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ADIS DRUG EVALUATION

Darolutamide: A Review in Non-Metastatic Castration-Resistant Prostate Cancer

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Abstract

Oral darolutamide (Nubeqa™) is a novel second-generation, nonsteroidal, selective androgen receptor (AR) inhibitor indicated for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC). In the pivotal multinational, phase 3 ARAMIS trial in men with nmCRPC, relative to placebo plus ongoing androgen deprivation therapy (ADT), darolutamide (+ ADT) significantly prolonged metastasis-free survival (MFS) at the time of the primary analysis and overall survival (OS) at the time of the final OS analysis and was generally well tolerated in extended follow-up. Albeit long-term data from the real-world setting are required to fully define the safety profile of darolutamide, current evidence from the final ARAMIS analysis indicates that darolutamide has a low propensity for CNS-related adverse events (AEs) associated with other currently approved second-generation AR inhibitors. Given the efficacy and safety evidence from the final ARAMIS analysis and the key role of second-generation AR inhibitors in the management of nmCRPC, darolutamide + ADT represents an important emerging option for the treatment of men with nmCRPC who are at high risk of developing metastatic prostate cancer.

Darolutamide: clinical considerations in nmCRPC
Second-generation AR inhibitor, with a distinct chemical structure relative to other anti-androgens
Low blood-brain barrier penetration; low potential for drug-drug interaction
Significantly prolongs MFS and OS vs placebo (+ ADT)
Generally well tolerated, with the nature and incidence of most AEs similar to those of placebo

1 Introduction

Worldwide, prostate cancer (PC) is the second most common malignancy in men, with an estimated 1.3 million new cases in 2018 [1]. Although a high clinical cure rate is achievable with localized definitive treatment in the early stages of PC, 20–30% of men subsequently experience disease progression and require systemic treatment with androgen deprivation therapy (ADT) [2–4]. However, within 2–3 years, the vast majority of these patients become refractory to ADT and experience biochemical recurrence of PC and progression

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to castration-resistant PC (CRPC) [4, 5]. Given the highest risk for progression to metastatic CRPC (mCRPC) and death occurs in patients with non-metastatic CRPC (nmCRPC) who have a higher prostate-specific antigen (PSA) level and shorter PSA-doubling time (PSADT) [4], the main goal of treatment for nmCRPC is to delay metastasis [3, 4]. A better understanding of the crucial role that the androgen receptor (AR) signalling axis plays in the pathogenesis of CRPC led to the development of effective targeted treatment strategies to overcome AR signalling and consequently, delay progression of nmCRPC to mCRPC [3, 4, 6]. Indeed, during the past decade, the targeted second-generation AR inhibitors apalutamide and enzalutamide have revolutionized the landscape of nmCRPC management, with both agents prolonging metastasis-free survival (MFS) [3, 4, 6], which is considered a surrogate marker for overall survival (OS) [3].

Oral darolutamide (Nubeqa™) is a novel second-generation, nonsteroidal, selective AR inhibitor structurally distinct from apalutamide and enzalutamide, with increased flexibility and higher polarity that may be associated with low blood-brain barrier (BBB) penetration [7]. Darolutamide is approved in several countries, including EU countries [8], UK [9], the USA [10] and Japan [11], for the treatment of nmCRPC [10, 11] (for patients at high-risk of developing metastatic disease [8, 9]). This review focuses on therapeutic efficacy and tolerability data relevant to the use of darolutamide in nmCRPC and summarizes its pharmacological profile.

2 Pharmacodynamic Properties of Darolutamide

Darolutamide exists as the diastereomers (*S,R*)-darolutamide and (*S,S*)-darolutamide, which interconvert via the pharmacologically active metabolite keto-darolutamide, with a preference for (*S,S*)-darolutamide [8]. Darolutamide and keto-darolutamide are competitive AR inhibitors, with darolutamide having a distinct chemical structure that differs from that of other known anti-androgens, including other second-generation AR inhibitors [7]. This distinct chemical structure involves a flexible polar-substituted pyrazole structure that binds with high affinity directly to the AR ligand binding domain. AR inhibition by darolutamide, in turn, is associated with inhibition of androgen binding, AR nuclear translocation, AR binding to the genome and AR-mediated transcription [7, 12].

