CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Darolutamide (Nubeqa) for non-Metastatic Castration Resistant Prostate Cancer

April 22, 2020

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LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
AR	Androgen receptor
BICR	Blinded independent central review
BPI-SF	Brief pain inventory – short form
CGP	Clinical Guidance Panel
CI	Confidence interval
Crl	Credible interval
CT	Computed tomography
CYTOC	Cytotoxic chemotherapy
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-PR25	European Organization for Research and Treatment of Cancer Quality of life Questionnaire - Prostate Cancer Module
EQ-5D-3L	European Quality of Life 5-Domain Scale
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FACT-P PCS	Functional Assessment of Cancer Therapy-Prostate Prostate cancer subscale
FDA	Food and Drug Administration of the United States
HR	Hazard ratio
HRQoL	Health-related quality of life
ITC	Indirect-treatment comparison
ITT	Intent-to-treat population
MCMC	Markov Chain Monte Carlo
MCID	Minimally clinical important difference
MFS	Metastasis-free survival
MRI	Magnetic resonance imaging
NMA	Network meta-analysis
nmCRPC	Non-metastatic castration-resistant prostate cancer
OS	Overall survival
PFS	Progression-free survival
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time
SAE	Serious adverse event
SSE	Symptomatic skeletal event
TEAE	Treatment emergent adverse events
VAS	Visual analog scale

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding darolutamide (Nubeqa) for non-metastatic castration resistant prostate cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding darolutamide (Nubeqa) for non-metastatic castration resistant prostate cancer conducted by the Genitourinary Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on darolutamide (Nubeqa) for non-metastatic castration resistant prostate cancer, a summary of submitted Provincial Advisory Group Input on darolutamide (Nubeqa) for non-metastatic castration resistant prostate cancer, and a summary of submitted Registered Clinician Input on darolutamide (Nubeqa) for non-metastatic castration resistant prostate cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of darolutamide in combination with androgen depravation therapy (ADT) for patients with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastases (high risk defined as prostate-specific antigen (PSA) doubling time ≤ 10 months) during continuous ADT and who have a good Eastern Cooperative Oncology Group (ECOG) performance status.

Darolutamide is a next-generation androgen receptor inhibitor that binds to the ligand-binding domain of the androgen receptor, which prevents the synthesis of androgens; a mechanism that is distinct from the first generation anti-androgens. Darolutamide has been issued marketing authorization without conditions for the treatment of patients with nmCRPC. The Health Canada Product Monograph (PM) also notes that darolutamide has not been studied in patients with nmCRPC at low risk of developing metastatic disease. The benefit and risk profile in these patients is unknown.

Note that the Health Canada indication differs slightly from the pCODR reimbursement request, in that the Health Canada PM does not specify that patients be at 'high risk of developing metastases (high risk defined as prostate-specific antigen (PSA) doubling time ≤ 10 months) during continuous ADT' and 'have a good Eastern Cooperative Oncology Group (ECOG) performance status'.

The recommended dose of darolutamide (Nubeqa) is 600 mg (two film-coated tablets of 300 mg) administered orally twice daily, equivalent to a total daily dose of 1200 mg. If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Then treatment may be resumed at a dose of 600 mg twice daily. Dose reductions below 300 mg twice daily is not recommended. The maximum daily dose is 1200 mg (600 mg twice daily).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

ARAMIS Trial

The pCODR systematic review included one ongoing, randomized, double-blind, placebo-controlled, phase III trial (ARAMIS) that assessed the safety and efficacy of darolutamide as compared to placebo in men with nmCRPC and a PSA doubling time of 10 months or less. A total of 1,509 men were randomized to receive either 600 mg [two 300-mg tablets] of darolutamide twice daily (N=955) or placebo (N=554) while continuing androgen-deprivation therapy.

Patients were included in the trial if they met the following criteria: 18 years of age or older; histologically or cytologically confirmed adenocarcinoma of the prostate; castration-resistant prostate cancer; a baseline PSA level of at least 2 ng per milliliter; a PSA doubling time of 10 months or less; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.[1] Patients were excluded if they had detectable metastases or a history of metastatic disease; however, patients with the presence of pelvic lymph nodes less than 2 cm in diameter in the short axis below the aortic bifurcation were included in the trial. Patients who had a history of previous seizure or conditions predisposing to seizure were not excluded from participating in the trial.[1] Further details on the inclusion criteria and exclusion criteria are provided in Table 6.2.

