Short Communication

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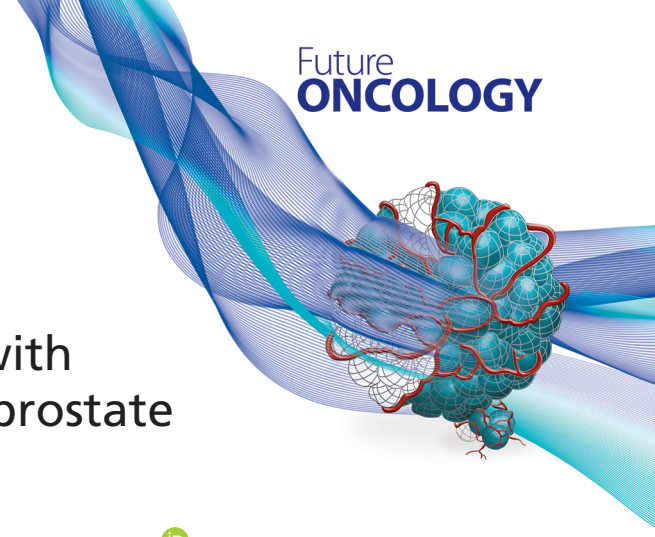

Darolutamide in Spanish patients with nonmetastatic castration-resistant prostate cancer: ARAMIS subgroup analysis

Joan Carles*[,1], Rafael A Medina-Lopez[2], Javier Puente[3], Álvaro Gómez-Ferrer[4], Javier Casas Nebra[5], María Isabel Sáez Medina[6], Maria J Ribal[7], Alfredo Rodríguez Antolín[8], José Luís Álvarez-Ossorio[9], José Francisco Suárez Novo[10], Cristina Moretones Agut[11], Shankar Srinivasan[12], Jorge Ortiz[12] & Karim Fizazi[13]

[1]Vall d'Hebron Institute of Oncology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[2]Urology Department, Vírgen del Rocío University Hospital, Seville, Spain
[3]Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), CIBERONC, Madrid, Spain
[4]Instituto Valenciano de Oncologia, Valencia, Spain
[5]Hospital Universitario Lucus Augusti, Lugo, Spain
[6]UGCI of Medical Oncology, Hospitales Regional & Universitario Virgen de la Victoria, IBIMA, UMA, Malaga, Spain
[7]Uro-Oncology Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain
[8]Hospital Universitario 12 de Octubre, Madrid, Spain
[9]Department of Urology, Puerta del Mar University Hospital, Cádiz, Spain
[10]Hospital Universitari de Bellvitge, l'Hospitalet de Llobregat, Spain
[11]Bayer Hispania, SL, Sant Joan Despí, Spain
[12]Bayer HealthCare, Whippany, NJ 07981, USA
[13]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France
*Author for correspondence: Tel.: +34 934 893 846; jcarles@vhio.net

Aim: Darolutamide significantly prolonged metastasis-free survival (MFS) versus placebo in the Phase III ARAMIS study. We analyzed outcomes in Spanish participants in ARAMIS. **Patients & methods:** Patients with high-risk nonmetastatic castration-resistant prostate cancer were randomized 2:1 to darolutamide 600 mg twice daily or placebo, plus androgen-deprivation therapy. The primary end point was MFS. Descriptive statistics are reported for this *post hoc* analysis. **Results:** In Spanish participants, darolutamide (n = 75) prolonged MFS versus placebo (n = 42): hazard ratio 0.345, 95% confidence interval 0.175–0.681. The incidence and type of treatment-emergent adverse events were comparable between treatment arms. **Conclusion:** For Spanish participants in ARAMIS, efficacy outcomes favored darolutamide versus placebo, with a similar safety profile, consistent with the overall ARAMIS population.