In preclinical studies, darolutamide (its diastereomers) and its active metabolite [respective inhibition constant (Ki) 11 and 8 nmol/L] exhibited more potent AR inhibition than enzalutamide (Ki 86 nmol/L) or apalutamide (Ki 93 nmol/L) in competitive AR binding assays [7]. In transactivation assays using human AR, darolutamide and keto-darolutamide exhibited potent full antagonism at AR wild type and at AR mutations shown to drive resistance to other second-generation AR inhibitors such as F877L, W742L and W742C [7, 13]. In another study, darolutamide inhibited transcriptional activity elicited by AR mutations detected in patients receiving enzalutamide, bicalutamide or abiraterone acetate, including F877L, H875Y/T878A, F877L/T878A and T878G [14]. In mouse xenograft models of PC, darolutamide exhibited more potent ($p < 0.05$) antitumour activity than enzalutamide in a castration-resistant VCaP model [7], and showed potent antitumour efficacy in models habouring wild type AR (namely KuCaP-1) [13]. In vivo efficacy was also observed in the MR49F xenograft model with the AR mutations F877L and T878A [14].

Unlike enzalutamide and apalutamide, darolutamide showed low penetration of the BBB in mouse and rat studies [7, 15] and did not increase serum testosterone levels in mice [7]. In healthy adult volunteers, treatment with enzalutamide resulted in a reduction in cerebral blood flow in whole-brain grey matter in regions relevant to cognitive function, which was not observed with placebo or darolutamide treatment [16]. This indirectly supports the preclinical evidence of the low BBB penetration potential of darolutamide [16].

No prolongation of the corrected QT interval (i.e. increase of > 10 ms [8] or > 20 ms [10]) was detected during darolutamide (600 mg twice daily) treatment (vs placebo) in patients with nmCRPC participating in the ARAMIS trial (Sect. 4).

3 Pharmacokinetic Properties of Darolutamide

Darolutamide and its active metabolite keto-darolutamide exhibit nearly dose-proportional exposure across a dose range of 100 to 700 mg, with no further increase in exposure to darolutamide observed at 900 mg twice daily [10]. The absolute bioavailability of darolutamide after a single oral dose is ≈ 30% under fasted conditions. The bioavailability of darolutamide increased ≈ 2- to 2.5-fold when administered with food, with a similar increase observed for keto-darolutamide [10]. After multiple darolutamide 600 mg doses twice daily (taken with food), steady-state pharmacokinetics were reached after 2–5 days, with a maximum plasma concentration of 4.79 mg/L attained ≈ 4 h post-dosing [8, 10]. Darolutamide and keto-darolutamide are 92% and 99.8% bound to plasma proteins, mainly to serum albumin. Darolutamide is widely distributed throughout the body, with an apparent volume of distribution after intravenous administration of 119 L [8, 10]. Preclinical animal studies indicate a low penetration of the drug across the BBB (Sect. 2) and a low likelihood that the drug crosses the intact BBB in humans to a clinically relevant extent [8].

Darolutamide is primarily metabolized by CYP3A4 and, to a lesser extent, by UGT1A9 and UGT1A1, with total plasma exposure to keto-darolutamide ≈ 1.7-fold higher than darolutamide. The effective half-life of darolutamide and keto-darolutamide is ≈ 20 h in patients. The clearance of intravenous darolutamide is 116 mL/min. After a single oral radiolabeled dose of darolutamide, 63.4% of the administered dose is excreted in the urine (≈ 7% as unchanged drug) and 32.4% in the faeces (≈ 30% as unchanged drug), with more than 90% of the dose recovered within 7 days [8, 10].

In patients with nmCRPC, no clinically relevant differences in the pharmacokinetics of darolutamide were observed based on age (48–95 years), race (White, Japanese, non-Japanese Asian, Black or African American), mild to moderate renal impairment [estimated glomerular filtration rate (eGFR) 30–89 mL/min/1.73 m^2], or mild hepatic impairment. Relative to healthy volunteers, exposure to darolutamide was increased ≈ 2.5 fold in non-cancer patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m^2) not receiving dialysis and by ≈ 1.9-fold in patients with moderate hepatic impairment (Child Pugh Class B). The effect of end-stage renal disease (eGFR < 15 mL/min/1.73 m^2) or severe hepatic impairment (Child Pugh Class C) on the pharmacokinetics of darolutamide have not been studied [8, 10].

