Prespecified third interim analysis of the DARolutamide ObservationaL (DAROL) study in patients with nonmetastatic castration-resistant prostate cancer: European subgroup analysis

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INTRODUCTION

- Darolutamide is a highly potent androgen receptor inhibitor (ARI) that is structurally distinct by design, with low blood–brain barrier penetration and limited potential for drug–drug interactions[1–5]
- Darolutamide is approved for the treatment of nonmetastatic castration-resistant prostate cancer (nmCRPC) on the basis of the phase 3 ARAMIS study (NCT02200614)
- In ARAMIS, darolutamide significantly improved median metastasis-free survival (MFS) by ~2 years and reduced the risk of death by 31% compared with placebo, with a favorable tolerability profile[6,7]

OBJECTIVE AND METHODS

- The DAROL study (NCT04122976) is assessing the real-world safety and effectiveness of darolutamide in patients with nmCRPC
- We report results from a subgroup analysis of European patients from the prespecified third interim analysis (IA3) of DAROL

Ongoing, global, prospective, open-label, single-arm, non-interventional study

Key eligibility criteria
- Confirmed nmCRPC:
  - Disease progression despite treatment with ADT
  - No evidence of metastasis on conventional imaging
- Decision to initiate darolutamide treatment made before enrollment

Darolutamide*
600 mg orally twice daily

FPFV January 30, 2020
LPFV July 7, 2023

Prespecified analyses	IA1	IA2	IA3	IA4	Final
Patients	100	300	550	800	800
Treatment duration†	≥6 months	≥6 months	**≥6 months**	≥12 months	≥36 months
	✓	✓	✓		

Data cut-off date for IA3: July 17, 2023

Primary outcome
- Safety: frequency, severity, and seriousness of TEAEs

Key secondary/exploratory outcomes
- OS
- MFS
- Time to mCRPC
- PSA progression
- PSA response

*Treatment is according to investigator's routine clinical practice, based on recommendations in the local product information. †Unless patient discontinued earlier.
ADT, androgen deprivation therapy; FPFV, first patient, first visit; IA, interim analysis; LPFV, last patient, first visit; mCRPC, metastatic castration-resistant prostate cancer; MFS, metastasis-free survival; nmCRPC, nonmetastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; TEAE, treatment-emergent adverse event.

BASELINE CHARACTERISTICS

- Of 550 patients assessed at IA3, 198 (36%) were from Europe (Austria n=12, Belgium n=1, Denmark n=1, France n=53, Germany n=47, Greece n=5, Italy n=20, Spain n=59)
- Patient and disease characteristics were generally similar between the European subgroup and the overall population

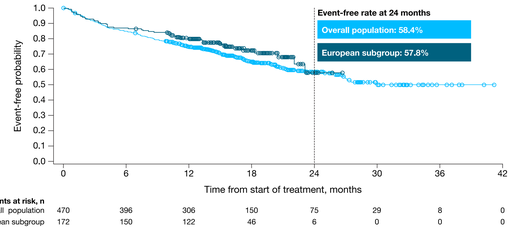
Demographics and baseline characteristics		European subgroup (N=198)	Overall population (N=550*)
Age, years	Median (IQR) [range]	80 (75–84) [56–95]	79 (73–84) [29–98]
Age category, n (%)	<65 years	12 (6.1)	30 (5.5)
	65–74 years	37 (18.7)	133 (24.2)
	75–84 years	104 (52.5)	258 (46.9)
	≥85 years	45 (22.7)	129 (23.5)
ECOG PS, n (%)†	0	111 (62.4)	306 (64.3)
	1	53 (29.8)	138 (28.9)
	2/3	14 (7.9)	32 (6.7)
Gleason score at initial diagnosis, n (%)‡	<8	95 (51.1)	242 (47.5)
	≥8	91 (48.9)	267 (52.5)
Serum PSA, ng/mL	Median (IQR) [range]	4.8 (2.5–11.3) [0.5–101]	4.1 (2.3–9.5) [0–248]
PSADT, months	Median (IQR) [range]	5.5 (3.3–9.8) [0–668]	5.4 (3.2–9.0) [0–668]
Lymph node involvement, n (%)§	N0	163 (88.6)	434 (87.5)
	N1	21 (11.4)	62 (12.5)
Method of nmCRPC confirmation, n (%)**	CT (± contrast)	144 (73.1)	373 (68.3)
	^{99m}Tc bone scan	123 (62.4)	306 (56.0)
	PET	49 (24.9)	104 (19.0)
	MRI	5 (2.5)	31 (5.7)
	Other	4 (2.0)	19 (3.5)

