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Original Research

Efficacy and safety outcomes of darolutamide in patients with non-metastatic castration-resistant prostate cancer with comorbidities and concomitant medications from the randomised phase 3 ARAMIS trial

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Abstract ***Purpose:*** In patients with non-metastatic castration-resistant prostate cancer (nmCRPC) in the Androgen Receptor Antagonizing Agent for Metastasis-free Survival (ARAMIS) trial, darolutamide significantly improved median metastasis-free survival by nearly 2 years and reduced the risk of death by 31% versus placebo, with a favourable safety/tolerability profile. This post hoc analysis of ARAMIS evaluated efficacy and safety in patients by number of comorbidities and concomitant medications.

Methods: Patients with nmCRPC were randomised 2:1 to darolutamide (n = 955) or placebo (n = 554) while continuing androgen-deprivation therapy. Overall survival (OS) and treatment-emergent adverse events (TEAEs) were evaluated in subgroups by median numbers

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of ongoing comorbidities and concomitant medications. HRs were determined from univariate analysis using Cox regression.

Findings: Median numbers of comorbidities and concomitant medications were 6 and 10, respectively, with 41.6% of patients having > 6 comorbidities and 48.8% taking > 10 concomitant medications. For patients with ≤ 6 and > 6 comorbidities, darolutamide increased OS versus placebo (hazard ratio [HR] 0.65 and 0.73, respectively), and this benefit was consistent for cardiovascular, metabolic, and other comorbidities (HR range: 0.39–0.88). For patients taking ≤ 10 and > 10 concomitant medications, increased OS was also observed with darolutamide versus placebo (HR 0.76 and 0.66, respectively), and the benefit was consistent across medication classes (HR range: 0.45–0.80). Incidences of TEAEs and TEAEs leading to treatment discontinuation with darolutamide were similar to placebo across subgroups by numbers of comorbidities and concomitant medications.

Conclusions: The OS benefit and safety of darolutamide remained consistent with that observed in the overall ARAMIS population, even in patients with high numbers of comorbidities or concomitant medications.

ClinicalTrials.gov registration: NCT02200614.

Tweetable abstract: Darolutamide increased overall survival versus placebo, and incidences of most adverse events were similar between treatments in patients with ≤ 6 or > 6 comorbidities and those taking ≤ 10 or > 10 concomitant medications.

1. Introduction

Patients with non-metastatic castration-resistant prostate cancer (nmCRPC) are usually elderly and have comorbidities that are treated with various medications [1,2]. As a result, some of these patients have an increased health care and drug burden that may lead to diminished physical function, attention, and concentration [3]. Polypharmacy is typically defined as use of 5 or more daily medications and is associated with an increased risk of adverse events and drug–drug interactions (DDIs) [4]. DDIs with clinical relevance may manifest as an increase in adverse events or a decline in therapeutic activity, potentially leading to compromised clinical outcomes [2,5]. Minimising risks associated with DDIs from polypharmacy is an important component of optimal care for patients with nmCRPC. Thus, treatment selection for these patients should consider treatment efficacy as well as the safety, tolerability, and DDI profile of medications [1,2]. Currently, limited data are available on the effects of underlying comorbidities and concomitant medications on outcomes for patients with nmCRPC [6].

In the phase 3 Androgen Receptor Antagonizing Agent for Metastasis-free Survival (ARAMIS) trial in patients with nmCRPC, the androgen receptor inhibitor (ARi) darolutamide improved median metastasis-free survival by almost 2 years and reduced the risk of death by 31% compared with placebo [7,8]. Darolutamide also demonstrated a favourable safety and tolerability profile with similar discontinuation rates due to treatment-emergent adverse events (TEAEs) in the darolutamide and placebo groups (8.9% and 8.7%, respectively). Darolutamide is structurally distinct and a highly potent ARi, with low blood–brain barrier penetration and a limited potential for clinically relevant DDIs [5,9–12]. This post hoc analysis of ARAMIS evaluated efficacy and safety outcomes of darolutamide in patients by number of ongoing comorbidities and use of concomitant medications.

2. Methods

The study design and methodology of ARAMIS have been previously published [7]. Briefly, this global, multicentre, double-blind, phase 3 trial randomised (2:1) adult patients with nmCRPC to darolutamide 600 mg twice daily (n = 955) or placebo (n = 554), in addition to ongoing androgen-deprivation therapy (ADT). Key inclusion criteria were baseline prostate-specific antigen (PSA) level ≥ 2 ng/mL, a PSA doubling time ≤ 10 months, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Assessment visits occurred every 16 weeks, and patients continued treatment until protocol-defined progression, discontinuation due to TEAEs, or withdrawal of consent. The trial protocol is available at https://clinicaltrials.gov/ProvidedDocs/14/NCT02200614/Prot_002.pdf.