Disease assessments, including CT and MRI, were performed by a blinded independent central review (BICR) every 16 weeks from Cycle 1 Day 1 until confirmed metastasis. Assessments could be performed if distant metastases were suspected. PSA levels were measured at a central laboratory and it was assessed on Day 1 of Cycles 1 to 6, on Day 1 every 2 cycles starting from Cycle 7 to Cycle 13, and at the end of treatment.[2]

Overall, the baseline characteristics of patients in the ARAMIS trial were well balanced between the two treatment groups.[1] The median age in both treatment arms was 74 years (darolutamide range: 48-95 and placebo range: 50 to 92). The median PSA doubling time at baseline was 4.4 months (range: 0.7 to 11.0) in the darolutamide arm and 4.7 months in the placebo arm (range: 0.7 to 13.2).[1] The median time from initial prostate cancer diagnosis to randomization was 86.2 months in the darolutamide group and 84.2 months in the placebo group.[3] As compared to the darolutamide group, slightly more patients in the placebo group had a history of treatment with a bone sparing agent (6% vs 3%), presence of lymph nodes on central imaging review (<2cm) (10.5% vs 11.9%) and an ECOG performance status of 0 (71% vs 68%); however, patients in both group had a similar proportion for those who have received two or more previous hormonal therapies (76% for both).[1]

Efficacy Outcomes

The primary endpoint in the ARAMIS trial was metastasis-free survival (MFS). Secondary outcomes were overall survival (OS), time to pain progression, time to cytotoxic chemotherapy and time to first symptomatic skeletal event (SSE). The main exploratory outcomes were progression-free survival (PFS), time to PSA progression, PSA response rate, health-related quality of life (HRQoL) and safety.

The trial was composed of two analysis populations: the intention-to-treat (ITT) population and the safety set population.[4] The efficacy analyses were conducted in the ITT population, which was composed of all randomized patients regardless of the actual treatment they received. The safety analyses were conducted in the safety set population, which was composed of all patients that received at least one dose of the study drug.[4]

The trial was designed to have 91% power to detect a hazard ratio (HR) of 0.71 for MFS with a two-sided significance level (α) of 0.05.[1] The assumed HR was 0.65 but a diluted HR of 0.71 was chosen to account for the 5% of patients with baseline metastasis.[2] Based on the results of a phase 3 study of denosumab versus placebo in high risk nmCRPC patients,[5] the median MFS was assumed to be 25 months in the placebo group. Approximately 1500 patients (1000 in the darolutamide group and 500 in the placebo group) were planned to be randomized and it was estimated that 385 MFS events were required for the primary analysis.[6] The trial was originally designed to detect a HR of 0.75 for MFS; however, based on the results from the PROPSER and SPARTAN trials, it was decided that the HR of 0.75 was too conservative. In June 2018, the FDA agreed to change the target HR from 0.75 to 0.65 thereby reducing the targeted number of MFS events from 572 to 385.[2]

The 03-September-2018 database cut-off represents the final analysis for MFS and an interim analysis for the secondary endpoints.[1] The final analysis for OS and the other secondary outcomes occurred on 15-November-2019.[7]

MFS was the primary outcome in the trial. At the 03-September-2018 data cut, 23.1% of patients in the darolutamide group had a metastasis or died (N = 221) as compared to 39.0% of patients in the placebo group (N=216).[1] The median MFS in the darolutamide group was 40.4 months (95% CI: 34.3 to not reached [NR]) and it was 18.4 months (95% CI: 15.5 to 22.3) in the placebo group[1] [redacted].[8] (*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* Fizazi et al (2019) reported that treatment with darolutamide was associated with statistically significant prolonged MFS as compared to placebo (HR: 0.41, 95% CI: 0.34 to 0.50; P<0.001) (Table 1.1).[1] Sensitivity analyses were conducted to explore the effect of including patients in the primary analysis of MFS with baseline metastasis. Here, the 89 patients with baseline metastases were censored at the date of randomization.[2] The median MFS in the darolutamide group was 40.5 months (95% CI: 35.8 to NR) and it was 22.1 months (95% CI: 18.3 to 25.8) in the placebo group.[2] The sensitivity demonstrated a similar protective treatment effect of darolutamide on MFS as compared to placebo (HR: 0.356, 95% CI: 0.287 to 0.441).[1]

For the primary analysis of MFS, the secondary endpoints will be tested in the pre-specified sequence shown above. If at any point a secondary endpoint is not significant at the interim analysis, it will then be tested at final analysis followed by the remaining endpoints in the testing sequence. A similar strategy was employed for the final OS analysis.[7]