*Safety analysis set includes all patients enrolled in the study who have taken ≥1 dose of darolutamide and completed ≥6 months of treatment or discontinued treatment. †ECOG PS data were not recorded for 20 patients in the European subgroup and for 74 patients in the overall population. ‡Gleason data were not recorded for 12 patients in the European subgroup and 41 patients in the overall population. §Lymph node involvement data were not recorded for 14 patients in the European subgroup and for 54 patients in the overall population. **Method of nmCRPC confirmation was missing for 1 patient in the European subgroup and 4 patients in the overall population.
^{99m}Tc, technetium-99m; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; MRI, magnetic resonance imaging; nmCRPC, nonmetastatic castration-resistant prostate cancer; PET, positron emission tomography; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

TREATMENT DISCONTINUATION

- The median treatment duration was 18.0 months in the overall population and 15.9 months in the European subgroup
- The median time to darolutamide discontinuation or death was 29.9 months (95% confidence interval 26.7–not estimable) in the overall population and not reached (23.1–not estimable) in the European subgroup

Time to darolutamide discontinuation or death



Real-world safety and effectiveness of darolutamide in the DAROL IA3 overall population were confirmed in the European subgroup representing a clinically diverse range of patients and healthcare settings

Safety findings (primary outcome)

- Most TEAEs were grade 1 or 2 with few serious TEAEs and only one grade 5 TEAE; rates of discontinuation due to TEAEs were consistently low in the European subgroup and the overall population
- Incidences of TEAEs associated with ARI therapy were generally low; only fatigue had an incidence ≥10%

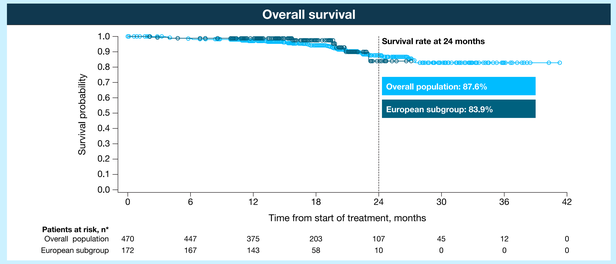
TEAE, n (%)*	European subgroup (N=198)	Overall population (N=550†)
Any grade	127 (64.1)	313 (56.9)
Grade 1/2	80 (40.4)	209 (38.0)
Grade 3/4	41 (20.7)	84 (15.3)
Grade 5	1 (0.5)	10 (1.8)
Serious	34 (17.2)	85 (15.5)
Leading to darolutamide discontinuation	16 (8.1)	38 (6.9)
Commonly associated with ARI therapy		
Fatigue	32 (16.2)	85 (15.5)
Rash	6 (3.0)	17 (3.1)
Hypertension	4 (2.0)	9 (1.6)
Falls	4 (2.0)	16 (2.9)
Fractures	3 (1.5)	7 (1.3)
Mental impairment disorder	2 (1.0)	4 (0.7)

*TEAEs include all events, including those not deemed by the investigator to be related to darolutamide.
†Safety analysis set includes all patients enrolled in the study who have taken ≥1 dose of darolutamide and completed ≥6 months of treatment or discontinued treatment.
ARI, androgen receptor inhibitor; TEAE, treatment-emergent adverse event.

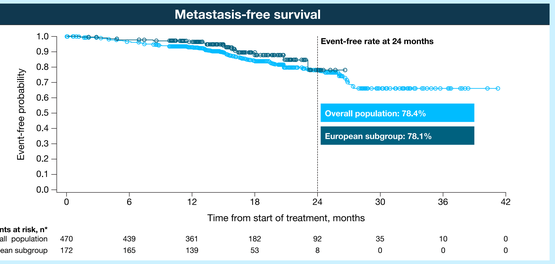
Effectiveness

- At 24 months, rates of overall survival, metastasis-free survival, and time to metastatic castration-resistant prostate cancer (nCRPC) were similar in the European subgroup and the overall population, with medians not yet reached; the 24-month PSA response and progression free rates could not be calculated in the European subgroup due to censoring
- Median time to undetectable PSA (<0.2 ng/mL) was 16.5 months in the overall population and 13.1 months in the European subgroup
- The proportions of patients who achieved 50% or 90% reductions in PSA from baseline were slightly higher in the European subgroup than in the overall population

