BRIEF COMMUNICATION OPEN

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DARolutamide ObservationaL (DAROL) study in patients with nonmetastatic castration-resistant prostate cancer: prespecified third interim analysis

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BACKGROUND: DAROL is an ongoing study of real-world safety and effectiveness of darolutamide in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC).
SUBJECTS/METHODS: This prespecified interim analysis included 550 patients with nmCRPC who completed ≥6 months of treatment with darolutamide 600 mg twice daily.
RESULTS: Darolutamide showed consistent safety and effectiveness in DAROL vs ARAMIS. Most treatment-emergent adverse events were grade 1/2. Two-year overall survival and metastasis-free survival rates and prostate-specific antigen responses were similar to ARAMIS.
CONCLUSIONS: These findings indicate that darolutamide offers effectiveness and a favorable safety profile in the broad range of patients seen in clinical practice.

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Darolutamide is an androgen receptor inhibitor that is structurally different by design, with limited potential for drug–drug interactions and low blood–brain barrier penetration [1–5]. In phase 3 trials, darolutamide significantly improved metastasis-free survival (MFS) and overall survival (OS) in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC), and significantly improved OS (with docetaxel) and radiologic progression-free survival (without docetaxel) in patients with metastatic hormone-sensitive prostate cancer, with a favorable safety profile in all phase 3 studies [6–9]. It is important to validate results from clinical trials with real-world evidence. Here, we report findings from a planned interim analysis of the DARolutamide ObservationaL study (DAROL, NCT04122976).

DAROL is an ongoing, global, open-label, single-arm, non-interventional real-world study in patients with nmCRPC for whom the decision to treat with darolutamide was made according to local practice before enrollment. The study was approved by the ethics committee/institutional review board at each participating center; all patients provided informed consent before participation.

The primary objective of DAROL is the assessment of safety outcomes, including treatment-emergent adverse events (TEAEs). Key secondary outcomes of DAROL include OS, MFS, time to prostate-specific antigen (PSA) progression, and PSA reduction of ≥90% (PSA90) from baseline. In DAROL, PSA progression did not require confirmation, reflecting real-world practice where treatment adjustment sometimes occurs after even just one PSA rise; this differed from ARAMIS, where PSA progression confirmation was mandatory. In DAROL, safety analyses include all patients who received at least one dose of darolutamide; effectiveness was assessed in the full analysis set, comprising patients who received at least one dose of darolutamide, met all eligibility criteria, and had at least one post-baseline assessment after the first dose of darolutamide.

This third planned interim analysis (IA3) of DAROL included 550 patients overall (North America 35%, Europe 36%, Asia–Pacific 28%, Latin America 1.5%), of whom 470 were included in the full

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Table 1. Treatment-emergent adverse events in DAROL IA3 and ARAMIS.

TEAEs, n (%)	DAROL IA3 SAF ($n = 550$)	ARAMIS darolutamide arm ($n = 954$)[a] [6]
Any grade	313 (56.9)	764 (83.2)
Worst grade		
Grade 3/4	84 (15.3)	236 (24.7)
Grade 5	10 (1.8)	37 (3.9)
Serious	85 (15.5)	237 (24.8)
Leading to darolutamide discontinuation	38 (6.9)	85 (8.9)
TEAEs occurring in ≥2.5% of patients in DAROL IA3		
Fatigue[b]	85 (15.5)	115 (12.1)
Asthenia	31 (5.6)	36 (3.8)
UTI	25 (4.5)	47 (4.9)
Hot flush	23 (4.2)	50 (5.2)
Constipation	20 (3.6)	60 (6.3)
Diarrhea	17 (3.1)	66 (6.9)
Dizziness	17 (3.1)	35 (3.7)
Falls[b]	15 (2.7)	36 (3.8)
Hematuria	15 (2.7)	41 (4.3)
Anemia	14 (2.5)	0
Nausea	14 (2.5)	48 (5.0)
Rash[b]	14 (2.5)	28 (2.9)[c]
COVID-19	14 (2.5)	N/A

Data for ARAMIS are adapted from Fizazi K, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2019;380:1235–1246 [6].
COVID-19 coronavirus 2019 disease, *IA3* third interim analysis, *N/A* not applicable, *SAF* safety analysis set, *TEAE* treatment-emergent adverse event, *UTI* Urinary tract infection.
[a]Only 945/955 patients started treatment with darolutamide.
[b]TEAE commonly associated with androgen receptor inhibitor therapy; other TEAEs commonly associated with androgen receptor inhibition include hypertension (reported in nine patients in DAROL IA3), bone fracture (seven patients), and mental impairment disorders (four patients).
[c]Grouped term.

analysis set. In DAROL IA3 versus ARAMIS, patients were slightly older (median 79 years, interquartile range [IQR] 73–84, vs 74 years, IQR 68–80), had proportionally greater representation of Asian and Black patients (35% vs 16%), a wider range of Eastern Cooperative Oncology Group performance status (0–1 81%, 2–3 5.8%, missing 13%, vs 0–1 100% in ARAMIS), and higher proportion with Gleason score ≥8 at diagnosis (49% vs 40%). Median (IQR) PSA before study start was lower in DAROL vs ARAMIS (4.1 ng/mL) [2.3–9.5] vs 9.0 ng/mL [4.4–6.6], and fewer patients had PSA doubling time ≤6 months (40% vs 70%). At the data cut-off date for DAROL IA3 (July 17, 2023), median (IQR) follow-up and treatment durations were 17 months (12–23) and 15 months (10–21), respectively.

