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Encore Presentation: Safety of Darolutamide for Nonmetastatic Castration-Resistant Prostate Cancer from Extended Follow-up in the Phase III ARAMIS Trial

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INTRODUCTION

- Darolutamide is a structurally distinct androgen receptor inhibitor (ARI) approved for treating nonmetastatic castration-resistant prostate cancer (nmCRPC))[1,2]
- In the phase III ARAMIS trial, darolutamide significantly prolonged survival outcomes[1,2]

Endpoint, median, months	Darolutamide	Placebo	HR (95% CI)	P-value
Metastasis-free survival	40.4	18.4	0.41 (0.34-0.50)	<0.001
Overall survival	NR	NR	0.69 (0.53-0.88)	0.003

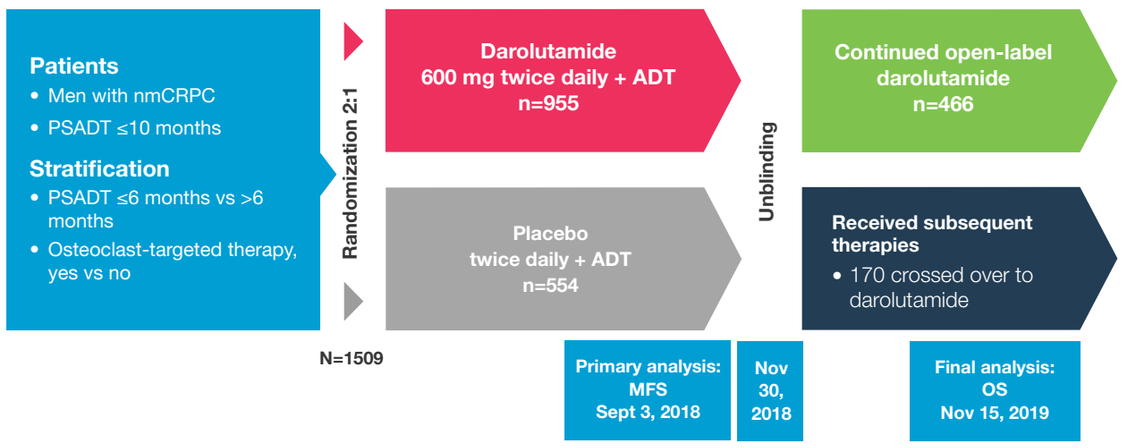
CI, confidence interval; HR, hazard ratio; NR, not reached.

- Adverse events (AEs) commonly associated with ARI therapy—such as fatigue, falls, fractures, rash, mental impairment, and hypertension—can impact patients' daily lives[1,2]
- In the final analysis of the double-blind (DB) period of ARAMIS, darolutamide had a favorable safety profile, and the difference in the incidence of most AEs of interest was ≤2% between darolutamide and placebo groups[2]
  - Fatigue was the only AE that had a >10% incidence with darolutamide (13.2% vs 8.3% in the placebo arm)
- In the final analysis, the incidence of permanent discontinuations due to AEs remained low and was similar between darolutamide and placebo (8.9% vs 8.7%)
- Here we present safety data for prolonged treatment with darolutamide from the final analysis of the DB + open-label (OL) period of ARAMIS

METHODS

- ARAMIS was a double-blind, randomized, multicenter, global phase III trial that evaluated the efficacy and safety of darolutamide versus placebo in addition to androgen deprivation therapy in men with nmCRPC **(Figure 1)**

Figure 1: ARAMIS trial design (NCT02200614)

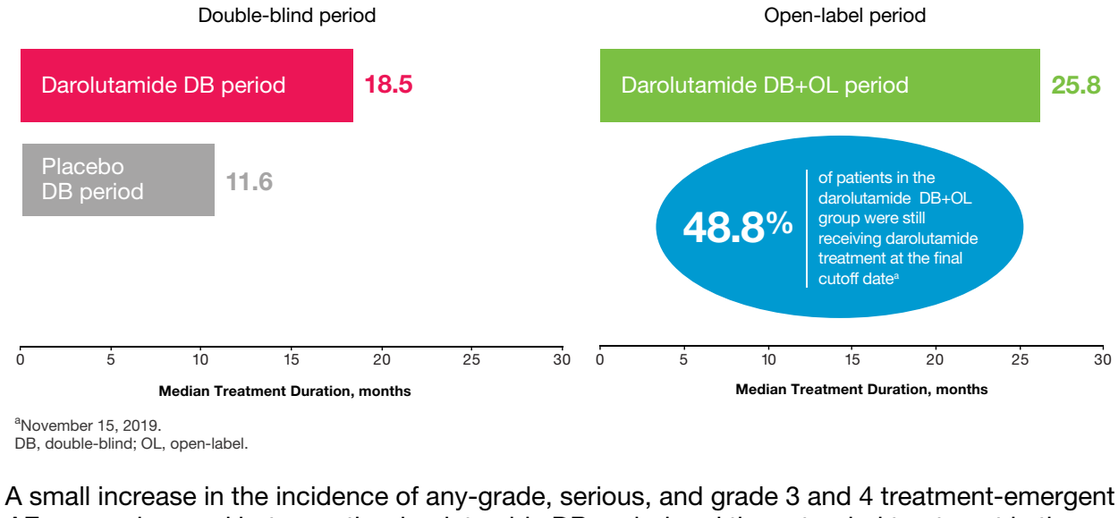


ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, nonmetastatic castration-resistant prostate cancer; OS, overall survival; PSADT,prostate-specific antigen doubling time.

RESULTS

- During the OL period, patients who continued to receive darolutamide had an extended follow-up, with an additional 7.3 months for a total median treatment duration of 25.8 months **(Figure 2)**

Figure 2: Median treatment duration at final analysis[a]



[a]November 15, 2019.
DB, double-blind; OL, open-label.

