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ARASENS Trial: Should darolutamide now be added to androgen-deprivation therapy and docetaxel in patients with metastatic, hormone-sensitive prostate cancer?

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SUMMARY

ARASENS is a phase 3 international, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of darolutamide in addition to androgen-deprivation therapy (ADT) and docetaxel in patients with metastatic, hormone-sensitive prostate cancer (mHSPC).[1]

Patients included had ECOG performance-status score of 0 or 1, histologically confirmed prostate cancer, and metastases detected on bone scanning, contrast-enhanced computed tomography, or magnetic resonance imaging (MRI), and were candidates for ADT and docetaxel.

All patients received ADT (luteinizing hormone-releasing hormone [LHRH] agonist or LHRH antagonist or underwent orchiectomy) and received six cycles of docetaxel (75 mg/m^2 on day 1 and every 21 days) initiated within 6 weeks after randomization. Through a 1:1 randomization, either darolutamide (600 mg twice daily with food) or matched placebo was administered until symptomatic disease progression, a change in antineoplastic therapy, unacceptable toxic effects, patient or physician decision, death, or nonadherence.

The primary endpoint was overall survival and secondary endpoints were time to castration-resistant prostate cancer, time to pain progression, symptomatic skeletal event – free survival, time to first symptomatic skeletal event, time to initiation of subsequent systemic antineoplastic therapy, time to worsening of disease-related physical symptoms, and time to initiation of opioid treatment for 7 or more consecutive days, and safety.

Six hundred and fifty-one patients were included in the darolutamide group and 654 in the placebo group. The overall survival at 4 years was 62.7% (95% confidence interval [CI], 58.7–66.7) in the darolutamide group and 50.4% (95% CI, 46.3–54.6) in the placebo group. Darolutamide was significantly more effective than placebo for the first five secondary endpoints. The median treatment duration was longer in the darolutamide group (41.0 months) than in the placebo group (16.7 months). The incidence of adverse events (AEs) of any grade, grade 3–5 and serious AEs were similar in the two groups.

COMMENTS

The current first-line treatment of mHSPC includes ADT with the addition of docetaxel or androgen antagonists such as abiraterone, enzalutamide, or apalutamide.[2,3]

However, ADT combined with both docetaxel and androgen antagonists has not become the standard of care for mHSPC due to contradictory results between the two-phase 3 trials conducted earlier, with PEACE-1 trial showing survival benefit for abiraterone in combination with ADT and docetaxel while subgroup analysis of ENZAMET trial not showing the benefit of enzalutamide in combination with ADT and docetaxel.[4,5]

Darolutamide is a novel androgen-receptor blocker with low blood–brain barrier penetration, approved by the Food and Drug Administration for nonmetastatic hormone-resistant prostate cancer (M0 castrate-resistant prostate cancer [CRPC]) along with ADT.[6] Both the NCCN and EAU guidelines recommend darolutamide in setting of M0 CRPC, based on the ARAMIS trial.[2,3,7] In the ARAMIS trial, metastasis-free survival was almost 2 years longer and the risk of death was 31% lower with darolutamide than with placebo and the incidence of AEs was similar for darolutamide and placebo. However, no phase 3 trial has yet evaluated darolutamide in the setting of metastatic prostate cancer, whether hormone-sensitive or hormone-resistant.

In the present ARASENS trial, darolutamide significantly improved overall survival in patients started on ADT and docetaxel, even in the setting of subsequent treatment in the placebo group. It was associated with a 32.5% reduction in the risk of death. There was no difference in the incidence

of reported AEs between treatment arms. Darolutamide has lower AEs such as fatigue, falls, and fractures compared with previous third-generation ARIs. As it does not penetrate blood–brain barrier, no central nervous system AEs, such as seizures, have been reported thus far.[8]

Large sample size along with an extended follow-up period is strength of this trial leading to robust statistical analysis with the darolutamide group having significantly better outcomes across most of the endpoints compared to the control group. However, it has a few limitations too. Subgroup analysis was not performed in this trial. Furthermore, darolutamide with ADT (not including docetaxel) was not evaluated as a treatment option for mHSPC. This trial did not include patients with poor performance status (ECOG 2 or more), which form a major portion of mHSPC patients. Furthermore, darolutamide with ADT for patients ineligible for docetaxel for mHSPC patients has not been evaluated yet in a trial.

Darolutamide is prohibitively expensive at present with monthly cost of therapy exceeding □5 lakhs and is not readily available and so, it may not yet be considered the standard of care in a developing country like India. However, this trial has confirmed the survival benefit of adding darolutamide to the standard regimen of ADT and docetaxel and if the cost of this drug is reduced, this triple combination therapy may become the next standard of care in coming years.

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