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Safety and tolerability of long-term treatment with darolutamide in patients with metastatic castration-resistant prostate cancer

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BACKGROUND: In patients with metastatic castration-resistant prostate cancer, darolutamide was well tolerated for 25 months, but minimal long-term safety data are available.

METHODS: Treatment-emergent adverse events (TEAEs) for patients receiving darolutamide for a median of 38 months ($n = 13$) are described in this pooled analysis of individual patient data from phase 1/2 studies.

RESULTS: All patients reported TEAEs (mostly grade 1/2). The most common TEAEs were diarrhea, abdominal pain, and nausea. Serious TEAEs were reported in six patients (none related to darolutamide). All treatment-related TEAEs ($n = 5$) were grade 1.

CONCLUSIONS: Long-term darolutamide treatment was well tolerated; no new safety signals observed.

TWEETABLE ABSTRACT: In patients with mCRPC, long-term darolutamide treatment was well tolerated and no new safety signals were observed. These findings are consistent with previous reports, demonstrating a favorable safety and tolerability profile of darolutamide.

Prostate Cancer and Prostatic Diseases; <https://doi.org/10.1038/s41391-023-00740-9>

Darolutamide is a structurally distinct and highly potent androgen receptor inhibitor (ARI) that demonstrated strong efficacy and a consistently favorable safety and tolerability profile in the phase 3 ARAMIS and ARASENS studies in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) and patients with metastatic hormone-sensitive prostate cancer (mHSPC) [1, 2]. Darolutamide in combination with androgen-deprivation therapy (ADT) or ADT and docetaxel, respectively, reduced the risk of death by more than 30% compared with placebo [1, 2]. In ARAMIS, most treatment-emergent adverse events (TEAEs) commonly associated with ARI therapy showed $\leq 2\%$ difference between darolutamide and placebo, and discontinuation rates due to TEAEs were low and similar to placebo (8.9% vs 8.7%) [1]. The overall incidence of TEAEs was also similar between darolutamide and placebo in ARASENS, with the highest incidences of TEAEs occurring during the overlapping docetaxel treatment period [2].

Among patients with metastatic castration-resistant prostate cancer (mCRPC), darolutamide was well tolerated for up to 25 months in the previously reported ARADES, ARAFOR, and

Japanese phase 1/2 studies [3–5]. ARADES was a phase 1 dose-escalation/phase 2 randomized dose-expansion study (NCT01317641/NCT01429064) of 136 patients in whom darolutamide was administered twice daily (BID) at doses of 200, 300, or 700 mg [3]. The ARAFOR study (NCT01784757) was a food-effect study that enrolled 30 patients who received darolutamide 600 mg BID [4]. A Japanese phase 1 study (NCT02363855) included nine patients who received darolutamide 300 mg or 600 mg BID [5]. Minimal safety data are available from extended treatment with darolutamide in this population. Thus, we performed a pooled analysis of individual patient data including mCRPC patients who were treated with darolutamide for >2 years. Patients were assessed every 3 months to evaluate the safety and tolerability of long-term darolutamide.

A total of 13 patients received darolutamide for >2 years, with seven patients receiving 2 to 4 years of treatment and six patients receiving more than 4 years of treatment. The median (range) age of patients was 68 (55–81) years, 12 patients were White, and one patient was Asian. Patients were treated in France ($n = 4$), the

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Received: 8 June 2023 Revised: 4 October 2023 Accepted: 11 October 2023

Published online: 26 October 2023

Table 1. Treatment-emergent adverse events during long-term darolutamide treatment.