Clinical Trials Registration: NCT02200614 (ClinicalTrials.gov)

Plain language summary - Reduced risk of cancer spreading in Spanish patients with nonmetastatic castration-resistant prostate cancer treated with darolutamide in the global ARAMIS study: Darolutamide is an oral treatment for a type of prostate cancer that has stopped responding to other treatments and is at risk of spreading to other parts of the body (termed 'nonmetastatic castration-resistant prostate cancer' or 'nmCRPC'). In the international ARAMIS study, patients treated with darolutamide lived longer without their cancer spreading than patients who were given placebo (sugar) pills. We wanted to know whether Spanish patients in ARAMIS had similar characteristics and treatment outcomes to other patients in the study. We found that the 75 Spanish patients who were treated with darolutamide had a significantly lower risk of their cancer spreading than the 42 Spanish patients who received placebo. The two groups of Spanish patients had similar side effects.

Tweetable abstract: For Spanish patients with nmCRPC in ARAMIS, darolutamide increased metastasis-free survival and PSA response versus placebo. Adverse event incidence was similar in both arms. Outcomes were consistent with the overall ARASENS population.

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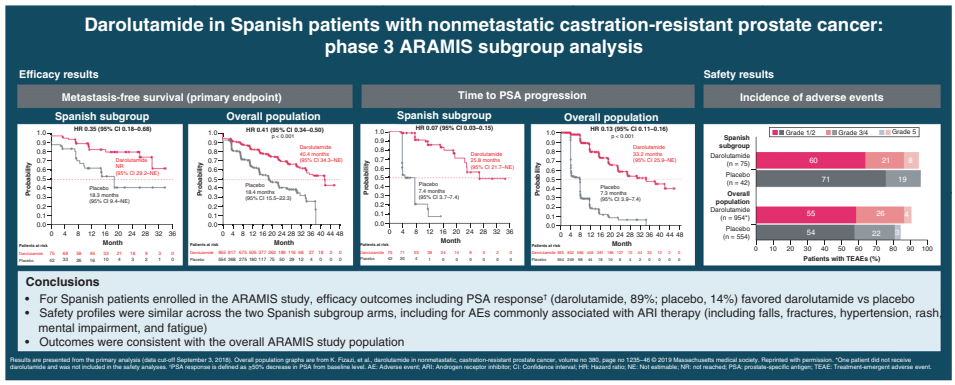
Graphical abstract:



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Keywords: androgen receptor inhibitor • castration-resistant prostate cancer • darolutamide • metastasis-free survival • nonmetastatic • prostate-specific antigen • PSA progression • Spain • Spanish

Prostate cancer is the most common cancer in men in Spain, with 34,613 new cases estimated in 2020 (21% of all new cases of cancer in men) and a 5-year prevalence of 596/100,000 population [1]. Although the average mortality rate across all stages of prostate cancer is relatively low, at 5% [1], approximately one third of patients will develop metastatic disease, for which the prognosis is poor [2–4]. Patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) and a prostate-specific antigen (PSA) doubling time (PSADT) of ≤10 months are at the highest risk of progression to metastatic disease [5–7]. Patients with nmCRPC are likely to be asymptomatic from their cancer; therefore, management goals are to delay progression to metastatic disease and prolong survival while minimizing treatment-related toxicity that can limit patients' daily activities and health-related quality of life [8–13].

Darolutamide is a structurally distinct and highly potent androgen receptor inhibitor (ARI) that has low blood-brain barrier penetration [14,15]. In the randomized, controlled, Phase III ARAMIS study (ClinicalTrials.gov: NCT02200614) in patients with high-risk nmCRPC, compared with placebo, darolutamide significantly reduced the risk of metastasis by almost 2 years (hazard ratio [HR]: 0.41, 95% CI: 0.34–0.50; $p < 0.001$) and the risk of death by 31% (HR: 0.69, 95% CI: 0.53–0.88; $p = 0.003$) and prolonged median time to PSA progression (exploratory end point; HR: 0.13, 95% CI: 0.11–0.16) [10,16]. The PSA response rate (≥50% reduction from baseline) was 84% in the darolutamide arm and 8% in the placebo arm [10]. Darolutamide also demonstrated a consistently favorable safety profile in ARAMIS, with the incidence of most adverse events commonly associated with ARIs showing a ≤2% difference between darolutamide and placebo [16]. Fatigue was the only adverse event with an incidence of >10% in either study arm (darolutamide 13.2% vs placebo 8.3%). Similar proportions of patients discontinued treatment due to adverse events in the darolutamide and placebo arms (8.9 vs 8.7%, respectively) [16].

