Efficacy and safety of darolutamide in combination with androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer: phase 3 ARANOTE trial

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Brenda K. Martone, RN, APP[1], Kunhi Parambath Haresh, MD[2], Neal Shore, MD, FACS[3], Isabella Testa, MD[4], Fred Saad, MD[5]

[1]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [2]All India Institute of Medical Sciences, New Delhi, India; [3]Carolina Urologic Research Center and AUC Urology Specialists, Myrtle Beach, South Carolina, USA; [4]Bayer S.p.A, Milan, Italy; [5]Department of Surgery/Urology, Centre Hospitalier de l'Université de Montréal, University of Montreal, Montreal, Quebec, Canada

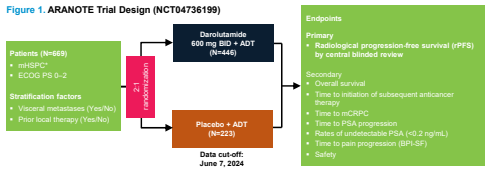
INTRODUCTION

- Patients with metastatic hormone-sensitive prostate cancer (mHSPC) may experience few disease-related symptoms but, without effective treatment, they have a high risk of progression to metastatic castration-resistant prostate cancer (mCRPC), which has a poor prognosis[1,2]
- In the phase 3 ARASENS study, the androgen receptor inhibitor (ARI) darolutamide in combination with androgen-deprivation therapy (ADT) and docetaxel significantly improved survival and delayed progression to mCRPC versus ADT and docetaxel in patients with mHSPC[3]
- Although survival is improved with the triple combination of darolutamide plus ADT and docetaxel, there is a need for effective treatment options that not only delay progression and improve survival but also minimize adverse events (AEs) to preserve patients' quality of life[4]
  - The burden of treatment with docetaxel includes AEs such as neuropathy and neutropenia and not all patients are willing or able to receive docetaxel treatment[1]
- The ARANOTE trial (NCT04736199) evaluated the efficacy and safety of darolutamide with ADT versus ADT alone in patients with mHSPC[5]
- Here we provide valuable information for oncology nurses on the outcomes of ARANOTE to effectively educate and counsel patients on treatment with darolutamide plus ADT

METHODS

- ARANOTE was a global, randomized, double-blind, placebo-controlled phase 3 trial (**Figure 1**)

Figure 1. ARANOTE Trial Design (NCT04736199)



*Metastatic disease confirmed by conventional imaging method as a positive ^{99m}Tc-phosphonate bone scan or soft tissue/visceral metastases on contrast-enhanced abdominal/pelvic/chest CT or MRI scan, assessed by central review.
ADT, androgen-deprivation therapy; BID, twice daily; BPI-SF, Brief Pain Inventory-Short Form; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.

RESULTS: PATIENTS

- From March 2021 to August 2022, 669 patients with mHSPC were randomized to darolutamide (n=446) or placebo (n=223), both with ADT
- Median (range) age was 70 (43–93) years, 31.2% of patients were Asian, 9.7% of patients were Black, and most patients had an ECOG PS of 0 (49.8%) or 1 (47.2%) and high-volume disease (70.6%)
- Demographic and baseline characteristics were well balanced between groups with global representation (**Table 1**)
- At the data cutoff date, more patients in the darolutamide group (53.8%) compared with the placebo group (28.3%) were still receiving study treatment

Table 1. Demographics and baseline characteristics

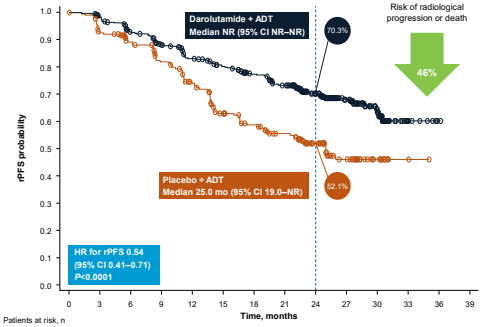
		Darolutamide + ADT (n=446)	Placebo + ADT (n=223)
Age, years	Median (range)	70 (43–93)	70 (45–91)
Race, n (%)	White	251 (56.3)	125 (56.1)
	Asian	144 (32.3)	65 (29.1)
	Black	41 (9.2)	24 (10.8)
	Other	10 (2.2)	9 (4.0)
ECOG PS, n (%)	0	235 (52.7)	98 (43.9)
	1	199 (44.6)	117 (52.5)
	2	12 (2.7)	8 (3.6)
Gleason score, n (%)	≥8	311 (69.7)	146 (65.5)
Serum PSA, ng/mL	Median (range)	21.4 (0.02–15,915)	21.2 (0.02–8533)
Metastases at initial diagnosis, n (%)	Yes (de novo)	317 (71.1)	168 (75.3)
	No (recurrent)	100 (22.4)	45 (20.2)
Disease volume, n (%)*	High	315 (70.6)	157 (70.4)
	Low	131 (29.4)	66 (29.6)
Visceral metastases, n (%)	Yes	53 (11.9)	27 (12.1)
	No	393 (88.1)	196 (87.9)
Prior local therapy, n (%)	Yes	80 (17.9)	40 (17.9)
	No	366 (82.1)	183 (82.1)