Treatment-emergent adverse events (TEAEs), ^a n (%)	Total: Darolutamide >2 years (n = 13)	Darolutamide >2 and ≤4 years (n = 7)	Darolutamide >4 years (n = 6)
Any TEAE	13 (100)	7 (100)	6 (100)
Worst grade			
1 or 2	7 (54)	6 (86)	1 (17)
3	6 (46)	1 (14)	5 (83)
Serious TEAE	6 (46)	2 (29)	4 (67)
TEAE leading to discontinuation of darolutamide	1 (8)	1 (14)	0
Any drug-related TEAE	5 (38)	3 (43)	2 (33)
Worst grade			
1 or 2	5 (38)	3 (43)	2 (33)
3	0	0	0
Serious drug-related TEAE	0	0	0
Drug-related TEAE leading to discontinuation of darolutamide	0	0	0
Most common TEAEs (occurring in ≥3 patients) ^b			
Diarrhea	5 (38)	2 (29)	3 (50)
Abdominal pain	4 (31)	2 (29)	2 (33)
Nausea	4 (31)	2 (29)	2 (33)
Arthralgia	3 (23)	1 (14)	2 (33)
Fatigue	3 (23)	2 (29)	1 (17)
Hematuria	3 (23)	1 (14)	2 (33)
Influenza	3 (23)	1 (14)	2 (33)

^aTreatment-emergent adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

^bAll TEAEs were grade 1 or 2 except 1 event each of grade 3 nausea and grade 3 hematuria.

United Kingdom ($n = 3$), Latvia ($n = 3$), Finland ($n = 2$), and Japan ($n = 1$). Most patients had normal renal and hepatic function (77%), Eastern Cooperative Oncology Group performance status of 0 (92%), and Gleason score of seven or higher (69%). The median (range) time from initial diagnosis until first darolutamide dose was 32.4 (9.7–191.0) months, and median (range) baseline prostate-specific antigen level before initiating darolutamide was 18.1 (4.6–53.6) $\mu\text{g/L}$. All patients received endocrine therapy before darolutamide treatment (bicalutamide, 77%; triptorelin acetate, 46%; goserelin/goserelin acetate, 31%; leuprorelin acetate, 23%; cyproterone acetate, 23%; degarelix/degarelix acetate, 15%; abiraterone, 8%). No patient received prior chemotherapy. The median (range) treatment duration of darolutamide was 38.1 (24.2–90.0) months for all 13 patients receiving >2 years of treatment and 62.6 (48.6–90.0) months for those receiving >4 years of treatment. One patient completed ARAFOR and entered the darolutamide rollover study (NCT04464226).

TEAEs were reported by all 13 patients, with worst grade 1 or 2 events in seven patients and worst grade 3 events in six patients; no grade 4 or 5 events were reported (Table 1). No grade 3 events occurred in more than one patient and none were considered related to darolutamide. Grade 3 TEAEs included rectal adenocarcinoma and presyncope in a patient treated for >2 and ≤4 years and one event each of nausea, hepatic cirrhosis, pyelonephritis, accident, femoral neck fracture, spinal compression fracture, paraneoplastic syndrome, hematuria, lung disorder, and pulmonary embolism in five patients treated for >4 years. Serious TEAEs were reported in six patients and none were considered related to darolutamide. One patient treated for >2 years developed a new locally advanced rectal adenocarcinoma that was not considered related to darolutamide but led to treatment discontinuation. Five patients reported TEAEs considered related

to darolutamide (tinnitus, abdominal distention, diarrhea, dyspepsia, fatigue, gynecomastia, and solar dermatitis) and all were grade 1 in severity. No treatment-related TEAEs led to discontinuation of darolutamide. The most common TEAEs were diarrhea, abdominal pain, and nausea (Table 1). During long-term darolutamide therapy, few patients experienced TEAEs commonly associated with ARI therapy (fatigue, $n = 3$; falls, including accidents, $n = 3$; bone fractures, $n = 2$; hypertension, $n = 2$; rash, $n = 1$).