For this post hoc analysis, the end-points were overall survival (OS) and TEAEs, defined as adverse events that occurred after the start of treatment and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.03). These end-points were analysed for subgroups of patients based on median numbers of comorbidities and concomitant medications ongoing at baseline. The frequencies of individual comorbidities were reported and grouped by preferred terms from the most common (occurring in > 5% of the total ARAMIS population) ongoing comorbid conditions by Shore et al using the *Medical Dictionary for Regulatory Activities* (MedDRA) [5]. Cardiovascular comorbidities included hypertension,

cardiac arrhythmias, and coronary artery disorders, including myocardial ischaemia. Metabolic comorbidities included obesity, lipid metabolism disorders, and various forms of diabetes mellitus. Other comorbidities included renal insufficiency, joint disorders, and gastrointestinal mobility and defecation disorders (gastroesophageal reflux disease and constipation).

Using all recorded medications ongoing at baseline of ARAMIS, concomitant medications subgroups were defined by classes and subclasses of medications per Shore et al [5]. Cardiovascular medications were divided into antihypertensives, including agents acting on the renin–angiotensin system, beta-blockers, calcium-channel blockers, and diuretics, and non-antihypertensives, including antithrombotics (antiplatelet agents and anticoagulants), lipid-modifying agents, cardiac therapy (glycosides, antiarrhythmics, and antianginals), and vasoprotectives. Medications used for pain and inflammation included analgesics, anti-inflammatory and disease-modifying antirheumatic products, and systemic corticosteroids. Medications for gastrointestinal and metabolic disorders included drugs for acid-related disorders, antidiabetics, antidiarrhoeals, intestinal anti-inflammatory and anti-infective agents, and drugs for constipation. Medications for urologic disorders included drugs for erectile dysfunction, benign prostatic hyperplasia, and overactive bladder; medications used for ADT were not included.

2.1. Statistical analysis

Data used for this analysis were from the final data cutoff date of 15th November 2019, for the double-blind period, which was defined as the time from randomisation to the start date of the open-label period. The data cutoff date for the Shore et al [5] publication was 17th January 2019. Forest plots of OS were generated with hazard ratios (HRs) and 95% confidence intervals (CIs) determined from univariate analysis using Cox regression. The 95% CIs were not controlled for multiple comparisons.

3. Results

In the ARAMIS study population, the median number of comorbidities was 6 and the median number of concomitant medications was 10, excluding ADT. Overall, 42.4% of patients receiving darolutamide and 40.1% of patients receiving placebo had > 6 comorbidities, and 48.6% of patients receiving darolutamide and 49.3% of patients receiving placebo had > 10 concomitant medications. Eleven patients receiving darolutamide and 6 patients receiving placebo had no comorbidities. Cardiovascular and metabolic comorbidities (including diabetes) were most common, occurring in 73.3% and 73.2% of patients receiving darolutamide, respectively, and 71.5% and 74.2% of patients receiving placebo, respectively. Data on concomitant medications were missing for 10 patients receiving darolutamide and 11 patients receiving placebo. Among patients assigned to darolutamide and placebo, the most common concomitant medication subgroups were antihypertensive medications (70.3% and 67.1%, respectively), medications for pain and inflammation (67.5% and 65.7%, respectively), and non-antihypertensive medications for cardiovascular disease (64.1% and 65.7%, respectively). Medications for gastrointestinal and metabolic disorders were reported in 52.5% and 54.0% and medications for urologic disorders were reported in 32.0% and 32.9% of patients in the darolutamide and placebo groups, respectively.

Demographics and baseline characteristics were generally consistent across patient subgroups by median numbers of comorbidities and concomitant medications (Table 1). For patients with > 6 comorbidities or > 10 concomitant medications, median time from diagnosis to study treatment was longer and more patients received bone-sparing agents compared with those with fewer comorbidities or concomitant medications. More patients with > 6 comorbidities had an ECOG PS of 1 versus those with ≤ 6 comorbidities.

Darolutamide increased OS compared with placebo with similar HRs in terms of reduction in risk of death in patients with ≤ 6 comorbidities (HR 0.65; 95% CI 0.45–0.93) and in patients with > 6 comorbidities (HR 0.73; 95% CI 0.51–1.04; Fig. 1). The survival benefit of darolutamide versus placebo was generally consistent in patients with cardiovascular disorders (hypertension HR 0.67; arrhythmias HR 0.49; coronary artery disorders HR 0.51), metabolic disorders (obesity HR 0.65; lipid disorders HR 0.65; diabetes HR 0.88), and other comorbidities (renal insufficiency HR 0.67; joint disorders HR 0.70; gastrointestinal disorders HR 0.39) (Fig. 2). Overall survival results for darolutamide versus placebo were also comparable among patients receiving ≤ 10 concomitant medications (HR 0.76; 95% CI 0.52–1.11) and patients receiving > 10 concomitant medications (HR 0.66; 95% CI, 0.47–0.92; Fig. 1). Patients receiving various classes of medications achieved a consistent trend of OS benefit with darolutamide versus placebo, with HRs ranging from 0.45 to 0.80 (Fig. 3).