Darolutamide has a low potential for clinically relevant drug-drug interactions. At clinically relevant concentrations, darolutamide did not inhibit major CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) or transporters (MRP2, BSEP, OATs, OCTs, MATEs, OATP2B1 and NCTP). In vitro, darolutamide inhibits BCRP, OATP1B1 and OATP1B3 [10, 17].

No clinically relevant drug-drug interaction is expected with concomitant use of darolutamide and P-gp substrates, CYP3A4 substrates, or inhibitors of CYP3A4, P-gp and BCRP [17]. Darolutamide plasma exposure is increased 1.7-fold when co-administered with the strong CYP3A4, P-gp and BCRP inhibitor itraconazole. No clinically significant effects on the pharmacokinetics of midazolam (sensitive CYP3A4 substrate) or dabigatran (sensitive P-gp substrate) were observed when these drugs were co-administered with darolutamide. Plasma exposure to darolutamide decreased by 72% when co-administered with the strong CYP3A4 and P-gp inducer rifampicin [17]. Concomitant administration of darolutamide and rosuvastatin (a BCRP, OATP1B1 and OATP1B3 substrate) increased plasma exposure to rosuvastatin by ≈ 5-fold [18].

In prespecified and post hoc analyses of the ARAMIS trial in patients with nmCRPC (Sect. 4), there were no clinically relevant effects on the pharmacokinetic profile of darolutamide when co-administered with concomitant drugs commonly used in this patient population, including statins, β-blockers, antithrombotics and systemic antibiotics [18].

4 Therapeutic Efficacy of Darolutamide

The efficacy of oral darolutamide for the treatment of men with nmCRPC was evaluated in the randomized, double-blind, multinational phase 3 ARAMIS trial (Fig. 1) [19]. Eligible patients (median age 74 years) had a baseline PSA level of ≥ 2 ng/mL, a PSADT of ≤ 10 months and Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Patients received darolutamide 600 mg twice daily (n = 955) or placebo (n = 554) until disease progression, discontinuation of treatment because of adverse events (AEs) or withdrawal of consent, with all patients continuing ADT throughout the trial. Patients were stratified at randomization based on the PSADT (≤ 6 or > 6 months) and the use of osteoclast-targeted therapy (yes or no). At baseline, in the darolutamide and placebo groups, the median time since initial diagnosis was ≈ 85 months, the median PSA level was ≈ 9.3 ng/mL, ≈ 68% of patients had median PSADT of ≤ 6 months and ≈ 5% were using osteoclast-targeted therapy [19].

The primary endpoint was MFS (as defined in Table 1), with the primary analysis conducted after 437 events had occurred. At data cut-off (September 2018), the median follow-up was 17.9 months and the median duration of treatment in the darolutamide and placebo groups was 14.8 months and 11.0 months [19].

4.1 Primary Analysis

At the time of primary analysis, darolutamide treatment significantly (p < 0.001) prolonged MFS compared with placebo, with a 59% reduction in the risk of metastasis or death from any cause (Table 1). The beneficial effects of darolutamide over placebo for MFS were generally consistent across all subgroups of patients [all hazard ratios (HRs) < 1; 95% CI did not cross 1, except where patient numbers were limited in the race/ethnic groups of Other and Hispanic/Latino], including those based on randomization stratification factors (PSADT and osteoclast-targeted therapy use) and baseline PSA level, PSA level relative to the median, Gleason score, age, geographic region, presence of regional pathological lymph nodes, ECOG performance status, race/ethnicity (for White and Asian populations) and the number of prior hormonal therapies. Results in subgroups of patients for MFS were consistent with that in the overall population (Table 1) [19]. Given the beneficial effects of darolutamide on MFS in this analysis, the study was unblinded on 30 November 2018 and all patients in the placebo group discontinued study treatment, with 55% of these patients (307 of 554) choosing