The global ARAMIS study was conducted in 36 countries worldwide, each with its own healthcare system and different patient care pathways. Assessment of the potential impact of darolutamide in an individual healthcare setting can provide reassurance that the global results are relevant at a local level and give confidence in the use of darolutamide within a specific care pathway. An analysis of outcomes in Japanese participants in ARAMIS has been previously published [17]. The high number of patients who participated in ARAMIS in Spain (>100) has allowed us to assess outcomes in patients treated within the Spanish healthcare system. With the objective to further the knowledge base of darolutamide treatment, we report baseline characteristics, clinical efficacy and safety outcomes in Spanish patients with nmCRPC from ARAMIS.

Patients & methods

Study design & patients

ARAMIS was a phase III, randomized, double-blind, global, multicenter study of darolutamide versus placebo in men with nmCRPC. Complete study methods have been previously reported [10,16] but are summarized here.

The study was approved by the review board at each participating institution and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent before starting study treatment.

Men aged ≥18 years with histologically or cytologically confirmed prostate adenocarcinoma were eligible to participate if they had a baseline PSA of ≥2 ng/ml, a PSADT of ≤10 months, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were excluded if they had a history of metastatic disease or evidence of metastases on conventional imaging (whole-body bone scan, CT, or MRI of the pelvis, abdomen and chest). For the present analysis, all patients treated in Spanish participating centers were identified from the electronic case report forms.

Eligible patients were randomized in a 2:1 ratio to receive darolutamide 600 mg orally twice daily with food or matched placebo. Randomization was stratified by PSADT (>6 vs ≤6 months) and the use of bone-targeted therapy (yes vs no). All patients in both treatment arms received androgen-deprivation therapy (ADT; luteinizing hormone-releasing hormone agonist or antagonist) throughout the study. Patients continued treatment until protocol-defined progression, occurrence of intolerable adverse events, or withdrawal of consent.

Assessments

Patient demographics and medical history were recorded at screening. Serum PSA concentrations were measured at screening, day 1, and every 16 weeks thereafter until the end of study or death. Evaluation of ECOG performance status, chest, abdomen and pelvic CT/MRI, and ^{99m}Tc bone scintigraphy were performed at screening and every 16 weeks. Imaging outputs were assessed locally and by blinded independent central review.

At each visit, treatment-emergent adverse events (TEAE) were recorded. TEAEs were defined using Medical Dictionary for Regulatory Activities version 20.0 system organ class and preferred term. TEAE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Serious TEAEs were recorded, which were defined as any untoward medical occurrence that meets at least one of the following criteria: results in death; is immediately life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly/birth defect; or is deemed to be an important medical event based on medical and scientific judgment (e.g. because it jeopardizes the health of the patient or may require intervention to prevent another serious condition). Relationship to the study treatment was assessed by the investigator.

Study end points

The primary end point of the study was metastasis-free survival (MFS), defined as the time from randomization to confirmed evidence of distant metastasis on imaging or to death from any cause, whichever occurred first. Additional efficacy end points included time to PSA progression (time from randomization to the date of first PSA progression, defined according to Prostate Cancer Working Group 2 criteria as an increase in PSA of ≥25% and an absolute increase in PSA of ≥2 ng/ml above the nadir, confirmed by a consecutive value obtained ≥3 weeks later; PSA progression was declared if observed at Week ≥16) and PSA response (defined as PSA reduction of ≥50% from the baseline level). Overall survival was not evaluated in the Spanish subgroup, because the sample size is too small for meaningful comparison. Safety analyses were based on adverse events, including incidence, severity, seriousness, action taken (interruption/reduction or permanent discontinuation of study drug), and relationship to study drug.

Statistical analyses

Post hoc analyses of the Spanish subgroup were performed for descriptive purposes, without hypothesis testing. Kaplan–Meier estimates were used to compute medians and 95% CIs for time-to-event variables, with HRs and 95% CIs based on Cox regression modeling without stratification. For PSA response, the difference between study arms was assessed using the Cochran–Mantel–Haenszel test.