OS was a secondary outcome in the trial. Approximately, eight percent of the patients in the darolutamide group died (8.2%; N = 78) while 10.5% of patients in the placebo group died (N=58).[2] The median OS in the darolutamide and the placebo groups was not reached.[1] There was no statistically significant difference between darolutamide and placebo on the effect of OS (HR: 0.71, 95% CI: 0.50 to 0.99; P= 0.045) (Table 1.1).[1] Although these results suggest that darolutamide has a protective effect on OS, the prespecified alpha split (α =0.05) between the primary and secondary outcomes was not met.[1] Since OS was not statistically significant, the remaining key secondary endpoints in the testing of the hierarchical gatekeeping procedure (i.e., time to pain progression, time to initiation of cytotoxic chemotherapy, and time to first SSE), were summarized descriptively and no statistical inference could be made at the time of the primary analysis. At the 15-November-2019 database lock, darolutamide was associated with statistically significant prolonged OS as compared to placebo (HR: 0.685, 95% CI: 0.533 to 0.881; P=0.003).[7]

Details of the secondary and exploratory outcomes are presented in Table 1.1. Chemotherapy-free survival and chemotherapy-free disease-specific survival was not reported in the trial.

Quality of Life

In the ARAMIS trial, HRQoL was measured using the following instruments: Brief pain inventory – short form (BPI-SF), European Organization for Research and Treatment of Cancer Quality of life Questionnaire - Prostate Cancer Module (EORTC-QLQ-PR25), European Quality of Life 5-Domain Scale (EQ-5D-3L), Functional Assessment of Cancer Therapy-Prostate (FACT-P) and the FACT-P Prostate cancer subscale (PCS).

The 100% completion rates for BPI-SF were high (> 90% for both groups) until the end of the study treatment visit.[2] The 100% completion rates were calculated by the Sponsor in response to the FDA. The 100% completion rates measure the completion rates among those who are expected to have completed all questions for each patient-related outcome (PRO) assessments.[2] The baseline BPI-SF scores were similar across treatment groups and remained stable over time. There was a significant decrease in both the BPI-SF pain interference and pain severity scores at Week 16 but the minimally clinical important difference (MCID) was not reached.[1] In addition, the pain interference score and pain severity score results favoured darolutamide (lower scores represent less pain) and were statistically significant but were not clinically meaningful, as the difference in least squares mean between the MCID threshold (MCID=2 points).[7]

The 100% completion rates for FACT-P were low (< 50%) but the FACT-P PCS subscale had a higher 100% completion rate for both treatment groups until the end of the study treatment visit (> 80%).[2] The baseline FACT-P total score was similar for both treatment groups and remained stable over time. There was a significant increase in the FACT-P total score at Week 16; however, the MCID was not reached.[1] Similar results were observed for the FACT-P PCS score.[1]

The 100% completion rates for EORTC-QLQ-PR25 were high (> 85% for both groups) until the end of the study treatment visit.[2] The baseline EORTC-QLQ-PR25 urinary symptoms score was similar for both treatment groups and remained stable over time. There was a significant increase in the EORTC-QLQ-PR25 urinary symptoms scale at Week 16; however, the MCID was not reached.[1]

The 100% completion rates for the EQ-5D-3L were high (> 90% for both groups) until the end of the study treatment visit.[2] The baseline EQ-5D-3L was similar for both treatment groups and remained stable over time. There was no difference in between the two treatment groups and the MCID was not reached.[1] Similar results were observed for the EQ-5D-3L visual analog scale (VAS).[1][NEJM]

Harms Outcomes

There was a total of 1,498 patients in the safety set, with 954 patients in the darolutamide group and 554 patients in the placebo group.[1] Overall, slightly more treatment-emergent adverse events (TEAEs) of any grade occurred in the darolutamide as compared to the placebo group (83.2% versus 76.9%).[1] Similar patterns were observed for grade 3 or 4 TEAEs (darolutamide: 24.7% versus placebo: 19.5%).[1] More patients in the darolutamide group had a serious adverse event (SAE) as compared to the placebo group (24.8% vs 20.0%).

Nine percent of patients in the darolutamide and placebo treatment groups discontinued their assigned therapies due to an AE (darolutamide N = 85 and placebo N = 48).[2] More patients in the darolutamide group (6%; N = 52) had an AEs that led to a dose reduction as compared to those in the placebo group (1.3%; N=7).[2] Moreover, 13% of patients in the darolutamide group had a dose interruption due to an AEs relative to 9% of patients in the placebo group (darolutamide N = 119 and placebo N = 48).[2]

Fizazi et al (2019) reported that one death in the darolutamide group and two deaths in the placebo group were drug-related.[1]

Limitations

Overall, ARAMIS was a well-designed RCT because it used several methods to minimize bias. The strengths of the trial include:

- The ARAMIS trial used a double-blind study design to minimize bias in the assessment of all study outcomes. Furthermore, the investigators, patients and sponsor were blinded to the results until the time of the primary analysis.

