Analysis of the Effect of Crossover From Placebo (PBO) to Darolutamide (DARO) on Overall Survival (OS) Benefit in the ARAMIS Trial.

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Background: DARO is a structurally distinct androgen receptor inhibitor approved for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) based on significantly prolonged metastasis-free survival compared with PBO (median 40.4 vs 18.4 months; hazard ratio [HR] 0.41; 95% confidence interval [CI] 0.34–0.50; P<0.0001) and a favorable safety profile in the phase III ARAMIS trial. Following unblinding at the primary analysis, crossover from PBO to DARO was permitted for the subsequent open-label treatment phase. Sensitivity analyses were performed to assess the effect of PBO–DARO crossover on OS benefit.

Methods: Patients (pts) with nmCRPC receiving androgen deprivation therapy were randomized 2:1 to DARO (n=955) or PBO (n=554). In addition to OS, secondary endpoints included times to pain progression, first cytotoxic chemotherapy, first symptomatic skeletal event, and safety. The OS analysis was planned to occur after approximately 240 deaths, and secondary endpoints were evaluated in a hierarchical order. Iterative parameter estimation (IPE) and rank-preserving structural failure time (RPSFT) analyses were performed as pre-planned sensitivity analyses to adjust for the treatment effect of PBO–DARO crossover. The IPE method used a parametric model for the survival times and iteratively determined the model parameter describing the magnitude of the treatment effect, whereas a grid search and non-parametric log-rank test were used for the RPSFT analysis. The IPE and RPSFT analyses both generated a Kaplan–Meier curve for the PBO arm that predicts what would have been observed in the absence of PBO–DARO crossover.

Results: After unblinding, 170 pts (30.7% of those randomized to PBO) crossed over from PBO to DARO; median treatment duration from unblinding to the final data cut-off was 11 months. Final analysis of the combined double-blind and open label periods was conducted after 254 deaths (15.5% of DARO and 19.1% of PBO pts) and showed a statistically significant OS benefit for DARO vs PBO (HR 0.69; 95% CI 0.53–0.88; P=0.003). Results from the IPE (HR 0.66; 95% CI 0.51–0.84; P<0.001) and RPSFT (HR 0.68; 95% CI 0.51–0.90; P=0.007) analyses were similar to those from the intention-to-treat population, showing that the impact of PBO–DARO crossover was small. Additional analyses accounting for the effect of PBO–DARO crossover will be presented. The safety profile of DARO continued to be favorable at the final analysis, and discontinuation rates at the end of the double-blind period remained unchanged from the primary analysis (8.9% with DARO and 8.7% with PBO).

Conclusions: Early treatment with DARO in men with nmCRPC is associated with significant improvement in OS regardless of pts crossing over from PBO to DARO. The safety profile of DARO remained favorable at the final analysis.

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