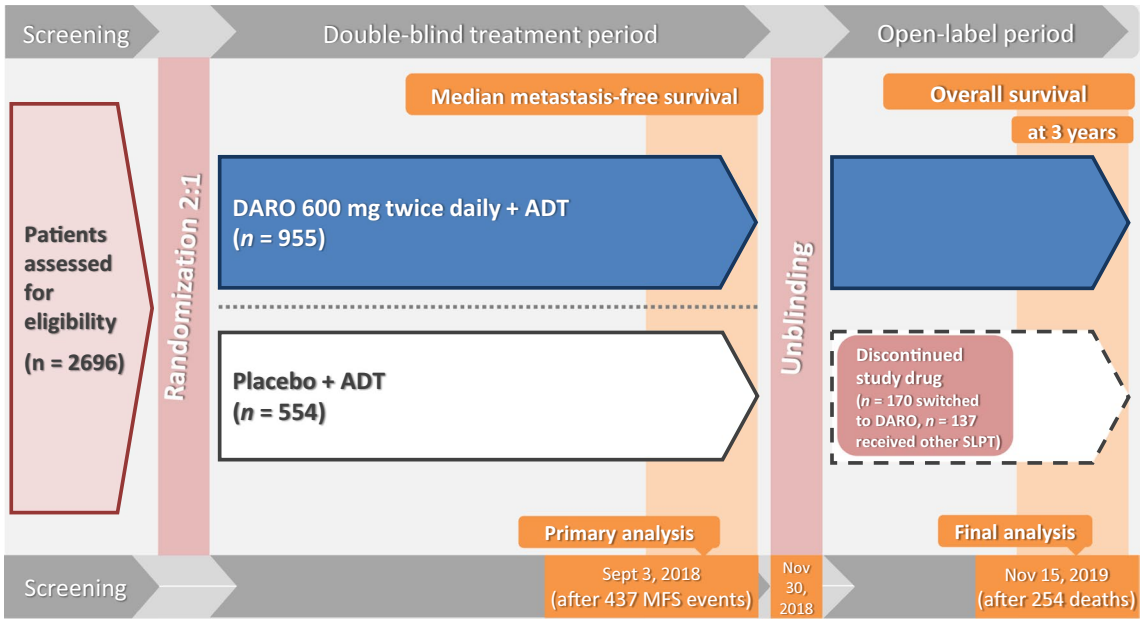

Fig. 1 Trial design of the randomized, double-blind, multinational phase 3 ARAMIS trial in men with non-metastatic castration-resistant prostate cancer [19, 20]. Primary endpoint and final analysis results are reported in the animated figure (available online). *ADT* androgen deprivation therapy, *DAR* darolutamide, *HR* hazard ratio, *MFS* metastasis-free survival, *SLPT* subsequent life-prolonging treatment

Table 1 Efficacy of oral darolutamide 600 mg twice daily in the ARAMIS trial in men with non-metastatic castration-resistant prostate cancer

Endpoint (median time to event; months)	Darolutamide ($n = 955$)	Placebo ($n = 554$))	Hazard ratio vs placebo (95% CI)
Primary analysis (data-cut-off Sep 2018) [19]			
Time to metastasis-free survival[a]	40.4 (95% CI 34.3–NR)	18.4 (95% CI 15.5–22.3)	0.41 (0.34–0.50)***
Overall survival[b]	NR	NR	0.71 (0.50–0.99)*
Time to pain progression[b, c]	40.3	25.4	0.65 (0.53–0.79)***
Time to first cytotoxic chemotherapy[b]	NR	38.2	0.43 (0.31–0.60)***
Time to first symptomatic skeletal event[b, d]	NR	NR	0.43 (0.22–0.84)**
Final overall survival analysis (data cut-off Nov 2019) [20]			
Overall survival[e]	NR	NR	0.69 (0.53–0.88)**
Time to first cytotoxic chemotherapy[e]	NR	NR	0.58 (0.44–0.76)***
Time to first symptomatic skeletal event[e]	NR	NR	0.48 (0.29–0.82)**

Intent-to-treat analyses; randomized, double-blind, international, phase 3 trial

BPI-SF Brief Pain Inventory-Short Form, *NR* not reached

*$p = 0.045$, **$p \leq 0.01$, ***$p < 0.001$ vs placebo

[a]Primary endpoint; time from randomization to confirmed evidence of distant metastasis or death from any cause, whichever occurred first

[b]Secondary endpoints tested in hierarchical order; interim analysis timepoint for all secondary endpoints. The prespecified alpha split between the primary and the final analysis prevented the significance criteria from being met in this interim analysis

[c]An increase of ≥ 2 points from baseline in the BPI-SF questionnaire or initiation of opioid pain relief for cancer pain, whichever occurred first

[d]External-beam radiation therapy to relieve skeletal symptoms, pathological bone fracture, occurrence of spinal cord compression or tumour-related surgical intervention

[e]All analyses for the placebo group included the 170 patients who crossed over from placebo to darolutamide during the open-label study period

to switch to a subsequent life-prolonging therapy, including 170 patients who switched from placebo to open-label darolutamide (placebo → darolutamide crossover group) [20].