Statistical analyses were performed with SAS software (SAS Institute Inc., NC, USA). Incomplete event occurrence dates were imputed as the earliest possible date.

Efficacy analyses were based on the intention-to-treat population, which comprised all randomized patients, with patients analyzed according to randomization arm, regardless of treatment actually received. Safety was evaluated in the safety population, which comprised all randomized patients who received at least one dose of study drug, with patients analyzed according to treatment received.

Table 1. Baseline patient demographics and clinical characteristics of the ARAMIS Spanish subgroup and overall population.

Characteristic	Spanish subgroup		All patients	
	Darolutamide (n = 75)	Placebo (n = 42)	Darolutamide (n = 955)	Placebo (n = 554)
Age, median (range, years)	76 (52–89)	75 (54–90)	74 (48–95)	74 (50–92)
ECOG PS, n (%)				
0	64 (85)	36 (86)	650 (68)	391 (71)
1	11 (15)	6 (14)	305 (32)	163 (29)
Gleason score ≥7, n (%)	60 (80)	28 (67)	711 (74)	395 (71)
Time from initial diagnosis, median (range, months)	112.2 (2.6–249.1)	111.1 (3.2–236.7)	86.2 (2.6–337.5)	84.2 (0.5–344.7)
Presence of lymph nodes on central imaging review, n (%)	10 (13)	11 (26)	100 (10)	66 (12)
Serum PSA level, median (range, ng/ml)	12.8 (2.3–130.5)	18.4 (4.5–108.7)	9.0 (0.3–858.3)	9.7 (1.5–885.2)
PSADT				
Median (range, months)	4.8 (1.1–9.9)	5.3 (1.1–10.2)	4.4 (0.7–11.0)	4.7 (0.7–13.2)
≤6 months, n (%)	53 (71)	25 (60)	667 (70)	371 (67)
>6 months, n (%)	22 (29)	17 (40)	288 (30)	183 (33)
Serum testosterone level, median (range, nmol/l)	0.6 (0.3–1.3)	0.6 (0.2–1.6)	0.6 (0.2–25.9)	0.6 (0.2–7.3)
Use of bone-sparing agent, n (%)	2 (3)	2 (5)	31 (3)	32 (6)
≥1 prior hormonal therapy, n (%)	73 (97)	41 (98)	904 (95)	523 (94)

ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: Prostate-specific antigen; PSADT: Prostate-specific antigen doubling time.
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Results

Patients

From the 1509 patients in the overall population, 117 patients (8%) were enrolled in Spain, of whom 75 were randomized to receive darolutamide and 42 to receive placebo. Demographic and baseline characteristics were generally balanced between the study arms, with minor variations (e.g., use of prior radiotherapy; Table 1). Across both study arms in this subgroup, the median age was 76 years, and 85% of patients had an ECOG performance status of 0. The median PSADT was 5 months, and 33% of patients had a PSADT of >6 months.

Efficacy

At the time of the primary analysis data cut-off (3 September 2018), MFS events were recorded in 15 patients (20%) in the darolutamide arm and 19 (45%) in the placebo arm. Darolutamide prolonged MFS compared with placebo in the Spanish subgroup, with an unstratified HR of 0.345 (95% CI: 0.175–0.681; Figure 1). The MFS benefit consistently favored darolutamide regardless of baseline PSADT (≤6 months [n = 78] unstratified HR: 0.392, 95% CI: 0.178–0.863; >6 months [n = 39] unstratified HR: 0.197, 95% CI: 0.040–0.960).

PSA progression events were recorded in 17 (23%) of patients in the darolutamide arm and 30 (71%) of patients in the placebo arm. The median time to PSA progression was longer in the darolutamide arm (25.8 months) than in the placebo arm (7.4 months), with an unstratified HR of 0.071 (95% CI: 0.033–0.152; Figure 2). Time to PSA progression was consistently longer in the darolutamide arm versus the placebo arm when measured by baseline PSADT (≤6 months unstratified HR: 0.078, 95% CI: 0.031–0.200; >6 months unstratified HR: 0.076, 95% CI: 0.020–0.286).