The incidences of TEAEs, grade 3/4 TEAEs, and serious TEAEs were higher in both arms for patients with > 6 comorbidities and for patients with > 10 concomitant medications compared with patients with fewer comorbidities and concomitant medications (Table 2). Incidences of most TEAEs, grade 3/4 TEAEs, and serious TEAEs were similar between darolutamide and placebo for each subgroup of patients based on the median numbers of comorbidities and concomitant medications. Among TEAEs commonly associated with ARi therapy, incidences of hypertension, fracture, fall, and mental impairment were similar between darolutamide and placebo in patient subgroups by comorbidities and concomitant medications. Incidences of rash and fatigue were generally comparable to the overall study

Table 1
Demographic and baseline characteristics for subgroups of patients by median numbers of comorbidities and concomitant medications.

Variable	Comorbidities[a]				Concomitant medications[b]				Overall ARAMIS population	
	≤ 6		> 6		≤ 10		> 10			
	DARO (n = 539)	PBO (n = 326)	DARO (n = 405)	PBO (n = 222)	DARO (n = 481)	PBO (n = 270)	DARO (n = 464)	PBO (n = 273)	DARO (n = 955)	PBO (n = 554)
Age, y	73 (51–94)	72 (50–92)	76 (48–95)	75.5 (57–91)	74 (52–94)	72 (50–92)	75 (48–95)	75 (52–91)	74 (48–95)	74 (50–92)
Time from diagnosis, mo	82.9 (4.8–337.5)	75.0 (1.3–266.6)	92.4 (2.6–302.3)	105.0 (0.5–344.7)	82.1 (2.9–337.5)	73.1 (1.3–239.1)	92.3 (2.6–302.3)	96.1 (0.5–344.7)	86.2 (2.6–337.5)	84.2 (0.5–344.7)
Lymph nodes on central imaging, n (%)	61 (11.3)	47 (14.4)	39 (9.6)	18 (8.1)	48 (10.0)	34 (12.6)	51 (11.0)	31 (11.4)	100 (10.5)	66 (11.9)
Serum PSA, ng/mL	8.6 (1.2–858.3)	9.5 (1.5–885.2)	10.2 (0.3–240.0)	9.8 (1.6–310.2)	9.8 (1.1–858.3)	9.6 (1.5–885.2)	8.7 (0.3–240.0)	9.4 (1.6–310.2)	9.0 (0.3–858.3)	9.7 (1.5–885.2)
PSA doubling time, mo	4.3 (0.9–11.0)	4.4 (0.7–12.0)	4.5 (0.7–10.4)	4.7 (0.9–13.2)	4.3 (0.7–10.4)	4.3 (0.7–13.2)	4.6 (0.9–11.0)	4.9 (0.9–10.2)	4.4 (0.7–11.0)	4.7 (0.7–13.2)
ECOG PS = 1, n (%)	130 (24.1)	78 (23.9)	172 (42.5)	85 (38.3)	140 (29.1)	73 (27.0)	163 (35.1)	86 (31.5)	305 (31.9)	163 (29.4)
Use of bone-sparing agent, n (%)	6 (1.1)	12 (3.7)	25 (6.2)	19 (8.6)	9 (1.9)	12 (4.4)	22 (4.7)	20 (7.3)	31 (3.2)	32 (5.8)
Prior hormonal therapy, n (%)										
1	110 (20.4)	69 (21.2)	65 (16.0)	32 (14.4)	96 (20.0)	58 (21.5)	80 (17.2)	43 (15.8)	178 (18.6)	103 (18.6)
≥ 2	294 (73.1)	237 (72.7)	325 (80.2)	179 (80.6)	353 (73.4)	193 (71.5)	369 (79.5)	220 (80.6)	726 (76.0)	420 (75.8)
Not applicable[c]	35 (6.5)	20 (6.1)	15 (3.7)	11 (5.0)	32 (6.7)	19 (7.0)	15 (3.2)	10 (3.7)	51 (5.3)	31 (5.6)

DARO, darolutamide; ECOG PS, Eastern Cooperative Oncology Group performance status; PBO, placebo; PSA, prostate-specific antigen.
Values are median (range) unless otherwise indicated.
Data for "Overall ARAMIS population" are from K. Fizazi, et al., Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide, Volume No 383, Page No 1040-9 Copyright © 2020 Massachusetts Medical Society, reprinted with permission, except for the presence of lymph nodes on central imaging and prior hormonal therapy, which were updated at the final analysis data cutoff of 15th November 2019.

