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Original Research

Darolutamide and health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: An analysis of the phase III ARAMIS trial

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Abstract ***Background:*** In the ARAMIS trial, darolutamide plus androgen deprivation therapy (ADT) versus placebo plus ADT significantly improved metastasis-free survival (MFS), overall survival (OS) and time to pain progression in patients with non-metastatic castration-resistant prostate cancer (nmCRPC). Herein, we present analyses of patient-reported health-related quality of life (HRQoL) outcomes.

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(nmCRPC);
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Patients and methods: This double-blind, placebo-controlled, phase III trial randomised patients with nmCRPC and prostate-specific antigen doubling time ≤10 months to darolutamide 600 mg ($n = 955$) twice daily or matched placebo ($n = 554$) while continuing ADT. The primary end-point was MFS; the secondary end-points included OS and time to pain progression. In this analysis, HRQoL was assessed by the time to deterioration using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) prostate cancer subscale (PCS) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module (EORTC QLQ-PR25) subscales.

Results: Darolutamide significantly prolonged time to deterioration of FACT-P PCS versus placebo (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.70–0.91; $P = 0.0005$) at the primary analysis (cut-off date: 3rd September 2018). Time to deterioration of EORTC QLQ-PR25 outcomes showed statistically significant delays with darolutamide versus placebo for urinary (HR 0.64, 95% CI 0.54–0.76; $P < 0.0001$) and bowel (HR 0.78, 95% CI 0.66–0.92; $P = 0.0027$) symptoms. Time to worsening of hormonal treatment–related symptoms was similar between the two groups.

Conclusion: In patients with nmCRPC who are generally asymptomatic, darolutamide maintained HRQoL by significantly delaying time to deterioration of prostate cancer–specific quality of life and disease-related symptoms versus placebo.

1. Introduction

Prostate cancer is the second most common malignancy in men and is a leading cause of mortality. In 2018, there were more than 360,000 deaths from prostate cancer in men worldwide [1]. Androgen deprivation therapy (ADT) is part of the standard of care for patients whose prostate cancer recurs after primary treatment. Although nearly all patients initially respond to ADT, most eventually develop castration-resistant prostate cancer (CRPC), defined as rising levels of prostate-specific antigen (PSA) despite continuous ADT [2]. CRPC in the absence of detectable metastases on conventional imaging is classified as non-metastatic CRPC (nmCRPC). Most patients with nmCRPC will progress to metastatic CRPC, which is associated with significantly reduced overall survival (OS). Patients with nmCRPC are generally older (median age ≥73 years in the SPARTAN and PROSPER trials), are asymptomatic and, compared with those with more advanced disease, tend to have reasonable health-related quality of life (HRQoL) [3–5]. Therefore, understanding the impact of treatment on QoL is clinically important.

Darolutamide is an oral androgen receptor inhibitor (ARI) approved for the treatment of nmCRPC, after demonstrating significantly prolonged metastasis-free survival (MFS) compared with placebo (median 40.4 months versus 18.4 months, hazard ratio [HR] 0.41, 95% confidence interval [CI] 0.34–0.50; $P < 0.001$) in the primary analysis of the phase III ARAMIS trial (data cut-off 3rd September 2018) [6]. Darolutamide also significantly improved OS (HR 0.69; 95% CI 0.53–0.88; $P = 0.003$) compared with placebo at the final analysis (data cut-off 15th November 2019) [7]. In addition, time to pain progression significantly improved with darolutamide versus placebo (HR 0.65, 95% CI 0.53–0.79; $P < 0.001$) [7]. At both the primary and final analyses, darolutamide demonstrated a favourable safety profile. Most adverse events (AEs) commonly associated with ARIs (e.g. fatigue, falls, mental impairment and hypertension) showed 2% or less difference between darolutamide and placebo groups; fatigue was the only AE with a more than 10% incidence in the darolutamide arm (13.2% versus 8.3% in the placebo arm) [6,7]. The low risk of central nervous system AEs associated with darolutamide may be due to the low blood–brain barrier penetration of darolutamide, as observed in non-clinical models and functional neuroimaging studies in humans [8,9]. Darolutamide also has a low potential for drug–drug interactions with comedications commonly taken for comorbid conditions by patients with nmCRPC [10]. Furthermore, at primary analysis (data cut-off 3rd September 2018), changes in HRQoL scores over time compared with baseline favoured darolutamide and showed statistically significant (but not clinically relevant) changes compared with placebo [6].

