incidence of hypertension with darolutamide than with placebo. The potential for mineralocorticoid alterations and subsequent cardiovascular dysfunction is an important consideration with androgen-targeted therapy. The between-group difference in the incidence of hypertension in our trial can be at least partially explained by the longer duration of exposure to darolutamide than to placebo (41.0 months vs 16.7 months). After adjustment for exposure, the incidence rate was similar (4.9 per 100 patient-years) in the two groups. The majority of hypertension events were grade 1 or 2. These findings are consistent with those seen with darolutamide plus androgen-deprivation therapy in patients with nonmetastatic castration-resistant prostate cancer in the phase 3 ARAMIS trial (also 4.9 per 100 patient-years).[1] We appreciate the call for standardized reporting of major adverse cardiovascular events and will continue to review and report all clinically relevant adverse effects of treatment with darolutamide in combination with androgen-deprivation therapy and docetaxel.

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Since publication of his article, the author reports no further potential conflict of interest.

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BNT162b2 Protection against the Omicron Variant in Children and Adolescents

TO THE EDITOR: Price and colleagues (published online on March 30 at NEJM.org)[1] describe the effectiveness of the BNT162b2 vaccine (Pfizer–BioNTech) against the B.1.1.529 (omicron) variant of SARS-CoV-2 in children and adolescents, findings that have important clinical relevance and policy implications. However, the study was designed without the inclusion of previous Covid-19 status as a confounding factor. It is well known that SARS-CoV-2 infection confers immune protection and appears to result in increased protection against severe Covid-19,[2] factors that could affect the evaluation of vaccine effectiveness. For instance, the vaccine effectiveness against hospitalization for Covid-19 did not appear to diminish over time during the surge in the B.1.617.2 (delta) variant, although studies have shown that levels of neutralizing antibodies decrease over time after receipt of the BNT162b2 vaccine whereas neutralizing-antibody and T-cell responses were retained 12 months after initial infection.[3,4] Thus, the inclusion of previous Covid-19 status should have been clearly mandated in the study design.

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