[a] Not including data for patients without comorbidities (DARO, n = 11; PBO, n = 6).
[b] Data on concomitant medications missing for 10 patients receiving DARO and 11 patients receiving PBO.
[c] Patients who underwent surgical castration.

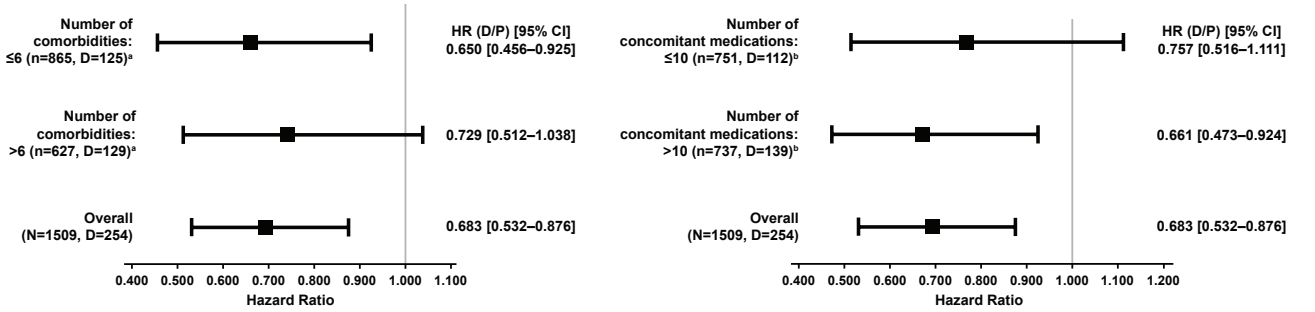

Fig. 1. Forest plots for HRs of overall survival for subgroups of patients by median numbers of comorbidities and concomitant medications. D, number of patients with an event (death); D/P, darolutamide/placebo; HR, hazard ratio. [a]Does not include data for patients without comorbidities (darolutamide, n = 11; placebo, n = 6); [b]Data on concomitant medications were missing for 10 patients receiving darolutamide and 11 patients receiving placebo.

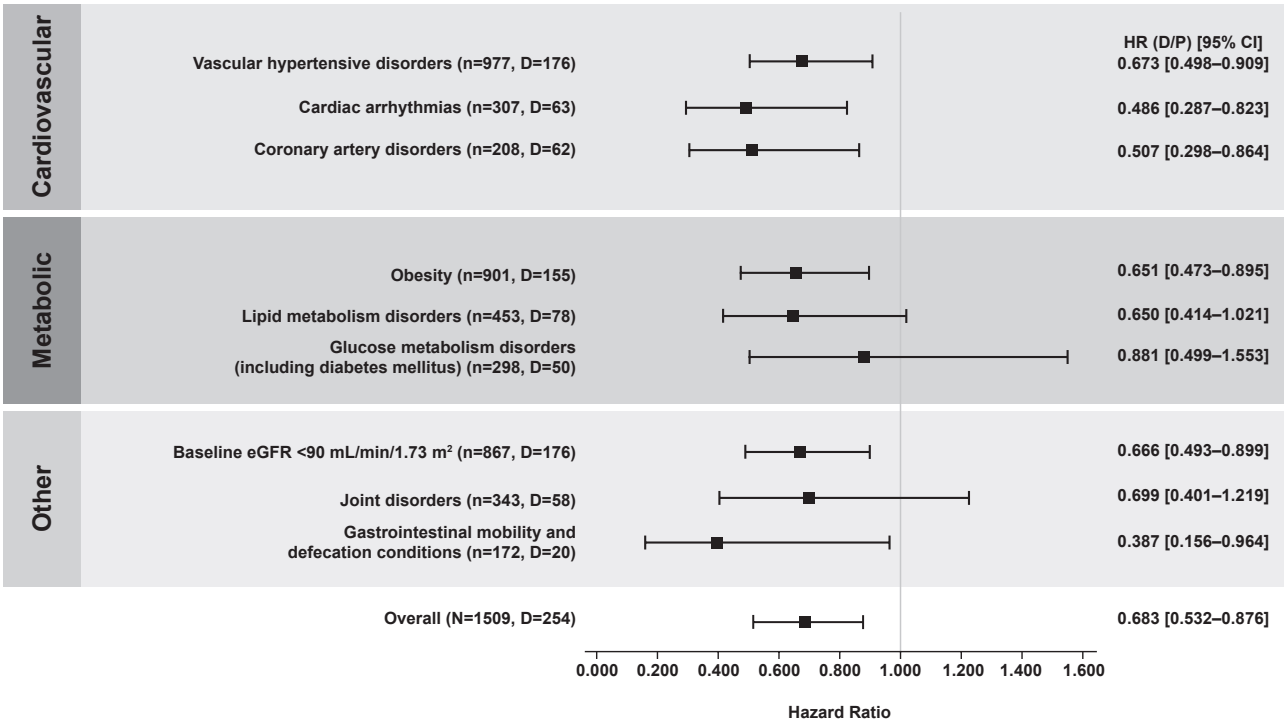

Fig. 2. Forest plots of overall survival for darolutamide versus placebo by comorbidity groups. D, number of patients with an event (death); D/P, darolutamide/placebo; eGFR, estimated glomerular filtration rate.