In this analysis, we use data from the primary analysis of the ARAMIS trial to compare changes in patient-reported HRQoL between darolutamide and placebo using multiple validated questionnaires.

2. Methods

2.1. Study design and participants

The ARAMIS trial (NCT02200614) was a phase III, randomised, double-blind, placebo-controlled trial

conducted at 409 centres in 36 countries worldwide. Full details of the study have been previously reported [6]. Briefly, eligible patients aged 18 years or older were diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate. Patients were required to have a confirmed diagnosis of nmCRPC, a baseline PSA level of at least 2 ng/ml, a PSA doubling time (PSADT) of 10 months or less and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were excluded if they had a history of metastatic disease or distant metastases detected by whole-body radionuclide bone scan and computed tomography or magnetic resonance imaging of the pelvis, abdomen and chest; the presence of pelvic lymph nodes less than 2 cm in the short axis below the aortic bifurcation was allowed. Prior seizure or conditions predisposing to seizure were permitted. The review board at each participating institution approved the trial, which was conducted in compliance with the principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice. An independent Data and Safety Monitoring Board reviewed unblinded safety data throughout the trial.

2.2. Randomisation and masking

At study initiation, patients were randomised 2:1 to oral darolutamide (600 mg [two tablets of 300 mg] twice daily with food) or matched placebo in a double-blind manner. Patients continued treatment until protocol-defined progression, intolerable AEs or withdrawal of consent. Patients continued ADT (luteinising hormone–releasing hormone agonist or antagonist) throughout the trial. Patients who initiated a prohibited therapy (detailed in the study protocol, available online [6]) before confirmation of metastasis were required to discontinue study treatment and were followed for survival status. Randomisation was stratified by PSADT ($\leq$6 months versus >6 months) and the use of osteoclast-targeted therapy at randomisation (yes versus no).

2.3. Procedures

The impact of prostate cancer and treatment on HRQoL was evaluated using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) prostate cancer subscale (PCS), assessed at screening, day 1, week 16 and at every subsequent visit throughout the double-blind period, until the end of treatment. The PCS contains 12 questions scored on a Likert-type scale from 0 to 4. Scores are combined for an overall score ranging from 0 to 48, where higher scores represent better QoL. The full 39-item FACT-P questionnaire (physical well-being, social and family well-being, emotional well-being and functional well-being in addition to PCS) was also assessed at screening, day 1, week 16 and the end of treatment.

The impact of treatment on prostate cancer–related QoL was evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module (EORTC QLQ-PR25), administered at screening, day 1, week 16 and every 16 weeks until the end of treatment or death throughout the double-blind period. The 25-item EORTC QLQ-PR25 questionnaire assesses the effect of urinary symptoms (8 items), bowel symptoms (4 items), hormonal treatment–related symptoms (6 items), incontinence aid use (1 item), sexual activity (2 items) and sexual functioning (4 items). For the EORTC QLQ-PR25, a higher functional score reflects better function (for sexual activity and function), whereas higher symptom scores reflect worsened symptoms. The EORTC QLQ-PR25 utilises a 1–4 Likert-type scale to answer items within a question format. These scores are linearly converted and summated into a scaled score from 0 to 100 [11].

2.4. Outcomes

The primary end-point in ARAMIS was MFS. The secondary end-points included OS and time to pain progression. QoL was an exploratory end-point. Here, we report time to deterioration of FACT-P PCS and EORTC QLQ-PR25 subscale scores.

2.5. Statistical analysis

The sample size was calculated based on the primary end-point of MFS [6]. The full analysis set was used for the HRQoL analysis reported herein, but it should be noted that the trial was not specifically powered for these HRQoL outcomes.

Time to deterioration for FACT-P PCS was defined as a decline of $\geq$3 points in the PCS score from baseline. Time to deterioration for EORTC QLQ-PR25 symptom subscales was defined as the first decline in the HRQoL score from baseline equal to or greater than the minimally important difference (MID, a measure of clinical significance) defined as half the standard deviation of the baseline value for each subscale. Patients who did not report a decrease in HRQoL equal to or greater than the MID were censored at the date of their last visit. Time to deterioration was analysed using a stratified log-rank test, with the same stratification factors as for randomisation; the HR and associated 95% CI were calculated using a Cox proportional-hazards model. As multiple comparisons were not accounted for, *P* values should be interpreted as descriptive in nature.