*Disease volume defined by CHAARTED criteria: presence of visceral metastases and/or ≥4 bone metastases with ≥1 beyond vertebral bodies and pelvis.[4]
ADT, androgen-deprivation therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen.

RESULTS: PRIMARY ENDPOINT

- Darolutamide plus ADT significantly improved radiological progression-free survival (rPFS) (**Figure 2**)
- Darolutamide reduced the risk of radiological progression or death by 40% in patients with high-volume mHSPC* and by 70% in patients with low-volume mHSPC*

Figure 2. ARANOTE primary endpoint: rPFS



*Disease volume defined by CHAARTED criteria: presence of visceral metastases and/or ≥4 bone metastases with ≥1 beyond vertebral bodies and pelvis.[4]
The primary analysis occurred after 222 events (darolutamide, 128; placebo, 94).
ADT, androgen-deprivation therapy; CI, confidence interval; HR, hazard ratio; NR, not reached; rPFS, radiological progression-free survival.

RESULTS: SAFETY

- Incidences of AEs, including those commonly associated with ARI therapy, were low and similar between treatment groups (**Figures 3A & 3B**)
- Notably, a smaller proportion of patients receiving darolutamide (6.1%) versus placebo (9.0%) discontinued treatment due to AEs, a measure of drug tolerability
- The incidence of fatigue, which places a substantial burden on patients' daily activities and lowers patients' quality of life,[7-9] was lower in patients receiving darolutamide (5.6%) versus placebo (8.1%)

Figure 3A. Incidences of adverse events

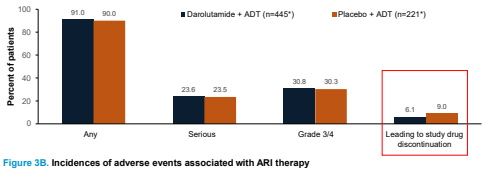
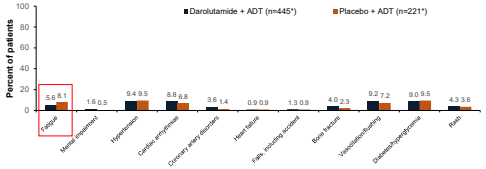


Figure 3B. Incidences of adverse events associated with ARI therapy

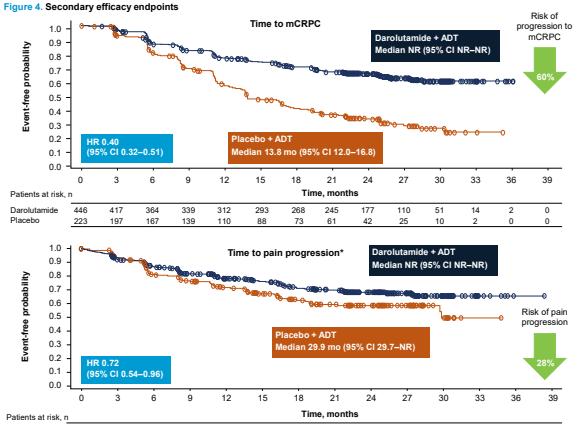


*Two patients who were randomized to the placebo group but received darolutamide are analyzed in the darolutamide group for safety.
ADT, androgen-deprivation therapy; AE, adverse event; ARI, androgen receptor inhibitor.