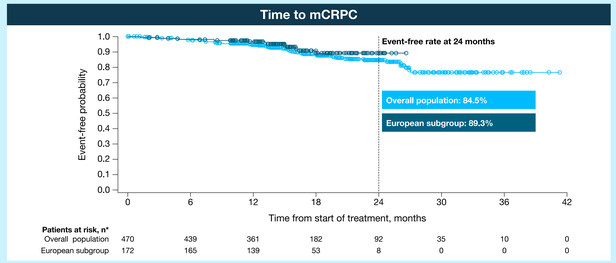
Overall survival



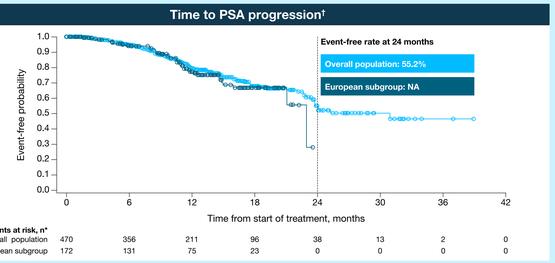
Metastasis-free survival



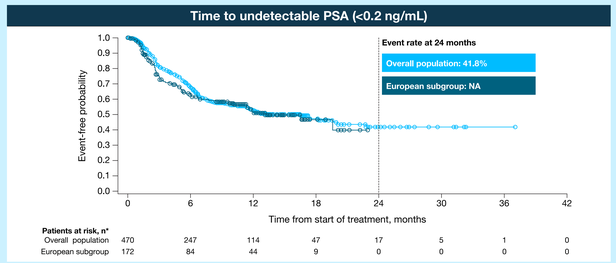
Time to mCRPC



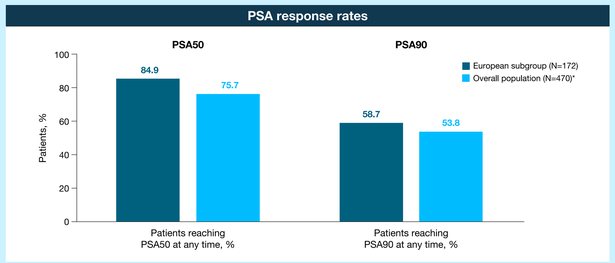
Time to PSA progression†



Time to undetectable PSA (<0.2 ng/mL)



PSA response rates



*Full analysis set: patients who received ≥1 dose of darolutamide, met inclusion/exclusion criteria, and had ≥1 postbaseline assessment after receiving darolutamide. †Unconfirmed PSA progression.
mCRPC, metastatic castration-resistant prostate cancer; NA, not assessable; PSA, prostate-specific antigen; PSA50, ≥50% reduction in PSA from baseline; PSA90, ≥90% reduction in PSA from baseline.

CONCLUSION

- Under real-world conditions, darolutamide was well tolerated in the European subgroup and had a favorable safety profile, consistent with the established safety profile of the compound, without any new safety findings
- Safety and effectiveness findings from the DAROL IA3 European subgroup were generally similar to those of the overall population
- These results confirm the findings of the phase 3 ARAMIS study[6,7] in a clinically diverse, real-world European population, representing patients treated in a range of healthcare systems

PLAIN LANGUAGE SUMMARY

- **Study overview:** The international DAROL study is looking at the safety and effectiveness of a drug called darolutamide for patients with nonmetastatic castration-resistant prostate cancer (nmCRPC). DAROL is a long-term study which is still ongoing. We have analyzed the information collected so far from the first 550 patients enrolled
- **Patients:** Out of these 550 patients, 198 live in Europe. Their average age was 80 years old
- **Safety findings:** Most side effects from darolutamide are mild, with fatigue being the most common. Around one in every six patients in the study has experienced fatigue. Serious side effects are rare, and very few patients have had to stop taking the drug because of side effects
- **Effectiveness findings:** So far, the survival rates and time before cancer worsened are similar for European patients compared with the overall study participants, showing that the drug works well for different groups of patients
- **Conclusion:** The results so far provide reassurance that darolutamide is well tolerated and effective in a broad range of patients with nmCRPC

References
1. Moilanen A-M, et al. *Sci Rep* 2015;5:12007. **2.** Zurth C, et al. *Clin Pharmacokinet* 2022;61:565–575. **3.** Williams SCR, et al. *Target Oncol* 2023;18:403–413. **4.** Zurth C, et al. *Eur J Drug Metab Pharmacokinet* 2019;44:747–759. **5.** Shore N, et al. *Target Oncol* 2019;14:527–539. **6.** Fizazi K, et al. *N Engl J Med* 2019;380:1235–1246. **7.** Fizazi K, et al. *N Engl J Med* 2020;383:1040–1049.

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Disclosures
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