Secondary outcomes also supported and were consistent with the beneficial effects of darolutamide over placebo at the time of the primary analysis (interim analysis for these endpoints), including OS and the time to pain progression, time to first cytotoxic chemotherapy and the time to first symptomatic skeletal event (Table 1). However, the prespecified alpha split between the primary and final analysis prevented the significance criteria from being met in this interim analysis. At this time, 78 and 58 patients had died in the darolutamide and placebo groups, with darolutamide treatment reducing the risk of death by 29% relative to placebo (Table 1) [19].

Exploratory time-to-event endpoints also significantly (all $p < 0.001$) favoured darolutamide treatment over placebo at the time of the primary analysis. In the darolutamide and placebo groups, respective median progression-free survival times were 36.8 months and 14.8 months (HR 0.38; 95% CI 0.32–0.45), the median time to PSA progression was 33.2 months and 7.3 months (0.13; 0.11–0.16), the median time to first PC-related invasive procedure was not yet reached in either group (0.39; 0.25–0.61) and the median time to initiation of subsequent antineoplastic therapy was also not yet reached in either group (0.33; 0.23–0.47) [19].

At the time of the primary analysis, the median reduction from baseline in PSA levels in the darolutamide group was 91.7% (median baseline PSA 9.0 ng/mL) versus a 31.9% reduction in the placebo group (9.7 ng/mL). A PSA response (i.e. ≥ 50% decrease from baseline) was achieved by 83.6% and 7.6% of patients in the darolutamide and placebo groups. Prolonged MFS was positively associated with a maximum decrease in PSA from baseline (based on pharmacodynamc modelling), with > 95% of patients who had a maximum decrease in baseline PSA level of > 90% remaining MFS-free at 1 year [21].

Patient-reported health-related quality of life (HR-QOL) was generally similar in the two treatment groups at the time of the primary analysis, although some HR-QOL measure scores favoured (based on 95% CIs) darolutamide over placebo. HRQOL measures favouring darolutamide over placebo included Brief Pain Inventory-Short Form (BPI-SF) pain severity and pain interference scores, Functional Assessment of Cancer Therapy-Prostate (FACT-P) PC subscale and total scores, and the European Organization for Research and Treatment of Cancer QOL questionnaire urinary symptoms subscale (EORTC-QLQ-PR25) score. However, although statistically significant, these between-group differences did not meet the respective clinically meaningful thresholds for each measure [19]. Darolutamide treatment delayed the time to worsening of disease-related urinary symptoms (assessed using EORTC-QLQ-PR25) relative to placebo (25.8 vs 14.8 months; HR 0.64; $p < 0.001$), with no significant between-group difference for the time to deterioration of hormonal treatment-related symptoms (18.9 vs 18.4 months; HR 1.06) [22].

4.2 Final Overall Survival Analysis

The median follow-up at the time of this final analysis was 29.0 months [20]. The median duration of exposure to darolutamide during the combined double-blind and open-label phases was 25.8 months, with exposure in those who crossed over from placebo to darolutamide of 11.0 months [20].

At the time of the final OS analysis (data cut-off 15 November 2019), OS was significantly prolonged in the darolutamide group compared with the placebo group, with the risk of death reduced by 31% in the darolutamide group (Table 1). The beneficial effect of darolutamide on OS occurred despite 55% of patients in the placebo group receiving subsequent life-prolonging therapy for CRPC (31% crossed over to darolutamide). The final OS analysis was conducted after 254 deaths had occurred, 148 in the darolutamide group (darolutamide during the double-blind and open-label phases) and 106 in the placebo group (included patients who had crossed over from placebo to subsequent life-prolonging therapy). In the darolutamide and placebo group, OS rates at 3 years were 83% (95% CI 80–86) and 77% (95% CI 72–81). The beneficial effects of darolutamide over placebo for OS were generally consistent across all prespecified subgroups of patients (HRs < 1), including based on baseline stratification factors of PSADT and use of osteoclast-targeted therapy, although the 95% confidence intervals crossed 1 (i.e. not statistically significant) in some groups [20].