Statistical analysis and subject data listings were performed with SAS® for Unix (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

Between September 2014 and March 2018, 1509 patients were randomly assigned in a 2:1 ratio (n = 955 to the darolutamide group, n = 554 to the placebo group). The clinical cut-off date for the analysis reported here was 3rd September 2018. The median follow-up time was 17.9 months. Median treatment duration was 14.8 months in the darolutamide group and 11.0 months in the placebo group. Patient baseline and clinical characteristics, including prior definitive treatment for prostate cancer, were well balanced between treatment groups and have been reported previously [6]. Baseline FACT-P PCS and EORTC QLQ-PR25 subscale scores were at the high end of the scale in both treatment groups (Table 1).

3.2. Questionnaire completion

Patient compliance for completion of questionnaires was assessed at each visit as the number of patients who answered all questions out of the total number of patients to whom it was administered. The completion rate for FACT-P PCS was 86% or higher in both groups, aside from screening, day 1, week 16 and the end of treatment when FACT-P PCS was collected as part of the overall assessment of the full FACT-P questionnaire. The compliance rate for completion of EORTC QLQ-PR25 was 82% or higher in each group at all assessment visits during the double-blind treatment period, with the

Table 1
Patient demographics and clinical characteristics at baseline.

Characteristic[a]	Darolutamide (n = 955)	Placebo (n = 554)
Median age (range), years	74 (48–95)	74 (50–92)
Median serum PSA (range), ng/ml	9.0 (0.3–858.3)	9.7 (1.5–885.2)
PSA doubling time		
Median (range), months	4.4 (0.7–11.0)	4.7 (0.7–13.2)
≤6 months, n (%)	667 (70)	371 (67)
>6 months, n (%)	288 (30)	183 (33)
ECOG performance status, n (%)		
0	650 (68)	391 (71)
1	305 (32)	163 (29)
Use of bone-sparing agent, n (%)		
Yes	31 (3)	32 (6)
No	924 (97)	522 (94)
Prior treatment, n (%)		
Chemical castration	403 (42)	252 (46)
Prostatectomy	239 (25)	134 (24)
Radiotherapy	177 (19)	89 (16)
Orchiectomy	91 (10)	50 (9)
Other	32 (3)	22 (4)
Active surveillance	12 (1)	7 (1)
Prior hormonal therapy,[b] n (%)		
1	177 (19)	103 (19)
≥2	727 (76)	420 (76)
Not applicable[c]	51 (5)	31 (6)
FACT-P PCS score, mean (SD) [range]	n = 949; 33 (6) [8–48]	n = 551; 33 (6) [10–47]
EORTC QLQ-PR25 score, mean (SD) [range][d]		
Bowel symptoms	n = 896; 6 (10) [0–56]	n = 511; 6 (10) [0–58]
Hormonal treatment–related symptoms	n = 896; 16 (13) [11–67]	n = 511; 17 (14) [17–61]
Incontinence aid use	n = 341; 12 (23) [0–100]	n = 180; 15 (26) [0–100]
Sexual activity	n = 888; 89 (19) [0–100]	n = 511; 90 (19) [0–100]
Sexual functioning	n = 191; 44 (26) [0–100]	n = 118; 46 (26) [0–100]
Urinary symptoms	n = 895; 23 (17) [0–88]	n = 511; 24 (18) [0–100]

ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module; FACT-P, Functional Assessment of Cancer Therapy–Prostate; MID, minimally importance difference; PCS, prostate cancer subscale; PSA, prostate-specific antigen; SD, standard deviation.

[a] Percentages may not total 100 because of rounding.

[b] Common prior hormonal therapies for prostate cancer (received by ≥ 10% of all patients) included leuprorelin (52%), goserelin (32%), triptorelin (29%), bicalutamide (66%), flutamide (13%) and cyproterone (11%).

[c] Subjects who underwent surgical castration.

[d] The MID for bowel symptoms = 4.91; hormonal treatment–related symptoms = 6.68; incontinence aid use = 12.15; sexual activity = 9.59; sexual functioning = 13.13; urinary symptoms = 8.73.

Table 2
EORTC QLQ-PR25 and FACT-P PCS completion rate.

