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Encore Presentation: Analysis of the Effect of Crossover From Placebo to Darolutamide on Overall Survival Benefit in the ARAMIS Trial

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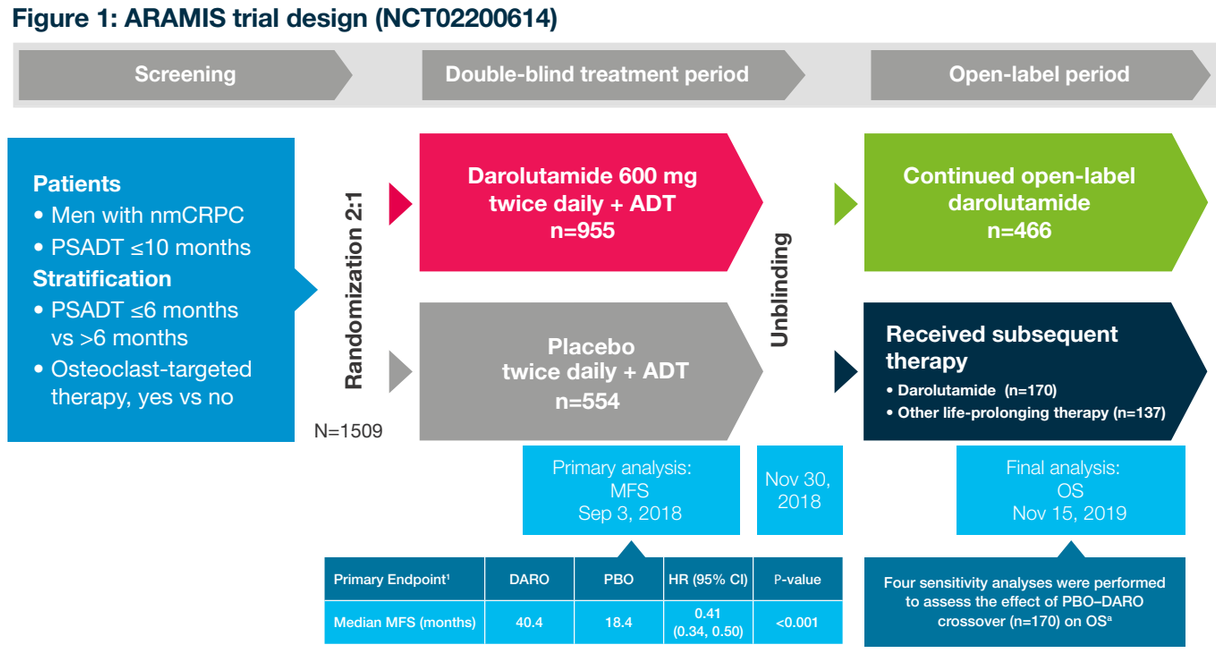
INTRODUCTION

- Darolutamide is a structurally distinct androgen receptor inhibitor approved for treating nonmetastatic castration-resistant prostate cancer (nmCRPC) on the basis of the ARAMIS trial **(Figure 1)**[1,2].
- Following unblinding at the primary analysis, crossover from placebo to darolutamide was permitted for the subsequent open-label period[1]
  - Sensitivity analyses were performed to assess the effect of placebo to darolutamide cross-over on overall survival (OS) benefit **(Table 1)**

METHODS

Figure 1: ARAMIS trial design (NCT02200614)



Primary Endpoint[1]	DARO	PBO	HR (95% CI)	P-value
Median MFS (months)	40.4	18.4	0.41 (0.34, 0.50)	<0.001

[a]Median treatment duration from unblinding to final data cut-off was 11 months. ADT, androgen deprivation therapy; DARO, darolutamide; MFS, metastasis-free survival; nmCRPC, nonmetastatic castration-resistant prostate cancer; OS, overall survival; PBO, placebo; PSADT, prostate-specific antigen doubling time.