All secondary outcomes significantly favoured darolutamide over placebo treatment at the time of this final analysis, including the time to first cytotoxic chemotherapy and the time to first symptomatic skeletal event (Table 1). The time to pain progression was not updated in the final analysis (see data for interim analysis; Table 1) [20].

Exploratory outcomes also favoured darolutamide over placebo, with darolutamide treatment associated with a longer time to first PC-related invasive procedure (HR 0.42; 95% CI 0.28–0.62) and time to initiation of subsequent antineoplastic therapy (HR 0.36; 95% CI 0.27–0.48) [20].

5 Safety and Tolerability of Darolutamide

Oral darolutamide (+ ADT) was generally well tolerated in the ARAMIS trial in men with nmCRPC, with the nature and incidence of AEs generally similar to that of placebo [19, 20]. No new safety signals were identified during the final analysis, with the safety and tolerability profile of

darolutamide consistent with that in the primary analysis [20].

In the primary analysis, although the majority of patients experienced treatment-emergent AEs (TEAEs; 83% vs 77% in the darolutamide and placebo group), most of these were grade 1 or 2 (55% vs 54%), with grade 3 or 4 TEAEs occurring in 25% and 20% of patients. Overall, 3.9% of patients in the darolutamide group and 3.2% in the placebo group died from TEAEs; one death in the darolutamide group and two in the placebo group were considered by investigators to be related to the trial regimen. TEAEs resulted in study treatment discontinuation in a similar proportion of patients in the darolutamide and placebo groups (8.9% vs 8.7%) [19]. Dose interruptions due to adverse reactions occurred in 13% of patients receiving darolutamide, most frequently because of hypertension (0.6%), diarrhea (0.5%) and pneumonia (0.5%) [10]. Dosage reductions because of adverse reactions occurred in 6% of patients receiving darolutamide, most frequently because of fatigue (0.7%), hypertension (0.3%) and nausea (0.3%) [10]. The tolerability profile of darolutamide was comparable between patients receiving a concomitant statin and those who were not receiving a statin (Sect. 3) [18].

TEAEs of any grade occurring with an absolute ≥ 2% higher incidence in the darolutamide than placebo group were fatigue/asthenia (16% vs 11%; exposure-adjusted incidence 11.3 vs 11.1 patients/100 years of exposure), pain in extremity (6% vs 3%; 4.1 vs 3.2 patients/100 years of exposure) and rash (3% vs 1%; not reported), with very few of these events being of grade 3 or 4 severity (fatigue/asthenia 0.6% vs 1.1%; pain in extremity 0% vs 0.2%; rash 0.1% vs 0%) [19]. Laboratory test abnormalities occurring in the darolutamide and placebo groups were decreased neutrophil count (any grade 20% vs 9%; grade 3–4 4% vs 0.6%), increased aspartate aminotransferase level (any grade 23% vs 14%; grade 3–4 0% vs 0.2%) and increased bilirubin level (any grade 16% vs 7%; grade 3–4 0.1% vs 0%) [10]. Clinically relevant adverse reactions occurring in ≥ 2% of patients receiving darolutamide included ischaemic heart disease (4% vs 3% of patients in the placebo group) and heart failure (2% vs 1%) [10].

AEs of special interest (AESI; i.e. AEs known to be associated with second-generation AR inhibitors) generally occurred with a similar incidence in the darolutamide and placebo groups, including fatigue (any grade 12.1% vs 8.7%; grade 3–4 0.4% vs 0.9%), hypertension (any grade 6.6% vs 5.2%; grade 3–4 3.1% vs 2.2%; 4.7 vs 5.1 patients/100 years of exposure), bone fracture (any grade 4.2% vs 3.6%; grade 3–4 0.9% vs 0.9%; 3.0 vs 3.5 patients/100 years of exposure), falls (any grade 4.2% vs 4.7%; grade 3–4 0.8% vs 0.7%; 2.7 vs 4.1 patients/100 years of exposure), rash (any grade 2.9% vs 0.9%; grade 3–4 0.1% vs 0%) and cognitive disorder (any grade 0.4% vs 0.2%; no grade 3–4 events; 0.3 vs 0.2 patients/100 years of exposure). Although there were slight differences between the darolutamide and placebo group for the incidence of some AESI, these differences either decreased or disappeared after adjustment for treatment duration or observation period [19].