population of ARAMIS (Table 2). Notably, TEAEs leading to permanent discontinuation of study drug were similar between darolutamide and placebo, even in patients with > 10 concomitant medications (10.8% and 10.6%, respectively).

4. Discussion

The ARAMIS population consisted of patients with nmCRPC with a median age of 74 years, a median of 6 comorbidities, and a median of 10 concomitant medications. In this post hoc analysis of ARAMIS, the OS benefit and safety of darolutamide compared with placebo were consistent across subgroups by numbers of comorbidities and concomitant medications and with the overall population. Incidences of most TEAEs, except fatigue and rash, as well as the incidences of grade 3/4 TEAEs, serious TEAEs, and TEAEs leading to discontinuation, were similar between darolutamide and placebo in each subgroup, including patients with high numbers of comorbidities and concomitant medications.

The results of this post hoc analysis add to available information regarding the treatment benefit, tolerability, and safety profile of darolutamide in various patient subgroups [13]. Darolutamide had a consistently favourable impact on OS in prespecified subgroup analyses of ARAMIS [8], which included various age groups and ECOG performance status. The survival benefit of darolutamide was also similar among patients with a PSA doubling time of ≤ 6 months (HR 0.55;

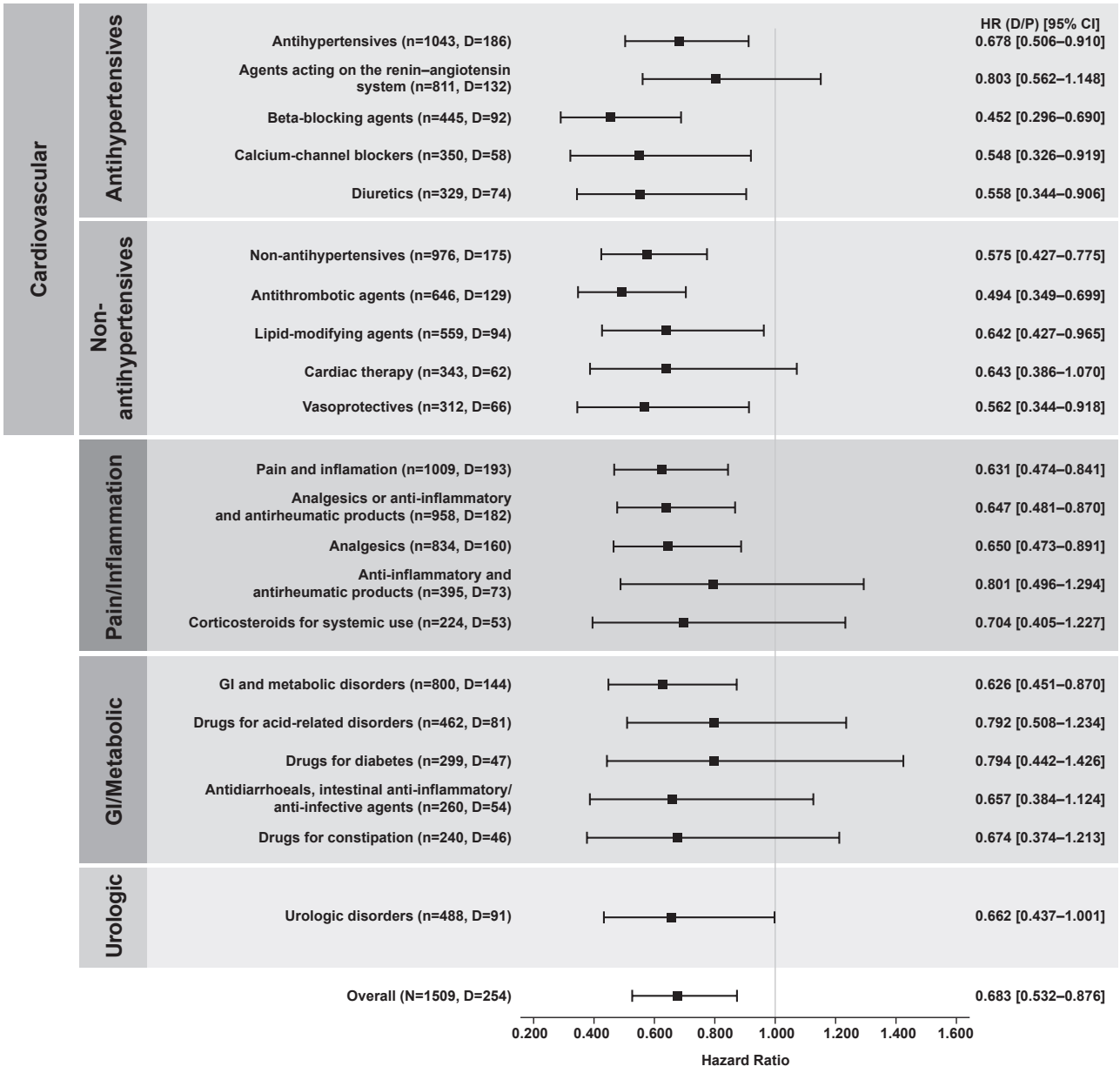

Fig. 3. Forest plots of overall survival for darolutamide versus placebo by class and subclass of concomitant medications. D, number of patients with an event (death); D/P, darolutamide/placebo; GI, gastrointestinal.

95% CI 0.35–0.88) and those with a PSA doubling time of ≥ 6 months (HR 0.74; 95% CI 0.55–0.99) [8,14]. In addition, darolutamide maintained health-related quality of life in patients with nmCRPC by significantly ($P < 0.01$) delaying the time to deterioration in prostate cancer-specific quality of life and urinary and bowel symptoms versus placebo [15,16]. The effects of darolutamide on local symptom control were also evident in fewer prostate cancer–related invasive procedures and similar incidences of urinary and bowel TEAEs versus placebo [16]. These outcomes offer important information for treatment selection in this population of patients who are generally asymptomatic and may receive treatment for prolonged periods of time.