The favorable safety and tolerability profile of long-term darolutamide treatment in patients with mCRPC are consistent with that previously reported from the early phase studies and in patients with nmCRPC and mHSPC [1–5]. In addition, extended treatment with darolutamide in the open-label phase of the ARAMIS trial (median treatment duration 25.8 months) showed minimal increase in the incidences of TEAEs from the darolutamide double-blind period (18.5 months) that disappeared when adjusted for longer exposure, and no new safety signals were observed [6, 7]. The randomized, crossover, phase 2 ODENZA trial compared darolutamide and enzalutamide in 200 patients with mCRPC for treatment preference and cognitive outcomes [8]. Darolutamide was preferred by 48.5% of patients versus 40.0% for enzalutamide ($P = 0.92$). A clinically meaningful benefit in episodic memory and less fatigue was observed in patients receiving darolutamide compared with those receiving enzalutamide. Matching-adjusted indirect comparisons and meta-analyses have shown a lower risk of adverse events and similar efficacy with darolutamide versus apalutamide and enzalutamide [9, 10].

In conclusion, long-term treatment with darolutamide in this small group of patients with mCRPC was well tolerated. These findings provide valuable information for patients and clinicians in selecting treatment for prostate cancer.

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 scope, timepoint and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014. Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal. Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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ACKNOWLEDGEMENTS

Jorge Ortiz, MD, of Bayer provided review of the manuscript. Writing and editorial support in the development of this manuscript was provided by Michelle McDermott, PharmD, and Lauren Gallagher RPh, PhD, of OPEN Health Communications, London, UK, with financial support from Bayer Healthcare. The authors retained full editorial control over the content of the manuscript and the decision to publish.

AUTHOR CONTRIBUTIONS

Provision of study materials/patients/data collection: RHJ, KF, NDJ, TLT, NM, FP, PB, TL, PB, VK, JAG, AP, NS, EV. Data analysis: IK, SF-B. Supervision: JA, HJ, IK, SF-B. Manuscript

writing: RHJ, KF, NDJ, TLT, NM, FP, PB, TL, PB, VK, JAG, AP, NS, JA, HJ, IK, SF-B, EV. All authors reviewed the paper and agreed to the published version of the manuscript.

FUNDING

This work was supported by Bayer AG and Orion Pharma.