There was no difference in the risk of AEs leading to hospitalization between the darolutamide and placebo groups in post hoc analyses of the ARAMIS trial [23]. The estimated hospitalization rate ratio between the darolutamide and placebo groups was 1.05 (95% CI 0.73–1.45) and the risk for first hospitalization was 0.99 (95% CI 0.73–1.34), as assessed using a binomial regression model and a Cox regression model, respectively [23].

With longer-term follow-up and duration of treatment in the final analysis, the safety profile of darolutamide remained consistent with that of the placebo group, with a generally similar incidence of AEs in each group. Exposure-adjusted incidences of AESI commonly associated with second-generation AR inhibitors that may impact HRQOL (e.g. falls, fractures, rash, cognitive impairment and hypertension) continued to show a ≤ 2% difference between the darolutamide and placebo groups. In the darolutamide group, the only AE to occur with an incidence of > 10% was fatigue (13.2% vs 8.3% in the placebo group). Discontinuation rates due to AEs in the darolutamide and placebo groups were consistent with those in the primary analysis, with similar rates in both groups (8.9% vs 8.7%) [20].

6 Dosage and Administration of Darolutamide

Oral darolutamide is approved in several countries, including EU countries [8], the UK [9], the USA [10] and Japan [11], for the treatment of men with nmCRPC (who are at high risk of developing metastatic cancer [8, 9]). The recommended dosage of darolutamide is 600 mg twice daily, taken with [8, 10] or after food [11]. Medical castration with a luteinizing hormone-releasing hormone analogue [8] or gonadotropin-releasing hormone [10] should be continued during treatment in patients not surgically castrated. If a patient experiences a grade ≥ 3 toxicity or an intolerable adverse reaction, darolutamide treatment should be interrupted or the dosage reduced to 300 mg twice daily until symptoms improve; treatment may then be resumed at a dosage of 600 mg twice daily [8, 10]. Consult local prescribing information for detailed information, including specific indications, contraindications, potential drug-drug interactions, precautions and warnings.

7 Place of Darolutamide in the Management of Non-Metastatic CRPC

The paradigm for treating patients with nmCRPC at high risk of developing metastases has substantially altered in the past decade with the approval of the second-generation AR inhibitors enzalutamide and apalutamide, reflecting their beneficial effects on MFS [3, 4, 6]. Darolutamide, a novel second-generation AR inhibitor, was recently approved for use in nmCRPC (Sect. 6). Current 2020 EU [24], EU/international [25], NCCN [26] and international advanced prostate cancer consensus [27] guidelines recommend darolutamide, enzalutamide and apalutamide for treating men with nmCRPC at high risk of developing metastasis; NCCN guidelines also recommend secondary hormone therapy [26]. Continuation of ADT to maintain castrate serum testosterone levels of < 50 ng/dL is mandatory; monitoring (typically using PSA, physical examination, repeat biopsy and/or imaging dependent on previous PC treatment) is recommended in patients whose PSA levels do not increase [24–27].

In the pivotal phase 3 ARAMIS trial in men with nmCRPC and at high risk of metastasis, relative to placebo (+ ADT), darolutamide (+ ADT) significantly prolonged MFS at the time of the primary analysis (Sect.4.1) and significantly prolonged OS at the time of the final OS analysis (Sect. 4.2). Other secondary outcomes also favoured darolutamide over placebo, including median times to pain progression, to first cytotoxic chemotherapy and to first symptomatic skeletal event. Furthermore, the beneficial effects of darolutamide in prolonging MFS at the time of the primary analysis and OS at the time of the final OS analysis were observed in the vast majority of prespecified subgroups of patients, including those based on randomization stratification factors (PSADT and osteoclast-targeted therapy). At the time of the primary analysis, darolutamide maintained HR-QOL (Sect. 4.1).

