Evaluating hospitalization rates for darolutamide in patients with metastatic hormone sensitive prostate cancer (mHSPC): Insights from ARANOTE trial

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BACKGROUND

- Prostate cancer is the second most frequently diagnosed cancer in men and the fifth leading cause of cancer death in the world among men.[1]
- Despite advancements in early detection and treatment, a considerable number of cases progress to advanced stages such as metastatic hormone-sensitive prostate cancer (mHSPC); also referred to as metastatic castration-sensitive prostate cancer (mCSPC). [2-3]
- The ARANOTE trial (NCT04736199) is a randomized, double-blind, placebo-controlled Phase III study designed to assess the efficacy and safety of NUBEQA plus androgen deprivation therapy (ADT) in patients with mHSPC.
- mHSPC has significant economic implications for healthcare systems; with inpatient hospital admissions representing a significant economic burden in patients with metastatic prostate cancer.[4-5]
- Darolutamide is a distinct androgen-receptor inhibitor (ARPI) with a design that limits potential for clinically relevant drug-drug interactions. Due to a high affinity and selectivity to androgen receptors, darolutamide has a low blood-brain barrier penetration, offering the potential for few and less severe toxic central nervous system-related effects.

OBJECTIVE

- To analyze clinical trial data from ARANOTE to assess the impact of adding darolutamide to ADT on hospitalization rates in comparison to placebo plus ADT.

METHODS

ARANOTE data

- ARANOTE collected data on adverse events (AEs) requiring hospitalization using electronic case report forms. Patient-level data were available for 403 patients receiving darolutamide (and ADT) and 201 patients receiving placebo (and ADT). [6]
- Information on all-cause AEs requiring hospitalization was used as an indicator for hospitalization in ARANOTE.
- The analysis focused on treatment-emergent adverse events (TEAEs) in both analyses.
- Duplicate and overlapping records were condensed, taking the earliest start date and latest end date (i.e. records with the same start date were considered duplicates and records that began before the end date of the previous visit were considered overlapping).

METHODS (Continued)

Statistical analysis

- Hospitalization rates were assessed using negative binomial regression. This is an established statistical method for discrete (or count) data.
- Treatment status was included as a covariate in the regression.
- An offset term was incorporated to account for time at risk, defined as the duration until the onset of radiographic progression-free survival (rPFS).
- Both all-cause hospitalization rates and rates of hospitalization due to Grade 3 or higher (Grade 3+) AEs for each treatment arm were estimated.
- All analyses were conducted using the statistical software R .

RESULTS

- Approximately 22% of patients required hospitalization at least once during treatment in ARANOTE, including those receiving darolutamide and placebo **(Table 1)**.
- Some differences in the proportion of patients requiring at least one hospitalization between darolutamide and placebo groups can be observed on race and Gleason score, but most characteristics were broadly comparable **(Table 2).**
- The treatment coefficient for darolutamide was 0.005 (P-value = 0.983), suggesting the addition of darolutamide to ADT is comparable to hospitalization rates of placebo **(Table 3)**.
- Of patients that were hospitalized (for any reason), the darolutamide group had an annual rate of hospitalization of 0.426 (95% CI: 0.174, 1.039), while the placebo group had a rate of 0.424 (95% CI: 0.278, 0.646) **(Table 3).**
- The results of all-cause hospitalization analysis suggests there is no meaningful numerical difference in hospitalization rates between the two groups.
- Of patients experiencing Grade 3+AEs, the darolutamide group had a rate of 0.771 per year (95% CI: 0.361, 1.645), while the placebo group had a rate of 0.847 per year (95% CI: 0.591, 1.215), indicating a numerical reduction of approximately 9% in the rate of these AEs in the darolutamide group compared to the placebo group **(Table 3).**
- Sensitivity analysis (not presented) using the entire trial population (in the denominator) found similar results (i.e., there was no difference in hospitalization rates between the darolutamide and placebo groups).