Visit	Darolutamide (n = 955)	Placebo (n = 554)	Total (n = 1509)
EORTC QLQ-PR25, *n/n* (%)			
Screening	773/955 (81)	436/554 (79)	1209/1509 (80)
Day 1	787/955 (82)	457/554 (83)	1244/1509 (82)
Week 16	766/913 (84)	445/516 (86)	1211/1429 (85)
Week 32	709/838 (85)	324/387 (84)	1033/1225 (84)
Week 48	583/684 (85)	232/283 (82)	815/967 (84)
Week 64	457/528 (87)	164/190 (86)	621/718 (86)
Week 80	349/393 (89)	106/124 (86)	455/517 (88)
Week 96	245/277 (88)	73/82 (88)	318/359 (88)
Week 112	176/206 (85)	46/55 (84)	222/261 (85)
Week 128	112/123 (90)	29/33 (88)	141/156 (90)
Week 144	65/73 (89)	13/15 (87)	78/88 (89)
Week 160	32/37 (87)	8/8 (100)	40/45 (89)
Week 176	16/19 (84)	1/1 (100)	17/20 (85)
Week 192	2/2 (100)	0	2/2 (100)
End of study treatment	164/229 (71)	208/288 (72)	372/517 (72)
FACT-P PCS,[a] *n/n* (%)			
Screening	438/955 (46)	271/554 (49)	709/1509 (47)
Day 1	424/955 (44)	251/554 (45)	675/1509 (45)
Week 16	370/913 (41)	218/516 (42)	588/1429 (41)
Week 32	770/838 (92)	344/387 (89)	1114/1225 (91)
Week 48	635/684 (92)	250/283 (88)	885/967 (91)
Week 64	484/528 (92)	177/190 (93)	661/718 (92)
Week 80	366/393 (93)	111/124 (90)	477/517 (92)
Week 96	254/277 (91)	73/82 (88)	327/359 (91)
Week 112	188/206 (91)	47/55 (86)	235/261 (90)
Week 128	118/123 (95)	29/33 (88)	147/156 (94)
Week 144	71/73 (97)	15/15 (100)	86/88 (98)
Week 160	36/37 (97)	8/8 (100)	44/45 (98)
Week 176	19/19 (100)	1/1 (100)	20/20 (100)
Week 192	2/2 (100)	0	2/2 (100)
End of study treatment	64/229 (28)	100/288 (35)	164/517 (32)

EORTC QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module; FACT-P, Functional Assessment of Cancer Therapy–Prostate; PCS, prostate cancer subscale.
[a] Patients were asked 12 questions (FACT-P PCS) with the exception of screening, day 1, week 16 and the end of treatment, when patients were asked 39 questions (FACT-P PCS was collected in combination with overall FACT-P).

exception of screening and the end of treatment visits (Table 2).