A PSA response (≥50% decrease from baseline at any time during treatment) was achieved in 67 patients (89%) in the darolutamide arm and six patients (14%) in the placebo arm (Table 2), which is consistent with the findings in the overall population. A PSA decrease of ≥90% from baseline was achieved by 39 patients (52%) who received darolutamide compared with two patients (5%) who received placebo.

Safety

In Spanish patients, the incidence of any TEAEs was similar in the darolutamide (89%) and placebo (90%) arms. Most TEAEs were grade 1 or 2 (darolutamide 60 vs placebo 71%). More patients in the darolutamide arm than in the placebo arm required dose modifications (interruptions or reductions) to manage TEAEs (19 vs 10%); however, the percentage of patients who discontinued treatment because of TEAEs was similar in the two arms (8 and 5%,

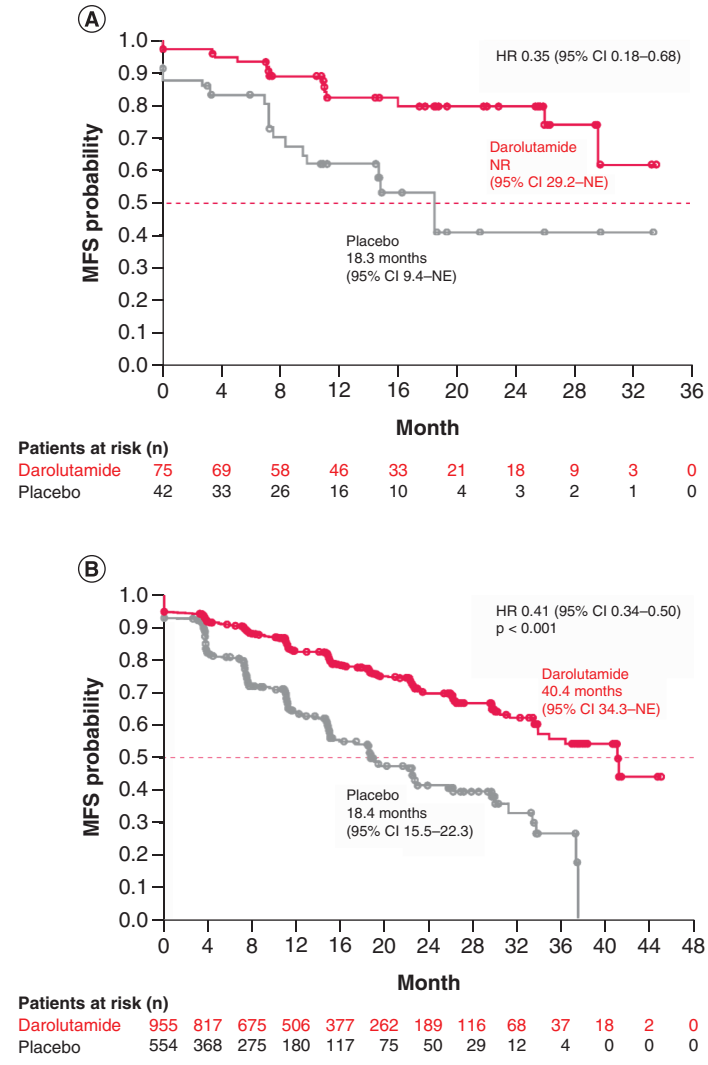

Figure 1. Kaplan-Meier estimates of MFS at the primary analysis (intention-to-treat population). (A) Spanish subgroup; **(B)** overall population. HR: Hazard ratio; MFS: Metastasis-free survival; NE: Not estimable; NR: Not reached. Data for 'All patients' are from [10] Copyright © 2019 Massachusetts Medical Society. Reprinted with permission.

respectively). Adverse events commonly associated with ARIs, including falls, fractures, hypertension, rash, mental impairment and fatigue, had similar incidences in both study arms (Table 3).