Table 1: Sensitivity analyses of OS

Planned sensitivity analyses		Additional sensitivity analyses	
RPSFT Rank-preserving structural failure time	**IPE** Iterative parameter estimation	**Censoring at crossover**	**IPCW** Inverse probability of censoring weighting
RPSFT and **IPE** methods construct a placebo arm that is expected to resemble the KM curve that would have been observed if the switch from placebo to darolutamide had not occurred[a]		Censors patients in the placebo arm at time of crossover to darolutamide[b]	**Step 1:** Probability of switch predicted on the basis of time-dependent factors (prostate-specific antigen and testosterone levels) by fitting a logistic regression model **Step 2:** OS analyzed with the censored dataset and observations weighted by the inverse of the predicted probability of censoring[c]
Uses a grid search and the nonparametric log-rank test to estimate the adjusted treatment effect size	Uses a parametric model for the survival times and iteratively determines the model parameter describing the treatment effect size		

[a]RPSFT and IPE are considered more reliable than censoring and IPCW. [b]The censoring method removes significant portions of lifetime from placebo recipients who crossed over; it therefore introduces a bias unfavoring the placebo arm. [c]This analysis may be limited if not all relevant parameters for prediction are considered or insufficient number of patients similar to crossover patients are available. KM, Kaplan–Meier; OS, overall survival.

RESULTS

- At the final analysis, after 254 deaths (darolutamide 15.5%, placebo 19.1%), OS HR was 0.69 (95% CI 0.53, 0.88; P=0.003).
- For placebo patients, the proportion that crossed over to darolutamide was small (31%) and time on darolutamide vs overall time on treatment was reduced. Therefore, the effect of crossover on the OS results was estimated as being small; the more reliable methods RPFST and IPE suggest that the hazard ratio (0.68, 0.66 vs 0.69) would be slightly stronger if no crossover had occurred **(Figure 2)**
- The safety profile of darolutamide remained favorable at the final analysis **(Table 2)**

Figure 2: Overall survival analyses

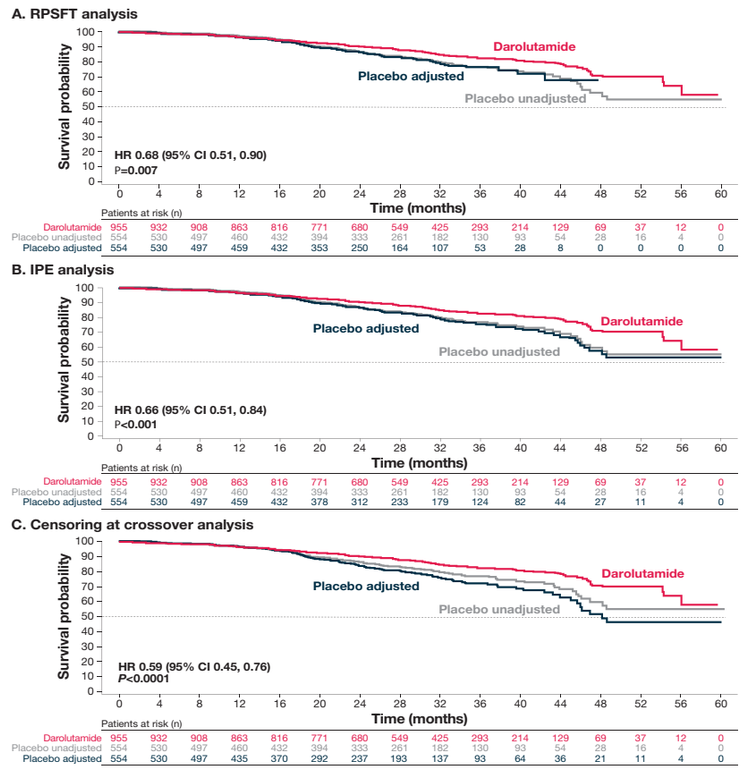


Table 2: Treatment-emergent adverse events[a]