Darolutamide (+ ADT) was generally well tolerated in men with nmCRPC, with a safety and tolerability profile that was generally similar to that of placebo during the ARAMIS trial (Sect. 5). Furthermore, there was no change in discontinuation rates due to AEs in the final analysis compared with the primary analysis indicating that darolutamide is generally well tolerated with longer-term treatment. Most AEs were of mild to moderate severity and relatively few patients discontinued treatment because of these events. Although ongoing clinical experience is required to fully define the long-term safety profile of darolutamide (+ ADT), no new safety signals were identified at a median follow-up of 29.0 months in the final analysis of ARAMIS. AESI generally occurred at a similar low incidence in the darolutamide and placebo groups in ARAMIS, including the incidence of fatigue, fractures, falls, rash, mental impairment and hypertension. Albeit there are no head-to-head comparisons, unlike clinical trials of enzalutamide + ADT (PROSPER [28]) and apalutamide + ADT (SPARTAN [29]), in which both AR inhibitors were associated with a higher incidence of falls and fractures than placebo + ADT, there was ≤ 2% difference in the incidence of these events between the darolutamide and placebo groups in ARAMIS despite very few patients (3%) using osteoclast-targeted therapies at randomization (Sect. 5).

Unlike the PROSPER [28] and SPARTAN [29] trials, ARAMIS permitted patients with a history of seizures to enrol [19], with preclinical and clinical data suggesting a low propensity for darolutamide to exhibit any proconvulsive potential [30]. In ARAMIS, the incidence of seizures, dizziness and cognitive impairment in the darolutamide group were similar to those in the placebo group (Sect. 5), for the most part, reflecting the low penetration of darolutamide across the BBB (Sect. 2). By contrast, relative to placebo, CNS-related disorders (e.g. mental-impairment disorders and dizziness) occurred more frequently in the enzalutamide and apalutamide groups than in the placebo group in PROSPER [28] and SPARTAN [29], with seizures also occurring with a higher incidence in the enzalutamide than placebo group [28]. These data are supported by a matching-adjusted indirect comparison (MAIC), in which darolutamide was associated with significantly ($p < 0.05$) lower incidences of fall, dizziness, cognitive impairment, hypertension and fatigue than enzalutamide and significantly ($p < 0.05$) lower incidences of fall, fracture and rash than apalutamide (abstract) [31]. This differential aspect of safety is an important consideration in the selection of second-generation AR inhibitors, particularly in men with nmCRPC where an increased propensity for seizures, dizziness and cognitive impairment may discourage clinical utilization of enzalutamide and apalutamide. Indeed, surveys of physician [32] and patient and caregiver benefit-risk preferences [33] suggest that from both groups preferred treatments associated with a lower risk of AEs and were prepared to forego OS to reduce the risk of AEs.

To date, there have been no prospective head-to-head trials comparing darolutamide with other second-generation AR inhibitors or other treatment options for nmCRPC; such trials would be of interest in determining their relative role in nmCRPC. A systematic review and network meta-analysis demonstrated similar efficacy between darolutamide, apalutamide and enzalutamide (all + ADT) with respect to MFS and, relative to placebo, a similar risk of serious AEs or grade 3 or 4 AEs [34]. Results from a MAIC demonstrated there were no statistically significant differences between darolutamide and enzalutamide or darolutamide and apalutamide based on HRs for MFS (abstract) [35]. Given the

inherent limitations of such analyses, these data should be interpreted with caution. Ultimately, several factors should be considered when deciding on treatment for nmCRPC, including patient preferences and characteristics (e.g. age, presence of comorbidities), and drug properties (e.g. availability, costs, potential drug interactions and tolerability).

In conclusion, darolutamide + ADT prolonged MFS and OS relative to placebo + ADT and was generally well tolerated in the multinational phase 3 ARAMIS trial in men with nmCRPC. Albeit long-term data from the real-world setting are required to fully define the safety profile of darolutamide, current evidence from the final ARAMIS analysis indicates that darolutamide has a low propensity for CNS-related AEs associated with other currently approved second-generation AR inhibitors. Given the efficacy and safety evidence from the final ARAMIS analysis and the key role of second-generation AR inhibitors in the management of nmCRPC, darolutamide + ADT represents an important emerging option for the treatment of men with nmCRPC who are at high risk of developing metastatic prostate cancer.

Data Selection Darolutamide: 140 records identified	
Duplicates removed	34
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	52
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	19
Cited efficacy/tolerability articles	5
Cited articles not efficacy/tolerability	30
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were darolutamide, NUBEQA, non-metastatic castration-resistant prostate cancer. Records were limited to those in English language. Searches last updated 9 November 2020	

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