Discussion

Clinical guidelines for the treatment of advanced prostate cancer are consistent in recommending next-generation ARI therapy in addition to ADT in patients with high-risk nmCRPC [2,12,18,19]. Nevertheless, each country and healthcare system has its own care pathways and approval processes, resulting in potential variation in the patients who are eligible for treatment, which may in turn affect outcomes. The global Phase III ARAMIS study was carried out across a broad range of countries and healthcare systems, including 117 patients in Spain. This has allowed us to assess outcomes in patients treated within one national healthcare system, which will help physicians make informed therapeutic decisions based on the demonstrated clinical benefits of darolutamide in prolonging MFS and delaying PSA progression, and the well-tolerated safety profile.

The consistency of the findings with those of the overall population provides reassurance that darolutamide will be a useful addition to the treatment options for patients in nonmetastatic castration-resistant prostate cancer in Spain, despite some small baseline differences in the Spanish subgroup compared with the overall population, which may reflect differences in the care pathway from diagnosis to initiation of treatment for nmCRPC compared with other countries. For example, the median PSA level at baseline was higher and the median time from initial diagnosis was longer in the Spanish subgroup than in the overall population [10]. Nevertheless, the unstratified HRs for MFS (0.345) and time to PSA progression (0.071) in the Spanish subgroup are consistent with the

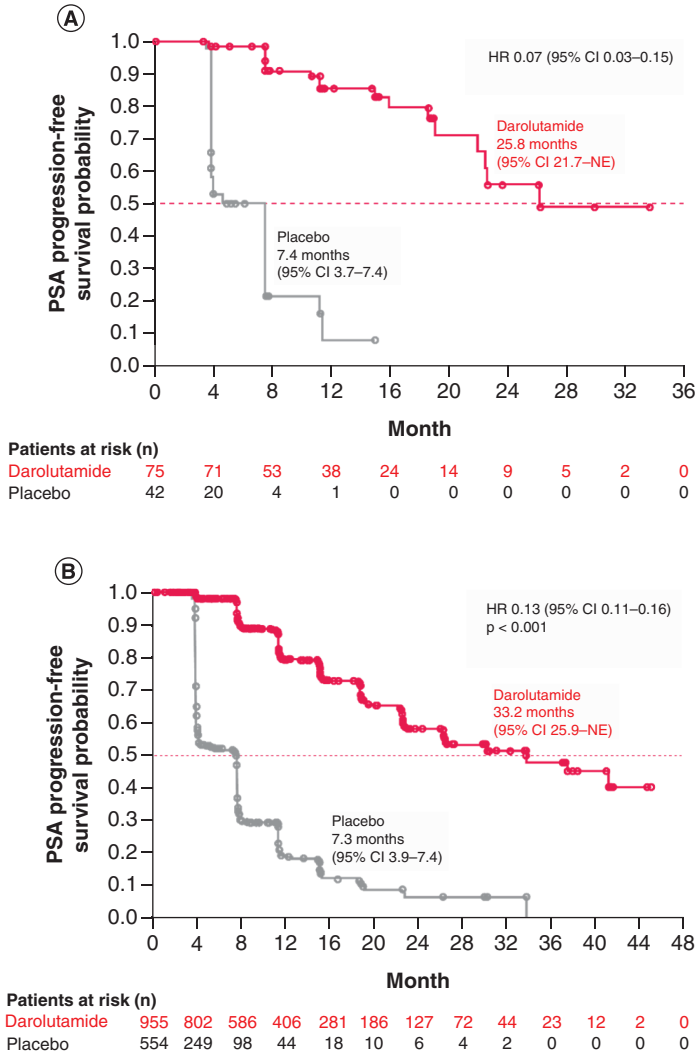

Figure 2. Kaplan-Meier estimates of time to PSA progression at the ARAMIS primary analysis (intention-to-treatpopulation). (A) Spanish subgroup; **(B)** overall population.
HR: Hazard ratio; NE: Not estimable; PSA: Prostate-specific antigen.
Data for 'All patients' are from [10]

Table 2. Prostate-specific antigen response† in the ARAMIS Spanish subgroup and overall population.