3.3. FACT-P PCS

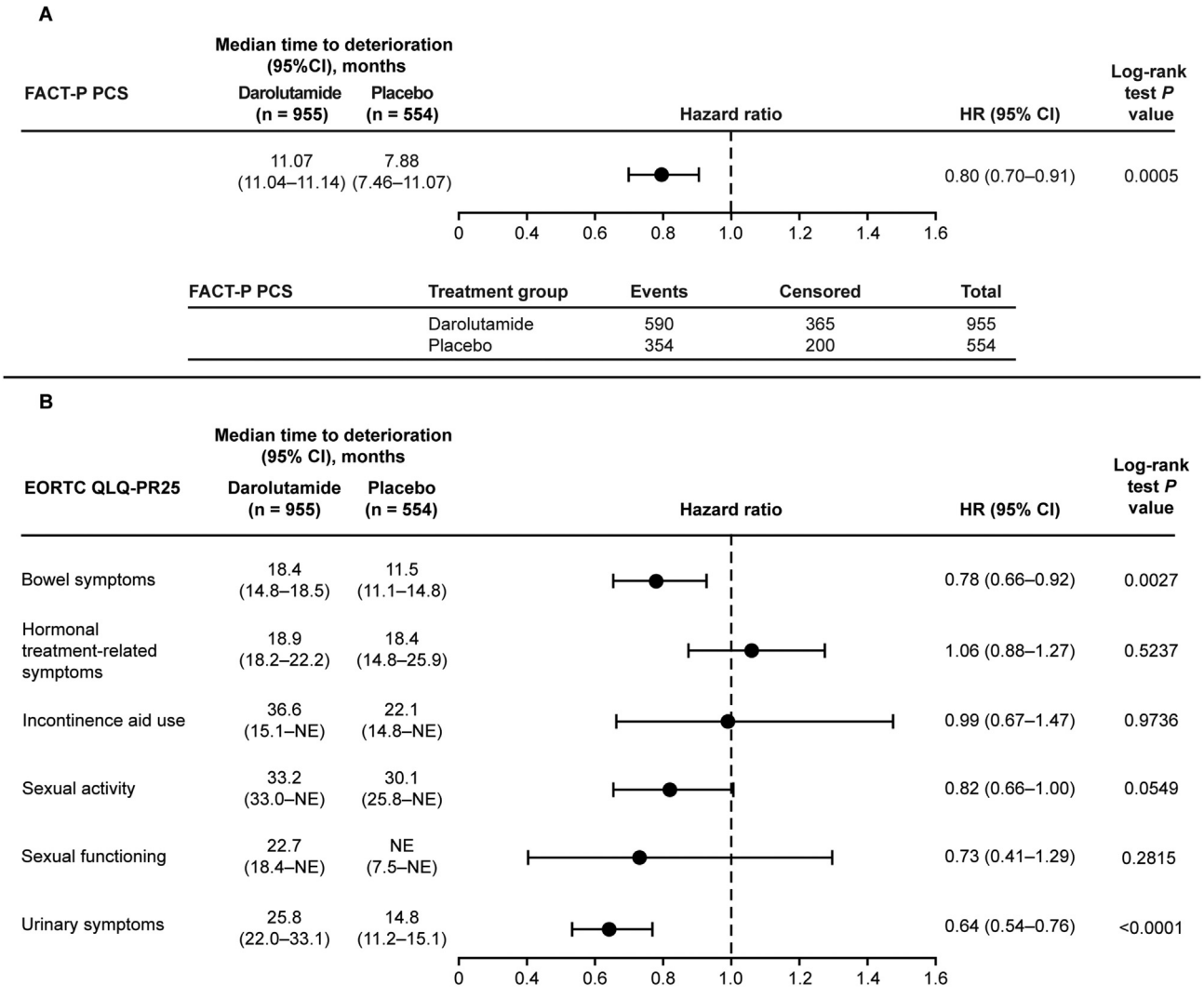
This analysis assessed those patients who showed a MID in scores from baseline. Darolutamide significantly delayed time to deterioration of FACT-P PCS by 3.2 months more than placebo (darolutamide, median 11.1 months versus placebo, 7.9 months; HR 0.80, 95% CI 0.70–0.91; $P = 0.0005$; Fig. 1A).

3.4. EORTC QLQ-PR25

A post hoc analysis of time to deterioration in EORTC QLQ-PR25 subscales showed statistically significant delays in progression of urinary and bowel symptoms with darolutamide versus placebo (Fig. 1B). Median time to deterioration was 25.8 months versus 14.8 months (treatment difference of 11 months; HR 0.64, 95% CI 0.54–0.76; $P < 0.0001$) for urinary symptoms and 18.4 months versus 11.5 months (treatment difference of 6.9 months; HR 0.78, 95% CI 0.66–0.92; $P = 0.0027$) for bowel symptoms with darolutamide versus placebo, respectively. There was no significant difference between darolutamide and placebo in the time to deterioration of hormonal treatment–related symptoms (breast tenderness, swelling in legs or ankles, hot flushes, problems due to weight loss or gain and feelings of reduced masculinity).

4. Discussion

In the ARAMIS trial of darolutamide plus ADT versus placebo plus ADT, treatment with darolutamide significantly delayed the time to worsening of prostate cancer–related HRQoL, as measured by the FACT-P PCS scores, thereby maintaining patients' QoL for a longer period than placebo. Urinary and bowel symptoms are the major contributing factors leading to deterioration of QoL in patients with nmCRPC [12,13]. The post hoc analysis of time to deterioration of EORTC



FACT-P PCS	Treatment group	Events	Censored	Total
	Darolutamide	590	365	955
	Placebo	354	200	554

EORTC QLQ-PR25	Treatment group	Events	Censored	Total
Bowel symptoms	Darolutamide	415	540	955
	Placebo	235	319	554
Hormonal treatment-related symptoms	Darolutamide	385	570	955
	Placebo	172	382	554
Incontinence aid use	Darolutamide	83	169	252
	Placebo	36	93	129
Sexual activity	Darolutamide	253	702	955
	Placebo	143	411	554
Sexual functioning	Darolutamide	29	71	100
	Placebo	22	48	70
Urinary symptoms	Darolutamide	321	634	955
	Placebo	215	339	554

Fig. 1. Cox regression analysis of time to deterioration in FACT-P PCS scores (A) and EORTC QLQ-PR25 subscale scores[†] (B). [†]The hazard ratio for sexual function was not significant because of the small numbers of patients who were sexually active: 100 in the darolutamide group and 70 in the placebo group. CI, confidence interval; EORTC QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate Cancer Module; FACT-P, Functional Assessment of Cancer Therapy–Prostate; NE, not estimable; PCS, prostate cancer subscale.