- A 2:1 randomization ratio was used to increase the probability that eligible patients would be randomized to receive darolutamide and to increase feasibility. In addition, a stratified randomization procedure based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results.

- Analyses of efficacy endpoints were based on radiographic tumor assessments by BICR.

- The primary outcome in the ARAMIS trial was MFS. Several studies have demonstrated that MFS is a valid surrogate endpoint for OS in the localized setting and is a clinically meaningful endpoint for men with nmCRPC.[9,10]

There are also some limitations in the trial that warrant discussion, more specifically:

- In the ARAMIS trial, two independent BICR reader pools assessed patients for eligibility and efficacy. It was noted that during the central efficacy imaging review some patients were retrospectively classified as having metastases at baseline.[1] Here, 50 patients in the darolutamide group and 39 in the placebo group were misclassified as metastasis-free at baseline. These patients were included in the primary analysis of MFS; however, an additional sensitivity analysis was conducted whereby events of baseline metastases were censored to explore the effect of the trial design flaw. The results of this sensitivity analysis showed a consistent treatment benefit in favor of darolutamide.[2]

- Although the statistical analysis of secondary outcomes used a hierarchical gatekeeping procedure to control for type 1 error, OS was not statistically significant at this interim analysis because the prespecified alpha split (α =0.05) between the primary and secondary outcomes was not met.[1] Here, the alpha spending function was used for sequential testing of the secondary variables and a predefined interim alpha significance level of 0.0005 was used for OS.[2] Thus, the remaining key secondary endpoints in the testing hierarchy (i.e., time to pain progression, time to initiation of cytotoxic chemotherapy, and time to first SSE) were summarized descriptively and no statistical inferences should be made at the time of the OS interim analysis

- Patients randomized to placebo in the treatment phase of the trial were permitted to cross-over and receive darolutamide during the open-label phase. However, this cross-over could confound the results of the final OS analysis and other secondary outcomes.

- Patient-reported and HRQoL outcomes were exploratory endpoints in the ARAMIS trial.

- All the subgroup analyses should be considered exploratory or hypothesis generating due to small sample sizes and the descriptive nature of the analysis.

Table 1.1: Highlights of Key Efficacy Outcomes from the ARAMIS trial

Efficacy outcomes	ITT population	
	Darolutamide (N = 995)	Placebo (N = 554)
Primary Outcome		
MFS		
Number of events (%)	221 (23.1)	216 (39.0)
Median time to event, months (95% CI)	40.4 (34.3, NR)	18.4 (15.5, 22.3)
HR (95% CI)	0.41 (0.34, 0.50)	
p-value	< 0.001	
Key Secondary Outcomes		
Overall Survival (interim analysis)[B]		
Number of events (%)	78 (8.2)	58 (10.5%)
Median, months (95% CI)	NR	NR
HR (95% CI)	0.71 (0.50, 0.99)	
p-value	0.045 [A]	
Overall Survival (final analysis) [C]		
Number of events (%)	148 (15.5)	106 (19.1%)
Median, months (95% CI)	NR	NR
HR (95% CI)	0.685 (0.533, 0.881)	
p-value	0.003 [A]	
Time to pain progression (interim analysis)[B]		
Number of events (%)	251 (26.3)	178 (32.0)
Median time to event, months (95% CI)	40.3 (33.2, 41.2)	25.4 (19.1, 29.6)
HR (95% CI)	0.65 (0.50, 0.79)	
Time to first use of cytotoxic chemotherapy (interim analysis) [B]		
Number of events (%)	73 (7.6)	79 (14.3)
Median, months (95% CI)	NR	38.2 (35.5, 41.9)
HR (95% CI)	0.43 (0.31, 0.60)	
Time to first use of cytotoxic chemotherapy (final analysis)[C]		
Number of events (%)	127 (13.3)	98 (17.7)
Median, months (95% CI)	NR	NR
HR (95% CI)	0.579 (0.444, 0.755)	
p-value	0.00004	
Time to first SSE (interim analysis) [B]		
Number of events (%)	16 (1.7)	18 (3.2)
Median, months (95% CI)	NR	NR
HR (95% CI)	0.43 (0.22, 0.84)	
Time to first SSE (final analysis)[C]		
Number of events (%)	29 (3.0)	28 (5.1)
Median, months (95% CI)	NR	NR
HR (95% CI)	0.484 (0.287, 0.815)	
p-value	0.0053	
Exploratory Outcomes		
Progression-free survival [B]		
Number of events (%)	255 (26.6)	258 (46.6)
Median time to event, months (95% CI)	36.8 (32.9, NR)	14.8 (11.8, 18.4)
HR (95% CI)	0.38, 95% CI: 0.32 to 0.45	
Time to PSA progression [B]		
Number of events (%)	226 (23.7)	368 (66.4)
Median time to event, months (95% CI)	33.2 (25.9, NR)	7.3 (3.9, 7.4)
HR (95% CI)	0.13 (0.11, 0.16)	
Time to initiation of subsequent antineoplastic therapy [B]		
Number of events (%)	48 (5.0)	70 (12.6)
Median, months (95% CI)	NR	NR
HR (95% CI)	0.33 (0.23, 0.47)	