Darolutamide combined with ADT showed an all-cause hospitalization rate similar to that of the placebo group, along with a trend indicating a lower rate of hospitalizations due to Grade 3 or higher adverse events

Table 1. Breakdown of hospitalizations by treatment in ARANOTE

Group	N	>=1 hospitalization, n (%)	No hospitalization, n (%)
All patients	604	138 (22.85%)	466 (77.15%)
Darolutamide	403	92 (22.83%)	311 (77.17%)
Placebo	201	46 (22.89%)	155 (77.11%)

Table 2. Overview of patient characteristics in ARANOTE according to treatment and hospitalization status

Characteristic	Darolutamide >=1 hospitalization	Darolutamide, no hospitalization	Placebo >=1 hospitalization	Placebo, no hospitalization
	N=92	N=311	N=46	N=155
Age (years), mean (SD)	70.6 (9.0)	69.6 (8.6)	71.1 (9.0)	69.0 (9.0)
Race, White, %	47.8	55.6	52.2	54.8
Race, Black, %	9.78	10.3	17.4	10.3
Race, Asian, %	41.3	31.5	30.4	29.0
Race, Other, %	1.1	2.6	0.0	2.6
Region, Latin America, %	22.8	30.2	28.3	36.8
Region, Asia, %	40.2	30.9	30.4	27.7
Region, RoW, %	37.0	38.9	41.3	35.5
ECOG 0, %	50.0	52.4	43.5	44.5
ECOG 1, %	46.7	44.7	50.0	52.9
Low volume, %	16.3	31.2	21.7	31.2
High volume, %	83.7	68.8	78.3	68.8
Gleason score, <8, %	21.7	29.6	37.0	26.5
Gleason score, >=8, %	76.1	66.9	60.9	69.0
Metastasis: M1a, %	2.2	3.2	6.52	7.1
Metastasis: M1b, %	85.9	85.9	82.6	81.9
Metastasis: M1c, %	12.0	10.9	10.9	11.0
ALP Category <=ULN, %	43.5	51.1	43.5	47.1
ALP Category >ULN, %	55.4	48.2	50.0	51.0

ALP: Alkaline phosphatase, ECOG:Eastern Cooperative Oncology Group, RoW: Rest of the World, SD: standard deviation, ULN: Upper limit of laboratory normal

Table 3. Annualized rate of hospitalization by treatment and analysis outcome

Outcome	Sample size	Darolutamide (95% CI)	Placebo (95% CI)
All cause hospitalization per year[a]	604	0.426 (0.174, 1.039)	0.424 (0.278, 0.646)
Hospitalization rates due to Grade 3+ AEs per year[b]	237	0.771 (0.361, 1.645)	0.847 (0.591, 1.215)

[a] Negative binomial regression coefficients: intercept = -6.760; treatment status (darolutamide) = -0.005 (p-value = 0.983)
[b] Negative binomial regression coefficients: intercept = -6.065; treatment status (darolutamide) = -0.094 (p-value = 0.667)
AE, adverse event, CI: confidence interval

CONCLUSIONS

- Darolutamide was associated with an all-cause hospitalization rate that was similar to that of the placebo group.
- The darolutamide group experienced a lower rate of hospitalizations due to Grade 3 or higher AEs.
- Darolutamide is a structurally distinct non-steroidal ARPI that binds with a high affinity and selectivity to androgen receptors.
- As such, darolutamide has a low blood-brain barrier penetration which offers the potential for fewer and less severe toxic central nervous system-related effects.
- Analysis is ongoing to further explore the impact of hospitalization on health-related quality of life (i.e., utility scores), overall survival (OS), and equal value Life Years gained (evLYG) in mCSPC.

Limitations

- A limitation of this analysis is that it was not possible to analyze the length of stay associated with hospitalizations.

References

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Scan here to learn more about the about the rate of hospitalizations in ARANOTE.