	Spanish subgroup		All patients	
	Darolutamide (n = 75)	Placebo (n = 42)	Darolutamide (n = 955)	Placebo (n = 554)
Overall PSA response during study drug treatment n (%)	67 (89)	6 (14)	798 (84)	42 (8)
Difference (darolutamide vs placebo)	-75 (95% CI -88, -62)		-76 (95% CI -79, -73)	
Maximal decline from baseline n (%)				
No post-baseline value	2 (3)	0	55 (6)	24 (4)
No decline	3 (4)	29 (69)	34 (4)	383 (69)
≥0 and <30%	2 (3)	5 (12)	30 (3)	84 (15)
≥30 and <50%	1 (1)	2 (5)	38 (4)	21 (4)
≥50 and <90%	28 (37)	4 (10)	312 (33)	32 (6)
≥90%	39 (52)	2 (5)	486 (51)	10 (2)

†Defined as an ≥50% decrease in PSA level from baseline.
Difference in response rate calculated using the Cochran-Mantel-Haenszel test.
PSA: Prostate-specific antigen.

Table 3. Treatment-emergent adverse events in the ARAMIS Spanish subgroup and overall population (safety population).

n (%)	Spanish subgroup		All patients	
	Darolutamide (n = 75)	Placebo (n = 42)	Darolutamide (n = 955[†])	Placebo (n = 554)
Any	67 (89)	38 (90)	818 (86)	439 (79)
Grade 1 or 2	45 (60)	30 (71)	521 (55)	300 (54)
Grade 3 or 4	16 (21)	8 (19)	251 (26)	120 (22)
Grade 5	6 (8)	0	38 (4)	19 (3)
Serious	18 (24)	8 (19)	237 (25)	111 (20)
Leading to dose modification	14 (19)	4 (10)	135 (14)	52 (9)
Leading to discontinuation	6 (8)	2 (5)	85 (9)	48 (9)
Drug-related	25 (33)	11 (26)	258 (27)	110 (20)
Adverse events of special interest				
Fatigue/asthenic conditions	14 (19)	7 (17)	164 (17)	63 (11)
Fatigue	9 (12)	3 (7)	126 (13)	46 (8)
Asthenia	6 (8)	6 (14)	38 (4)	17 (3)
Bone fracture	3 (4)	2 (5)	52 (5)	20 (4)
Falls, including accident	1 (1)	3 (7)	50 (5)	27 (5)
Weight decrease	0	0	40 (4)	14 (3)
Seizure	1 (1)	0	2 (<1)	1 (<1)
Mental impairment disorder	1 (1)	1 (2)	19 (2)	10 (2)
Depressed-mood disorder	4 (5)	1 (2)	21 (2)	10 (2)
Rash	1 (1)	1 (2)	30 (3)	6 (1)
Hypertension	8 (11)	3 (7)	74 (8)	36 (6)
Hot flush	7 (9)	3 (7)	57 (6)	25 (5)
Cardiac arrhythmia	4 (5)	2 (5)	70 (7)	24 (4)
Coronary artery disorder	1 (1)	1 (2)	38 (4)	15 (3)
Heart failure	2 (3)	0	18 (2)	5 (1)

[†]One patient did not receive darolutamide and was not included in the safety analyses.
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stratified HRs in the overall population (stratified HRs 0.41 and 0.13, respectively) in favoring darolutamide over placebo [10]. Similarly, the safety profile of darolutamide in the Spanish subgroup is consistent with that in the overall population, with similar low incidences of any TEAEs, grade 3 or 4 TEAEs, and low rate of discontinuations due to TEAEs. With regard to adverse events that are known to be associated with ARI therapy, the incidence reported with darolutamide in the Spanish subgroup was generally as low as in the overall population [10]. The only TEAEs that occurred in more than 10% of patients in the darolutamide arm were fatigue (12 vs 7% in the placebo arm) and hypertension (11 vs 7%). In both treatment arms in the Spanish subgroup, the rates of fatigue and hypertension were slightly higher than in the overall population, but the differences likely reflect the small patient numbers, resulting in wider variation in percentages. Differences in previous treatments and primary tumor management could also have influenced outcomes.

In addition to the small number of Spanish patients included in the ARAMIS study, this subgroup analysis is limited by the *post hoc* design, although the baseline characteristics of the Spanish patients were generally similar between the two study arms and consistent with the overall population.