- A small increase in the incidence of any-grade, serious, and grade 3 and 4 treatment-emergent AEs was observed between the darolutamide DB period and the extended treatment in the DB+OL period
  - Incidences of any-grade, serious, and grade 3 and 4 AEs were lower in the placebo DB group **(Table 1)**
- The incidence of discontinuations due to AEs was increased slightly for darolutamide DB+OL patients

Table 1: Treatment-emergent Adverse Events[a]

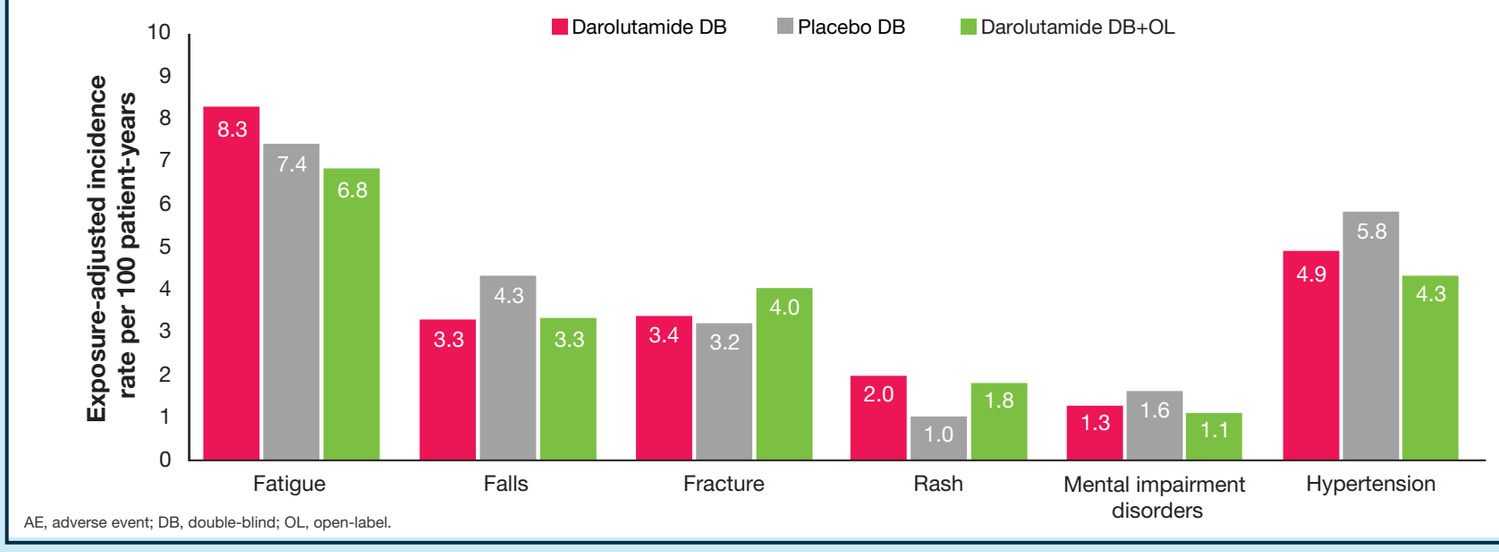
Treatment-emergent AEs, n (%)	Darolutamide DB (n=954)	Placebo DB (n=554)	Darolutamide DB+OL (n=954)
Any treatment-emergent AE	818 (85.7)	439 (79.2)	857 (89.8)
Serious AE	249 (26.1)	121 (21.8)	306 (32.1)
Worst CTCAE grade: 3 or 4	251 (26.3)	120 (21.7)	303 (31.8)
AE leading to permanent discontinuation of study drug	85 (8.9)	48 (8.7)	100 (10.5)
AEs of interest			
Fatigue	126 (13.2)	46 (8.3)	136 (14.3)
Falls, including accidents	50 (5.2)	27 (4.9)	66 (6.9)
Fracture[b]	52 (5.5)	20 (3.6)	79 (8.3)
Rash[c]	30 (3.1)	6 (1.1)	36 (3.8)
Mental impairment disorder[d]	19 (2.0)	10 (1.8)	22 (2.3)
Hypertension	74 (7.8)	36 (6.5)	86 (9.0)

[a]Treatment-emergent AEs were assessed according to National Cancer Institute CTCAE version 4.03.
[b]This category combines the following MedDRA version 20.0 terms: any fractures and dislocations, limb fractures and dislocations, skull fractures, facial bone fractures and dislocations, spinal fractures and dislocations, and thoracic cage fractures and dislocations.
[c]This category combines several MedDRA terms: rash, macular rash, maculopapular rash, papular rash, and pustular rash.
[d]This category is a MedDRA High Level Group Term.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DB, double-blind; MedDRA, Medical Dictionary for Regulatory Activities; OL, open-label.

The safety profile of darolutamide remains consistent with prolonged treatment

When adjusted for longer exposure, differences in incidence rates for AEs of interest between the darolutamide DB and DB+OL periods were minimal

Exposure-adjusted incidence rates for AEs of interest



AE, adverse event; DB, double-blind; OL, open-label.

CONCLUSIONS

- **With longer treatment exposure, darolutamide remained well tolerated**
- **No new safety signals were observed during the DB+OL period of darolutamide treatment**
- **For AEs of interest, the expected increases in incidence between the darolutamide DB and DB+OL periods largely disappeared when adjusted for longer exposure**
- **These results confirm the favorable safety profile of darolutamide with prolonged treatment**

References: 1. Fizazi K, et al. N Engl J Med. 2019;380:1235-1246. 2. Fizazi K, et al. N Engl J Med. 2020;383:1040-1049.

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