RESULTS: SECONDARY EFFICACY ENDPOINTS

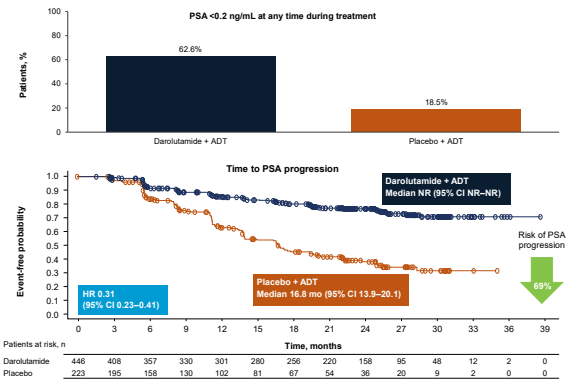
- There was a positive trend in overall survival, with a reduction in risk of death of 19% (HR 0.81; 95% CI 0.59–1.12)
- Darolutamide showed clear benefits over placebo in all other secondary efficacy endpoints, including the patient-relevant endpoints of time to mCRPC and time to pain progression (**Figure 4**)
- Patients receiving darolutamide achieved deep and durable PSA responses, with higher rates of PSA <0.2 ng/mL and delayed time to PSA progression versus placebo (**Figure 5**)

Figure 4. Secondary efficacy endpoints



*Pain progression was defined by change in the Brief Pain Inventory–Short Form questionnaire worst pain score or initiation of opioid therapy for ≥7 consecutive days.
ADT, androgen-deprivation therapy; CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; NR, not reached.

Figure 5. Proportion of patients achieving undetectable PSA (<0.2 ng/mL) and time to PSA progression



ADT, androgen-deprivation therapy; CI, confidence interval; HR, hazard ratio; NR, not reached; PSA, prostate-specific antigen.

CONCLUSIONS

- When discussing treatment options with patients, it is important to consider efficacy, safety, and the impact of treatment on patients' quality of life
  - Nurses play an important role in providing education to help patients manage disease symptoms and treatment side effects
- The ARANOTE study demonstrates that darolutamide plus ADT significantly delays radiological progression and helps patients live longer, with a well-tolerated safety profile, including a low incidence of adverse events that can be troublesome for patients, such as fatigue
- Clear benefits were also observed in other secondary endpoints, including deep and durable PSA responses and increased time to pain progression, suggesting a positive impact on patients' quality of life
- Together with the positive results of the ARASENS study, the findings from ARANOTE provide the option to select treatment in mHSPC with and without docetaxel to meet patients' individual needs and preferences

PLAIN LANGUAGE SUMMARY

- The ARANOTE study was conducted in patients who had metastatic hormone-sensitive prostate cancer (mHSPC), a type of cancer that starts in the prostate gland, has spread to other body parts, and responds to hormone therapy
- The study compared the effects of the combination of darolutamide, an androgen receptor inhibitor that blocks the activity of sex hormones such as testosterone, and androgen-deprivation therapy, or ADT, a hormone therapy that lowers levels of testosterone, with placebo (inactive pill) plus ADT
- Patients who took darolutamide plus ADT had an increased chance of their cancer not getting worse and staying alive compared with patients who took placebo plus ADT
- Patients on darolutamide also had other benefits including a reduced risk of their cancer becoming resistant to hormone therapy, a reduced risk of increased pain, and a higher chance of having low levels of prostate-specific antigen, or PSA, in the blood
- The overall safety of taking darolutamide was similar to that of taking placebo and a lower percentage of patients on darolutamide stopped taking their study medicine because of adverse events versus patients on placebo
- The positive results of the ARANOTE study add to earlier evidence from another study, called ARASENS, showing that patients benefit from treatment with darolutamide, ADT, and a chemotherapy (docetaxel); thus, combining darolutamide and ADT benefits patients with mHSPC whether or not they also take docetaxel

References: **1.** Hussain M, et al. *JAMA Oncol* 2024;10:807-820. **2.** Shore ND, et al. *Clin Genitourin Cancer* 2021;19:199-207. **3.** Smith MR, et al. *N Engl J Med* 2022;386:1132-1142 **4.** Mottet N, et al. https://uroweb.org/guideline/prostate-cancer/. 5. Saad F, et al. *J Clin Oncol* 2024;42:4271-4281. **6.** Sweeney CJ, et al. *N Engl J Med* 2015;373:737–746 7. Cornford P, et al. *Eur Urol Open Sci* 2024;63:119-125. 8. Freedland SJ, et al. *Clin Genitourin Cancer* 2024;22:102209.9. Uemura H, et al. *BMC Urol* 2016;16:63.

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Corresponding author contact: BMartone@nm.org