Incidences of any-grade TEAEs and serious TEAEs were numerically lower in DAROL IA3 than in ARAMIS, with a similar proportion of TEAEs leading to treatment discontinuation (Table 1). Only fatigue and asthenia had an incidence ≥5% (15.5% and 5.6%, respectively).

OS, MFS, and time to unconfirmed PSA progression data were not mature at DAROL IA3. However, OS rates at 24 months were similar to rates in ARAMIS (DAROL 88%; ARAMIS 90%), as were PSA progression-free rates at 24 months (DAROL 55%; ARAMIS 58%). PSA90 decline rates at any time were also similar (DAROL 54%; ARAMIS 51%). MFS rates at 24 months were numerically higher in DAROL than in ARAMIS (DAROL 78%; ARAMIS 70%).

The aim of DAROL is to assess the safety and effectiveness of darolutamide in patients with nmCRPC under real-world conditions, to support the findings from the phase 3 ARAMIS study. The DAROL IA3 population was more diverse than the ARAMIS population randomized to darolutamide; nevertheless, the safety profile of darolutamide in DAROL was consistent with that in ARAMIS [6, 7], with low TEAE incidences and no new safety signals. Darolutamide discontinuation incidences were low in DAROL IA3, with <10% of patients discontinuing due to TEAEs, similar to ARAMIS and to the frequency (10.2%) reported in a retrospective study of patients with nmCRPC treated in US urology practices (DEAR); in DEAR, darolutamide was associated with the lowest frequency of discontinuations due to adverse events among all androgen receptor inhibitors (including apalutamide and enzalutamide) [10]. The lower incidence of TEAEs and similar frequency of discontinuations may indicate that patients in the real world are less likely to report low-grade TEAEs but as likely to discontinue treatment once TEAEs become intolerable. These findings are important, because nmCRPC is usually asymptomatic, and TEAEs can reduce patients' quality of life; the availability of efficacious and well-tolerated treatments has been a key unmet need for patients with nmCRPC.

Although DAROL IA3 survival data are immature, 2-year MFS was numerically higher and OS and PSA progression-free rates were similar to the rates in ARAMIS [6, 7]. Moreover, darolutamide produced a PSA response in most patients that was consistent with ARAMIS, with >50% of patients reaching PSA90 at any time. These results indicate that the effectiveness of darolutamide in real-world settings could be consistent with efficacy demonstrated in clinical trials.

Findings from DAROL IA3 should be interpreted with caution, especially considering limitations inherent to noninterventional, real-world evidence studies. Visits were not on a fixed schedule, which could lead to capture of fewer adverse events or delays in notifications of death or progression events. In a single-arm study, it is not possible to distinguish between treatment effectiveness and the natural course of the disease. However, there can be relative confidence that observations reflect actual treatment effects, given the similarity in findings between DAROL IA3 and ARAMIS [6, 7]. Moreover, real-world studies have fewer eligibility criteria compared with clinical trials, which could introduce confounding factors, such as comorbidities and concomitant medications, potentially resulting in drug–drug interactions. Nevertheless, including a broader range of patients than in ARAMIS provides supporting evidence for use of darolutamide in the wide spectrum of patients seen in clinical practice. It increases the heterogeneity of the patient population and often includes patients with greater comorbidities and more limited performance status. Despite these differences, there was considerable consistency between DAROL and ARAMIS data, indicating that darolutamide offers favorable effectiveness and safety profiles in the real-world setting.

DAROL IA3 supports the established safety and effectiveness profiles of darolutamide in patients with nmCRPC in a varied and clinically diverse population in real-world settings. The study is ongoing, and the anticipated last patient last visit date is July 2026.

DATA AVAILABILITY

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to the scope, time point, and process for data access. Bayer commits to sharing, on request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from

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AUTHOR CONTRIBUTIONS

EYY had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. EYY, HS, CMP, AB, ML, DM, and AJA were involved in conceptualization, investigation, resource provision, and writing, reviewing, and editing of the manuscript. GG, RM, JH, JEC, PS, RWG, EH, TK, PS, AGC, YMA, HU, and NF were involved in resource provision, investigation, and writing, reviewing, and editing of the manuscript. PA and FV were involved in conceptualization and writing, reviewing, and editing of the manuscript. MG was involved in data curation, formal analysis, and writing, reviewing, and editing of the manuscript.

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COMPETING INTERESTS

EYY certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patients filed, received, or pending), are the following: the DAROL study was sponsored by Bayer, which also funded medical writing and editorial support in the development of this manuscript; EYY has received consulting fees from Johnson & Johnson, Bayer, Merck, Advanced Accelerator Applications/Novartis, AstraZeneca, Oncternal Therapeutics, Tolmar, Bristol-Myers Squibb, Loxo/Lilly, Aadi Bioscience, and Lantheus, and research funding paid to his institution from Dendreon, Merck, Seagen/Pfizer, Blue Earth Diagnostics, Bayer, Lantheus Medical Imaging, Tyra Biosciences, and Oncternal Therapeutics; HS has received fees and payment or honoraria from Janssen Research & Development, AstraZeneca, Astellas Pharma, Bayer Yakuhin, Bayer, Janssen Oncology, Pfizer, Takeda, Sanofi, Nippon Shinyaku, Daiichi Sankyo, Novartis, Kissei Pharmaceutical, and Merck Biopharma, and research funding paid to his institution from AstraZeneca, Astellas Pharma, Janssen, Nihon Kayaku, and Bayer Yakuhin; 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ADDITIONAL INFORMATION

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