The observed number of concomitant medications in the ARAMIS population is consistent with other reports of older patients with cancer, in whom the mean or median number of reported concomitant medications was 11 [4,17]. One of these studies evaluated 105 patients receiving enzalutamide for metastatic CRPC and found that 85% of patients were using at least 1 concomitant medication that interacted with enzalutamide and required treatment modification [17]. In another study of 86 patients with metastatic CRPC who received enzalutamide, 93% of patients had a potential DDI, with the highest risk of interactions occurring with drugs acting on the cardiovascular and nervous systems [18]. DDIs may lead to increased TEAEs, as shown in a retrospective review of

Table 2
Treatment-emergent adverse events for subgroups of patients by median numbers of comorbidities and concomitant medications.

AE, n (%)	Comorbidities[a]				Concomitant medications[b]				Overall ARAMIS population	
	≤ 6		> 6		≤ 10		> 10			
	DARO (n = 538)	PBO (n = 326)	DARO (n = 405)	PBO (n = 222)	DARO (n = 481)	PBO (n = 270)	DARO (n = 464)	PBO (n = 273)	DARO (n = 954[c])	PBO (n = 554)
Any	447 (83.1)	242 (74.2)	366 (90.4)	195 (87.8)	371 (77.1)	184 (68.1)	442 (95.3)	248 (90.8)	818 (85.7)	439 (79.2)
Grade 3/4	127 (23.6)	58 (17.8)	124 (30.6)	61 (27.5)	67 (13.9)	36 (13.3)	183 (39.4)	82 (30.0)	251 (26.3)	120 (21.7)
Serious	118 (21.9)	59 (18.1)	131 (32.3)	61 (27.5)	65 (13.5)	33 (12.2)	183 (39.4)	85 (31.1)	249 (26.1)	121 (21.8)
AE leading to permanent study drug discontinuation	43 (8.0)	20 (6.1)	42 (10.4)	28 (12.6)	35 (7.3)	17 (6.3)	50 (10.8)	29 (10.6)	85 (8.9)	48 (8.7)
AEs of interest										
Fatigue	49 (9.1)	19 (5.8)	76 (18.8)	27 (12.2)	42 (8.7)	12 (4.4)	84 (18.1)	33 (12.1)	126 (13.2)	46 (8.3)
Hypertension	43 (8.0)	23 (7.1)	30 (7.4)	13 (5.9)	29 (6.0)	15 (5.6)	44 (9.5)	21 (7.7)	74 (7.8)	36 (6.5)
Fracture	29 (5.4)	8 (2.5)	23 (5.7)	12 (5.4)	21 (4.4)	5 (1.9)	31 (6.7)	15 (5.5)	52 (5.5)	20 (3.6)
Fall	23 (4.3)	14 (4.3)	27 (6.7)	13 (5.9)	13 (2.7)	7 (2.6)	36 (7.8)	18 (6.6)	50 (5.2)	27 (4.9)
Rash	15 (2.8)	2 (0.6)	15 (3.7)	4 (1.8)	7 (1.5)	2 (0.7)	23 (5.0)	4 (1.5)	30 (3.1)	6 (1.1)
Mental impairment	9 (1.7)	4 (1.2)	10 (2.5)	6 (2.7)	7 (1.5)	3 (1.1)	12 (2.6)	7 (2.6)	19 (2.0)	10 (1.8)

