Safety of darolutamide (DARO) for non-metastatic castration-resistant prostate cancer (nmCRPC) from extended follow-up in the phase III ARAMIS trial

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Background: DARO is a structurally distinct androgen receptor inhibitor (ARI) approved for treating nmCRPC. In ARAMIS, DARO significantly reduced the risk of death by 31% (HR=0.69; 95% CI: 0.53-0.88; p=0.003) and prolonged median metastasis-free survival vs placebo (PBO; 40.4 months vs 18.4 months; HR=0.41; 95% CI: 0.34-0.50; p<0.001). Adverse events (AEs) of interest commonly associated with ARI therapy, such as fatigue, falls, fractures, rash, mental impairment, and hypertension, as well as interactions between ARIs and concomitantly administered drugs, can impact patient daily life. In the final analysis of the double-blind (DB) period of the ARAMIS trial, DARO had a favorable safety profile, showing ≤2% difference vs PBO for most AEs of interest. Fatigue was the only AE with >10% incidence with DARO. The incidence of permanent discontinuation due to AEs was also similar between DARO and PBO (8.9% vs 8.7%). Here we present safety data for prolonged treatment with DARO from the final analysis of the DB + open-label (OL) period of ARAMIS.

Methods: Patients (pts) with nmCRPC (N=1509) were randomized 2:1 to DARO or matched PBO while continuing androgen deprivation therapy. The data cut-off for the primary analysis of the DB period was September 3, 2018. Study unblinding occurred on November 30, 2018, after which pts in the DARO arm still receiving study treatment continued with OL DARO. The data cut-off for final analysis of the DB+OL period was November 15, 2019.

Results: At the final analysis, the median treatment duration for pts randomized to DARO was 18.5 months for the DB period and 25.8 months for the DB+OL period. At the final cut-off date, 48.8% of patients in the DARO DB+OL group were still receiving DARO treatment. The increase in the incidence of any-grade AEs (85.7% vs 89.8%) and serious AEs (26.1% vs 32.1%) between the DB and DB+OL period was small. Between the DB and DB+OL periods, only minor numerical changes for ARI-associated AEs were observed. When the incidences were corrected for exposure, there were minimal differences between the DB and DB+OL period, e.g., the fracture rate was 3.4 vs 4.0 per 100 patient-years for the DB vs DB+OL periods, respectively. Fatigue was the only ARI-associated AE of interest that exhibited >10% incidence in the DARO arm during the DB+OL period. The incidence of permanent discontinuation of DARO due to AEs increased slightly from 8.9% during the DB period to 10.5% during the DB+OL period; the incidence of discontinuation of PBO due to AEs during the DB period was 8.7%.

Conclusions: With longer treatment exposure, DARO remained well-tolerated. In the DB+OL period, no new safety signals were observed. The expected increases in incidence of AEs between the DB and DB+OL periods largely disappeared when adjusted for the longer exposure, confirming the favorable safety profile of DARO with prolonged treatment.

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