QLQ-PR25 subscales demonstrated that darolutamide significantly prolonged urinary symptom control by a median of 11.0 months compared with placebo and bowel symptom control by 6.9 months. Many patients with nmCRPC have cancer in the pelvic region, including local recurrence within the prostate [14], that may

account for local symptom improvement associated with darolutamide treatment. In addition, lower incidences of urinary tract infection (4.9% versus 5.1%) and urinary retention (3.5% versus 6.5%) were reported with darolutamide versus placebo [6]. Adding androgen-targeted therapy to ADT could negatively impact HRQoL because of an increase in the number or severity of symptoms associated with hormonal therapy [4]. However, in ARAMIS, no statistically significant differences were observed in QoL due to hormonal treatment–related symptoms between patients receiving darolutamide and placebo. Given that patients with nmCRPC are generally asymptomatic [5] and may receive darolutamide treatment for prolonged periods of time (median duration of darolutamide treatment was 14.8 months at the time of analysis), preventing deterioration in HRQoL and treatment-induced morbidity is an important clinical goal. Moreover, deterioration of HRQoL in patients with recurrent prostate cancer, including those with nmCRPC, as manifested by reduced energy levels and/or physical and social dysfunction, may result from advancing age of patients [15], the presence of comorbidities and adverse effects of prior surgery, radiation therapy and ongoing ADT [12,16]. As drugs that delay disease progression of nmCRPC cannot mitigate these factors, preventing deterioration of HRQoL is an important clinical outcome of additional pharmacotherapy.

The HRQoL results from the ARAMIS trial are consistent with those observed in the SPARTAN trial of apalutamide and the PROSPER trial of enzalutamide, both added to ongoing ADT in patients with nmCRPC. Assessment of FACT-P demonstrated that HRQoL was maintained over a substantial period with both apalutamide (for approximately 25.8 months) and enzalutamide (for 97 weeks [approximately 22 months]) [3,4]. However, assessment of HRQoL in ARAMIS, SPARTAN and PROSPER may lack sensitivity. Given that the three trials enrolled generally asymptomatic patients with baseline HRQoL scores at the high end of the assessed scale [3,4,6], this 'ceiling effect' limits the ability to identify further improvement in HRQoL during the specified duration of treatment. In addition, potential disease-related deterioration in HRQoL may not be apparent or manifested until several months after metastasis and not within the follow-up time for HRQoL assessments.

HRQoL analyses focussing on components specific for prostate cancer may be more informative, as shown for EORTC QLQ-PR25 in ARAMIS and PROSPER. Both trials reported similar times to deterioration of urinary and bowel symptoms that favoured darolutamide and enzalutamide, respectively [4], which in PROSPER was associated with disease control [17]. In contrast, time to deterioration of hormonal treatment–related symptoms was similar between darolutamide and placebo in ARAMIS, but occurred more quickly with enzalutamide versus placebo in PROSPER [4], which may reflect the reported differences in the safety profiles of darolutamide and enzalutamide [6,18].

This study has several strengths. The large study size and high questionnaire completion rates enabled robust statistical analysis. The analyses focussed on patients with a clinically significant change in QoL and used assessment tools that were designed and validated in prostate cancer. However, the results of the study may have been affected by patient dropout. The impact of treatment on HRQoL could have been underestimated if patients who experienced a deterioration in HRQoL were excluded from the study analyses (174 [18%] of 955 darolutamide-treated patients and 163 [29%] of 554 placebo-treated patients were lost to follow-up). The validity of the results may also have been affected as HRQoL could have differed between patients who completed the treatment and those who discontinued participation and failed to complete the assessments. In addition, the study was not designed to evaluate local progression of prostate cancer, limiting our ability to associate deterioration of these patient-reported outcomes with local or regional progression.

In conclusion, combined with the results in ARAMIS of significantly increased MFS [6], OS [7] and time to pain progression [7], these patient-reported outcomes demonstrate that darolutamide significantly delayed the time to deterioration of prostate cancer–specific QoL and disease-related symptoms, compared with placebo, in generally asymptomatic patients with nmCRPC.

Author statement

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Conflict of interest statement

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