AE, adverse event; ARAMIS, Androgen Receptor Antagonizing Agent for Metastasis-free Survival; DARO, darolutamide; PBO, placebo.
[a] Not including data for patients without comorbidities (DARO, n = 11; PBO, n = 6).
[b] Data on concomitant medications missing for 10 patients receiving DARO and 11 patients receiving PBO.
[c] One patient randomised to DARO did not receive treatment and was excluded from the safety analysis.

404 older patients with cardiovascular disease, in whom the most common potential interactions were drugs with an additive central nervous system–depressant effect [19]. A meta-analysis and systematic literature review of older patients with cancer found an association between polypharmacy and falls in 3 studies [20]. The risk of falls and other central nervous system–related adverse events in patients with polypharmacy should be considered when selecting anticancer drugs that will be given over extended periods of time. This is especially relevant for drugs such as enzalutamide and apalutamide that have higher incidences of central nervous system side effects, such as falls and mental impairment disorders compared with placebo, and a higher potential for clinically relevant DDIs [21–23]. By contrast, the incidence of these TEAEs of interest were similar between patients receiving darolutamide and those receiving placebo and darolutamide has been shown to have limited potential for DDIs in the ARAMIS study [5,7,8].

These findings highlight the importance of considering the impact of polypharmacy on the choice of drugs used for treatment of patients with nmCRPC [5,24]. The results of this post hoc analysis of ARAMIS suggest that the efficacy and safety of darolutamide are not impacted by commonly used concomitant medications in this population [5,11]. Darolutamide has been previously shown to have a low potential to interact with medications commonly used to treat comorbidities in the nmCRPC population, such as calcium-channel blockers and anticoagulants [5,11]. A subgroup analysis of ARAMIS patients who used statins versus non-users found no imbalance in treatment effects and the incidence of adverse events was similar between treatment groups, suggesting minimal effect of these DDIs [5,7]. Darolutamide inhibits the breast cancer resistance protein (BCRP) transporter, leading to a potential increase in exposure of BCRP substrates, such as rosuvastatin, which should be taken into consideration. In contrast, enzalutamide and apalutamide have been shown to induce key enzymes responsible for drug metabolism, including cytochrome P 450 3A4, 2C8, 2C9, and 2C19, and apalutamide has the potential to interact with drug transporters [25–27]. The effect of enzyme or transporter induction may result in lower concentrations of the coadministered drug (e.g. omeprazole, warfarin, and rosuvastatin), potentially leading to suboptimal clinical outcomes for related comorbid conditions.

The results of this analysis are limited by their post hoc nature, potential for selection bias, and small populations for certain comorbidities and concomitant medications. Patients were grouped by the number of comorbidities and concomitant medications without considering their potential prognostic implications. The ongoing PEACE-6 Vulnerable trial (NCT04916613) may add to the evidence regarding use of darolutamide in patients with limited functional ability and comorbidities who are not considered candidates for docetaxel or other androgen receptor pathway inhibitors. This international, multicentre, phase 3, randomised, double-blind, placebo-controlled trial will assess the effect of darolutamide versus placebo, in addition to ADT, on standard disease-related endpoints, including radiographic and clinical progression-free survival, time to CRPC, and OS, as well as health-related quality of life and geriatric status in patients with

decreased functional ability, chronic illnesses, and metastatic prostate cancer.

The results from this subgroup analysis of ARAMIS, even among patients with a high number of comorbidities and patients with a high number of concomitant medications, are consistent with the overall ARAMIS population, showing improved OS with darolutamide versus placebo and a favourable safety and tolerability profile of darolutamide. A plain-language summary of this report is available in the online Supplementary Material.

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CRediT authorship contribution statement

Karim Fizazi, Neal D. Shore, Matthew Smith, Rodrigo Ramos, Robert Jones, Günter Niegisch, Egils Vjaters: Investigation, Data Curation, Resources, Supervision, Visualisation, Writing – original draft, review & editing. Yuan Wang: Conceptualisation, Funding Acquisition, Methodology, Project Administration, Visualisation, Writing – original draft, review & editing. Shankar Srinivasan: Methodology, Formal Analysis, Software, Visualisation, Writing – original draft, review & editing. Toni Sarapohja: Visualisation, Writing – original draft, review & editing. Frank Verholen: Methodology, Visualisation, Writing – original draft, review & editing.

