

The ARAMIS trial: Why Darolutamide is better than apalutamide and enzalutamide in nonmetastatic castration-resistant prostate cancer

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SUMMARY

The follow-up of the ARAMIS trial (Androgen Receptor Antagonizing Agent for Metastasis-free Survival), which is a multicentric, randomized, double-blinded, phase III trial on patients with castration-resistant, nonmetastatic prostate cancer (nmCRPC) and a doubling time of 10 months or less for PSA, was published recently in *The New England Journal of Medicine*.^[1] 1509 patients across 36 countries were allocated to receive either Darolutamide (600 mg BD) or a placebo (in a 2:1 ratio) by stratified randomization using PSA doubling time and the use of osteoclast targeted therapy. All the patients were on continuous androgen deprivation therapy.^[2] Overall survival was analyzed after 254 deaths (Darolutamide = 148 and placebo = 106). At 3 years, 83% of the patients (95% confidence interval [CI], 80–86) were alive in the Darolutamide group compared to 77% of the patients (95% CI 72–81) in the placebo group. Patients in the Darolutamide group had a 31% (hazard risk for death 0.69; 95% CI, 0.53–0.88) lower risk of dying compared to the placebo group. Furthermore, the time to progression of pain was significantly longer in the Darolutamide group (40.3 months) compared to the placebo group (25.4 months). Similarly, the time to first use of cytotoxic chemotherapy was significantly longer in the Darolutamide group (hazard risk 0.58; 95% CI 0.44–0.76) compared to the placebo group. There was also a significant delay in the first skeletal-related event in the Darolutamide group (hazard risk 0.48; 95% CI, 0.29–0.82). The incidence or the grade of adverse events reported between the two groups were not statistically different.

COMMENTS

Over the past few years, there have been remarkable developments in the treatment landscape of caP owing to better clarity of tumor biology, availability of multiple new drugs, and landmark trials showing the benefit of these newer drugs. Based on three large, randomized placebo-controlled trials, Enzalutamide,^[3]

Apalutamide,^[4,5] and Darolutamide^[1,2] have gained FDA approval [Table 1]. However, only Apalutamide and Darolutamide have shown improvement in the overall survival.

Darolutamide and keto-Darolutamide, inhibit the proliferation of prostate cancer cells by blocking the testosterone-induced nuclear translocation and androgen receptor (AR) function. Darolutamide is a structurally distinct AR analog. The half-maximal inhibitory concentrations were lower for Darolutamide (11 nM) and keto-Darolutamide (8 nM), compared to Enzalutamide and Apalutamide (86 nM and 93 nM, respectively).^[6,7] The incidence of adverse events such as falls (4.2% vs. 4.7%), dizziness (4.5% vs. 4.0%), seizures (0.2% vs. 0.2%), cognitive disorder (0.4% vs. 0.2%), and memory impairment (0.5% vs. 1.3%) were comparable between the two groups.^[2] The incidence of central nervous system related adverse events were also lower suggesting a favorable safety profile for Darolutamide. The main adverse event was fatigue (15.8%) which much lower than that reported by patients in the PROSPER (33%) or the SPARTAN (30.4%) trial.

Since most of the patients with CaP are elderly and have comorbidities (hence are on other medications), drug-drug interaction (DDI) also plays paramount importance before prescribing Darolutamide. A study by Shore *et al.*^[8] as a post-Hoc and prespecified analysis of the ARAMIS trial has found that most of the participants (98.4% in both arms) had at least one comorbidity. Furthermore, 98.7% of the patients in the Darolutamide group used at least one other medication compared to 98.0% in the placebo group. Comedications included antithrombotic agents (42.8%), lipid-modifying agents (34.5%), beta-blockers (29.7%), and antimicrobial agents (26.9%). However, no significant effects on Darolutamide pharmacokinetics were identified despite the frequent use of co-medications with DDI potential.

The major advantage of the ARAMIS trial is its large sample size along with the extended follow up period leading to a better analysis of the overall survival. Exploratory data also favored Darolutamide in terms of longer time to additional treatment (invasive procedures and subsequent therapy).

Table 1: Comparison among trials

Trial	PROSPER ^[3]	SPARTAN ^[4,5]	ARAMIS ^[1,2]
Drug	Enzalutamide	Apalutamide	Darolutamide
Study design	Randomized (2:1), placebo-controlled	Randomized (2:1), placebo-controlled	Randomized (2:1), placebo-controlled
Sample size	1401	1207	1509
Study population	High-risk nmCRPC	High-risk nmCRPC	High-risk nmCRPC
Primary endpoint	MFS	MFS	MFS
Secondary endpoint	OS	OS	OS
MFS	36.6 versus 14.7 months ($P<0.001$)	40.5 versus 16.2 months ($P<0.001$)	40.4 versus 18.4 months ($P<0.001$)
OS	Not mature	73.9 versus 59.9 months ($P=0.016$)	83% versus 77% alive ($P=0.003$)

MFS=Metastasis- free survival, OS=Overall survival, nmCRPC=Nonmetastatic prostate cancer

A limitation of the trial was that the treatment effect of Darolutamide on the deaths due to prostate cancer alone could not be assessed as the trial was under powered for the same. Also because of the cross over and the initiation of other forms of life-prolonging therapies, the exact effect of Darolutamide could not be appreciated. Another limitation was the authors did not analyse the effect of Darolutamide in the subgroup analysis (e.g., N0 vs. N1 group or PSADT, 6 months vs. >6 months) as was performed for the primary analysis to detect the effects on MFS.^[1,2]

Considering the long-term treatment with these novel agents, cost factor automatically comes into play, especially in a developing country. Darolutamide costs \$11,500 for 30 days, which is similar to Enzalutamide (\$11,549) and Apalutamide (\$11,673). A recently published trial^[9] comparing the cost-effectiveness of Enzalutamide, Apalutamide, and Darolutamide has shown higher cost-effectiveness for Apalutamide + ADT in terms of QALYs (Quality Adjusted Life Years) compared to Enzalutamide and Darolutamide. However, considering the better CNS side effects profile and the minimal interaction with other drugs, Darolutamide is still a suitable choice amongst the three.

Based on the initial analysis of the ARAMIS trial, Darolutamide has been approved as the first-line therapy in treating patients with nmCRPC and the present study further strengthens the evidence in the continuing benefit of this treatment. However, head-on trials comparing Darolutamide with Enzalutamide/Apalutamide are the need of the hour to compare the efficacy, safety profile and DDI in both nmCRPC and mCRPC.

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