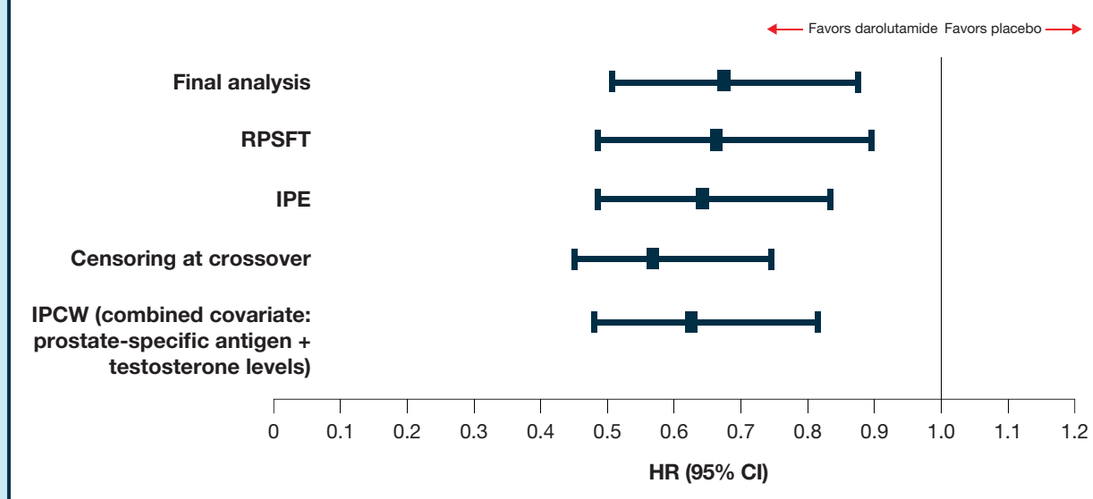
Treatment-emergent AEs, n (%)	DARO DB (n=954)	PBO DB (n=554)	PBO-DARO Crossover (n=170)
Any treatment-emergent AE	818 (85.7)	439 (79.2)	119 (70.0)
Serious AE	249 (26.1)	121 (21.8)	26 (15.3)
Worst CTCAE grade: 3 or 4	251 (26.3)	120 (21.7)	27 (15.9)
AE leading to permanent discontinuation of study drug	85 (8.9)	48 (8.7)	8 (4.7)
AEs of interest			
Fatigue	126 (13.2)	46 (8.3)	7 (4.1)
Falls, including accidents	50 (5.2)	27 (4.9)	4 (2.4)
Fracture[b]	52 (5.5)	20 (3.6)	5 (2.9)
Rash[c]	30 (3.1)	6 (1.1)	4 (2.4)
Mental impairment disorder[d]	19 (2.0)	10 (1.8)	0
Hypertension	74 (7.8)	36 (6.5)	3 (1.8)

[a]Treatment-emergent AEs were assessed according to CTCAE v4.03. [b]This category combines the following MedDRA v20.0 terms: any fractures and dislocations, limb fractures and dislocations, pelvic fractures, skull fractures, facial bone fractures and dislocations, spinal fractures and dislocations, and thoracic cage fractures and dislocations. [c]This category combines the following MedDRA terms: rash, macular rash, maculopapular rash, papular rash, pustular rash, erythema, and dermatitis. [d]This category is a MedDRA High Level Group Term. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DARO, darolutamide; DB, double-blind; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo.

Estimated OS improvement with darolutamide vs placebo is only weakly affected by placebo to darolutamide crossover

- At the ARAMIS final analysis, darolutamide was associated with significant improvement in OS vs placebo[2]
- Sensitivity analyses consistently demonstrated that crossover from placebo to darolutamide (31%, 170/554) had only a small impact on the estimated OS benefit

Overall survival hazard ratios



CI, confidence interval; HR, hazard ratio; IPE, iterative parameter estimation; OS, overall survival; RPSFT, rank-preserving structural failure time.

CONCLUSIONS

- In men with nmCRPC, darolutamide was associated with significant improvement in OS vs placebo at the final analysis
  - 31% reduction in risk of death (HR 0.69; 95% CI 0.53, 0.88; P=0.003) for the unadjusted analysis[2]
  - The effect of crossover on the OS results was estimated to be small and dilutive
- The favorable safety profile of darolutamide seen at the primary analysis was sustained at the final analysis
- These findings indicate that darolutamide is an effective and well-tolerated androgen receptor inhibitor as an early treatment option for patients with nmCRPC

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. 3. Jönsson L, et al. Value Health. 2014;17:707-713.

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