Declaration of Competing Interest

Karim Fizazi: Honoraria: Janssen (Inst), Sanofi (Inst), Astellas Pharma (Inst), Bayer (Inst). Consulting or advisory role: Janssen Oncology (Inst), Bayer, Astellas Pharma (Inst), Sanofi (Inst), Orion, AstraZeneca (Inst), ESSA (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Clovis Oncology (Inst), Curevac, Novartis (Inst), Pfizer (Inst). Travel, accommodations, expenses: Janssen, MSD, AstraZeneca. Neal D. Shore: Consulting or advisory roles: Bayer, Janssen Scientific Affairs, Dendreon, Tolmar, Ferring, Medivation/Astellas, Amgen, Pfizer, AstraZeneca, Myovant Sciences, Astellas Pharma, AbbVie, Merck, Bristol Myers Squibb/Sanofi, Clovis Oncology, Exact Imaging, FerGene, Foundation Medicine, CG Oncology, InVitae, MDxHealth, Myriad Genetics, Nymox, Propella Therapeutics, Genzyme, Sanofi, Sesen Bio, CG Oncology, Exact Sciences, Genesis Cancer Care, Pacific Edge Biotechnology, Phosphorus, Urogen Pharma, Specialty Networks, Peerview, Clarity Pharmaceuticals, Lantheus Medical Imaging, Lilly, Photocure, Sema4, Telix Pharmaceuticals, Tempus, Vaxiion. Speakers' bureau: Janssen, Bayer, Dendreon, Astellas Pharma, AstraZeneca, Clovis Oncology, Pfizer, Guardant Health, Merck, Foundation Medicine. Expert testimony: Ferring. Other relationship: Photocure, Alessa Therapeutics. Research funding: AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, Boston Scientific, Clovis Oncology, Dendreon, Exact Imaging, Ferring, Foundation Medicine, InVitae, Janssen, MDxHealth, Merck, Myovant Sciences, Myriad Genetics, Nymox, Pfizer, Sanofi, Sesen Bio, Tolmar, CG Oncology, DisperSol, FORMA Therapeutics, Guardant Health, Jiangsu Yahong Meditech, Novartis, Pacific Edge, POINT Biopharma, Propella Therapeutics, Seattle Genetics, MT Group, Theralase, Veru, Zenflow, Advantagene, Aragon Pharmaceuticals, Endocyte, Exelixis, FKD Therapies, Genentech, ISTARI Oncology, Medivation, OncoCellMDx, ORIC Pharmaceuticals, Palette Life Sciences, Plexxikon, RhoVac, Steba Biotech, Urogen Pharma, Urotronic, US Biotest, Vaxiion. Matthew Smith: Consulting or advisory role: Bayer, Janssen Oncology, Amgen, Pfizer, Lilly, Novartis, Astellas Pharma. Research funding: Janssen Oncology (Inst), Bayer (Inst), Lilly (Inst), ESSA (Inst), ORIC Pharmaceuticals (Inst). Rodrigo Ramos: Honoraria: Astellas Pharma, Bayer, Janssen-Cilag, Pfizer. Consulting or advisory roles: Astellas Pharma, Bayer, Janssen-Cilag; Travel, accommodations, expenses: Janssen-Cilag. Robert Jones: Honoraria: Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, Eisai, EUSA Pharma, Ipsen, Janssen, Merck Serono, MSD Oncology, Novartis. Fizer, Pharmacyclics, Roche/Genentech, Sanofi, Seagen. Consulting or advisory roles: Clovis Oncology. Research funding: Astellas Pharma (Inst), AstraZeneca (Inst), Bayer (Inst), Clovis Oncology (Inst), Exelixis (Inst), Novartis (Inst), Pfizer (Inst), Roche (Inst). Travel, accommodations, expenses: Astellas Pharma, Bayer, Ipsen, Janssen, MSD. Günter Niegisch: Honoraria: AstraZeneca, Medac, Roche Pharma AG. Consulting or advisory roles: Bristol Myers Squibb, Ipsen, Janssen Oncology, Merck/Pfizer, Pfizer, Roche Pharma AG, Sanofi-Aventis. Travel, accommodations, expenses: Bristol Myers Squibb/Celgene, Roche Pharma AG. Egils Vjaters: Consulting or advisory roles: Bayer, Ipsen, Janssen. Yuan Wang: Employment: Bayer. Stock and other ownership interests: Bayer. Shankar Srinivasan: Employment: Bayer. Stock and other ownership interests: Bayer. Toni Sarapohja: Employment: Orion. Frank Verholen: Employment: Bayer.

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Data sharing statement

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 1st January 2014. Interested researchers can use www.vivli.org to request access to anonymised 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 anonymised 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.

Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113258.

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