Conclusion

In Spanish patients with nmCRPC and a PSADT of ≤10 months, baseline characteristics and clinical outcomes were consistent with the overall ARAMIS population, with expected small variations due to the limited sample size. In this Spanish subgroup, darolutamide was associated with prolonged MFS, delayed time to PSA progression, and a substantially higher PSA response versus placebo. Efficacy benefits with darolutamide versus placebo were achieved in patients regardless of PSADT, although small patient numbers resulted in wide confidence intervals. The addition of darolutamide to ADT did not increase the incidence of adverse events compared with placebo.

Summary points

- Darolutamide is a structurally distinct androgen receptor inhibitor that significantly prolonged metastasis-free survival (MFS) and overall survival versus placebo and had a favorable tolerability profile in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) in the global Phase III ARAMIS study (NCT02200614).
- In the 117 Spanish patients enrolled in ARAMIS (darolutamide n = 75; placebo n = 42), baseline characteristics were generally similar between the treatment arms, with expected variations due to the small cohort size.
- In the Spanish patients, darolutamide prolonged MFS (hazard ratio 0.345, 95% confidence interval 0.175–0.681) and time to prostate-specific antigen (PSA) progression (hazard ratio 0.071, 95% confidence interval 0.033–0.152) versus placebo; the PSA response rate during treatment was 89% in the darolutamide arm versus 14% in the placebo arm.
- The incidence and type of treatment-emergent adverse events of any grade and of severity grade ≥3 was comparable between the two Spanish subgroup treatment arms.
- In conclusion, for Spanish patients with nmCRPC included in ARAMIS, efficacy outcomes favored darolutamide, with similar safety profiles in the two arms.
- Outcomes were consistent with the overall trial population.

Author contributions

S Srinivasan, J Ortiz and K Fizazi contributed to the conception and design of the study. J Casas Nebra, RA Medina-Lopez, J Puente, A Gómez-Ferrer, JC Nebra, MI Sáez Medina, MJ Ribal, AR Antolín, JL Álvarez-Ossorio, JF Suárez Novo and K Fizazi acquired the data. All authors contributed to analysis and interpretation of the data reported in this article and to drafting of the article and/or critically reviewing it for important intellectual content. All authors approved this version for publication and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Financial & competing interests disclosure

The ARAMIS study was sponsored by Bayer HealthCare and Orion Pharma. J Carles reports consulting and scientific advisory board attendee role for Amgen, Astellas, Bayer, Bristol Myers Squibb (BMS), Johnson & Johnson, Merck Sharp & Dohme (MSD), Pfizer, and Sanofi; he has participated in speaker bureau roles for Asofarma, Astellas, Bayer, Johnson & Johnson, and Sanofi. J Puente has received honoraria for speaker engagements, advisory roles, or continuous medical education from Astellas, AstraZeneca, Janssen, MSD, Bayer, Pfizer, Eisai, Ipsen, Sanofi, Roche, BMS, Pierre Fabre, and Merck; he has received research funding from Astellas and Pfizer; and has been a consultant for Astellas and Roche. J Casas Nebra reports participation in advisory boards or talks for Bayer, Janssen and Astellas. MI Sáez Medina reports financial interests with Roche, Pfizer, Merck, and Ipsen. K Fizazi reports honoraria paid to his institution (Gustave Roussy) for participation in advisory boards or talks for Amgen, Astellas, AstraZeneca, Bayer, Clovis Oncology, Daiichi Sankyo, Janssen, MSD, Novartis, Pfizer, and Sanofi; and personal honoraria for participation in advisory boards for Orion Pharma. C Moretones Agut, S Srinivasan, and J Ortiz are employees of Bayer. RA Medina-Lopez, Á Gómez-Ferrer, MJ Ribal, AR Antolín, JL Álvarez-Ossorio, and JF Suárez Novo have no relevant financial and/or nonfinancial relationships to disclose. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The study was approved by the institutional review board at each participating institution and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent to participate.

Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is: NCT02200614.

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 01, 2014.

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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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Papers of special note have been highlighted as: •• of considerable interest

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