COMPETING INTERESTS

The authors declare the following competing interests: RHJ has received honoraria from Merck Serono, Roche, and Starpharma; research funding from AstraZeneca; and compensation for travel, accommodations, and expenses from Bayer and Servier. KF and his institution have received honoraria from Astellas Pharma, Bayer, Janssen, and Sanofi; received compensation for a consulting or advisory role from Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, ESSA Pharma, Janssen Oncology, Novartis, Orion, Pfizer, and Sanofi; and received compensation for travel, accommodations, and expenses from AstraZeneca, Janssen, and MSD. NDJ has received honoraria from Astellas Pharma, Bayer, Janssen, and Sanofi; received compensation for a consulting or advisory role from Astellas Pharma, Bayer, Clovis Oncology, EUSA Pharma, Janssen, Pfizer, and Sanofi; is a member of the Speaker's Bureau for Astellas Pharma, AstraZeneca, Ferring Pharmaceuticals, Janssen Oncology, Merck, Pierre Fabre, and Sanofi; his institution has received research funding from Astellas Pharma, AstraZeneca, Janssen, Novartis, Pfizer, and Sanofi; and he received compensation for travel, accommodations, and expenses from Janssen and Sanofi. TLT has received research funding from Astellas Pharma, Bayer, Janssen, and Pfizer. NM has received honoraria from Bayer, Chugai Pharma (institution), and Janssen; received compensation for a consulting or advisory role from Amgen, AstraZeneca, Janssen, Lilly, and Sanofi; and his institution has received research funding from Amgen, Astellas Pharma, AstraZeneca, Bayer, Bayer Yakuin, Chugai Pharma, Eisai, Janssen, Lilly, MSD, and Takeda. FP has received compensation for a consulting or advisory role for AstraZeneca. PB has no competing interests to disclose. TL has received compensation for a consulting or advisory role from Incyte, MSD, and Pierre Fabre; and received research funding from Roche. PB is employed by, has a leadership role, and owns stock and other interests in Terveystalo; owns stock or has other ownership interests in Faron Pharmaceuticals and TILT Biotherapeutics; and has received compensation for a consulting or advisory role from EUSA Pharma, Faron Pharmaceuticals, Herantis Pharma, Ipsen, MSD Oncology, Oncorena, and TILT Biotherapeutics. VK is employed by and has a leadership role in Kaiku Health. JAG has received honoraria from Amgen, Bayer, Janssen, Merck, and MJH Associates; received compensation for a consulting or advisory role for Bayer, Clovis Oncology, Eisai, Sanofi, and Targeted Oncology; is a member of the Speaker's Bureau for Bayer, Merck, Sanofi, and Sanofi/Aventis; his institution has received research funding from Genentech/Roche, Janssen Oncology, Lilly, Merck, Orion, and Pfizer; and has received compensation for travel, accommodations, and expenses from Bayer, Clovis Oncology, Eisai, Janssen, Medivation/Astellas, Merck, and Sanofi. AP is employed by Genesis Cancer Care; received honoraria from Astellas Pharma, Eisai, Ipsen, Merck, Merck Serono, and MSD Oncology; and received compensation for travel, accommodations, and expenses from Bayer and EUSA Pharma. NS has received compensation for a consulting or advisory role from Abbvie, Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb/Sanofi, CG Oncology, Clarity Pharmaceuticals, Clovis Oncology, Dendreon, Exact Imaging, Exact Sciences, FerGene, Ferring Pharmaceuticals, Foundation Medicine, Genesis Cancer Care, Genzyme, InVita, Janssen Scientific Affairs, Lantheus Medical Imaging, Lilly, MDxHealth, Medivation/Astellas, Merck, Myriad Genetics, Myovant Sciences, Nymox, Pacific Edge Biotechnology, Peerview, Pfizer, Phosphorus, Photocure, Propella Therapeutics, Sanofi, Sema4, Sesen Bio, Specialty Networks, Telix Pharmaceuticals, Tempus, Tolmar, Urogen Pharma, and Vaxiion; is a member of the Speakers' Bureau for Astellas Pharma, AstraZeneca, Bayer, Clovis Oncology, Dendreon, Guardant Health, Janssen, Foundation Medicine, Merck, and Pfizer; has provided expert testimony for Ferring Pharmaceuticals; has received compensation for a relationship with Alessa Therapeutics and Photocure; and has received research funding from Abbvie, Advantagene, Amgen, Aragon Pharmaceuticals, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Boston Scientific, CG Oncology, Clovis Oncology, Dendreon, DisperSol, Endocyte, Exact Imaging, Exelixis, Ferring Pharmaceuticals, FKD Therapeutics, FORMA Therapeutics, Foundation Medicine, Genentech, Guardant Health, InVita, ISTARI Oncology, Janssen, Jianguo Yahong Meditech, MDxHealth, Medivation, Merck, MT Group, Myovant Sciences, Myriad Genetics, Novartis, Nymox, OncoCellIMdx, ORIC Pharmaceuticals, Pacific Edge, Palette Life Sciences, Pfizer, Plexikon, POINT Biopharma, Propella Therapeutics, RhoVac, Sanofi, Seattle Genetics, Sesen Bio, Steba Biotech, Theralase, Tolmar, Urogen Pharma, Urotronic, US Biotech, Vaxiion, Veru, and Zenflow. JA is an employee of and owns stock and other interests in Orion. HJ has received fees and other support from Orion Pharma; personal fees from Deciphera Pharmaceuticals and Neutron Therapeutics; and other support from Defence Therapeutics, Merck KGaA and Mersana Therapeutics; in addition, H.

Joensuu owns stock of Sartar Therapeutics and has a patent for Sartar Therapeutics issued. IK is an employee of Bayer. SF-B is an employee and owns stock and other interests in Bayer. EV has no competing interests to disclose.

ADDITIONAL INFORMATION

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