CI = confidence interval, **HR** = hazard ratio, **ITT** = intent-to treat, **MFS** = metastasis-free survival, **NR** = not reached, **PSA** = prostate-specific antigen, **SD** = standard deviation, **SSE** = symptomatic skeletal event

Efficacy outcomes	ITT population	
	Darolutamide (N = 995)	Placebo (N = 554)

[A] p-values are provided for descriptive purposes and are no statistical inferences can be made.
[B] Database cut-off 03-September-2018.
[C] Database cut-off 15-November-2019.

Sources: Fizazi et al (2019); FDA;[2] Additional Information provided by the Sponsor.[7]

1.2 2. Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

One patient advocacy group, the Canadian Cancer Survivor Network (CCSN), provided input for darolutamide (Nubeqa) for non-metastatic castration resistant prostate cancer (nmCRPC).

The symptom most affecting patient's quality of life due to prostate cancer was reported to be erectile dysfunction. Erectile dysfunction was also a reported side effect of treatments patients were currently taking. Some quotes suggest that patients wish to have been better informed about the issues with erectile dysfunction.

Of the five patients with direct experience with darolutamide that CCSN conducted qualitative interviews with, all reported that there were no side effects experienced while they were receiving darolutamide. Men commented on being able to engage in daily activities while taking darolutamide and maintain a good quality of life. In general, the men reported positive experiences with darolutamide and would recommend it as an option for other patients with prostate cancer. However, one patient did indicate feelings of nausea if they took darolutamide without food. One patient experienced issues with their cardiovascular health, CCSN stated that he still thought the benefits of darolutamide outweighed the side effects. Overall, from a patient's perspective, patients value treatments that allow them to maintain their quality of life, have reduced side effects (e.g., erectile dysfunction), and lead to a longer life.

Provincial Advisory Group (PAG) Input

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Comparative information with apalutamide or enzalutamide

Economic factors:

- Twice daily whereas apalutamide and enzalutamide are taken once daily

Registered Clinician Input

Input was received from 10 individual clinicians and two joint clinician inputs on behalf of Prostate Cancer Canada (PCC, representing four clinicians) and Cancer Care Ontario (CCO, representing three clinicians) for the review for darolutamide (TBD) for non-metastatic

castration resistant prostate cancer (nmCRPC). Overall, input was received from 17 clinicians from Alberta, Ontario, Nova Scotia, New Brunswick, and British Columbia.

Eligibility criteria of the ARAMIS trial were considered as being clinically relevant and applicable to practice. Unmet need for nmCRPC patients was highlighted as they represent a relatively new patient group with minimal available treatment options. Apalutamide and enzalutamide were stated to be the most appropriate comparators to darolutamide, although neither treatment is currently funded in Canada; only ADT is currently funded for patients with nmCRPC. Patients may access apalutamide and enzalutamide through compassionate access programs. Compared to apalutamide and enzalutamide, darolutamide was stated to show similar efficacy but a potentially favourable side effect profile. However, it was acknowledged that no direct comparative evidence between apalutamide, enzalutamide and darolutamide exists.

Clinicians agreed that generalization of evidence for darolutamide to patients who had received prior chemotherapy was acceptable. Clinicians expressed mixed opinions regarding generalization to patients who had received prior immunotherapy; a lack of evidence to support the use of darolutamide for these patients was acknowledged, however some clinicians highlighted that patients who received immunotherapy would be unfairly disadvantaged for participating in a clinical trial. All clinicians agreed that a PSA doubling time of ≤ ten months and an ECOG performance status of 0 or 1 were acceptable eligibility criteria for darolutamide. One clinician stated that androgen receptor inhibitors are generally benign and may be worth using on patients with poorer ECOG performance status.

Should patients progress on darolutamide, clinicians did not support the use of another anti-androgen therapy as a subsequent treatment. Enzalutamide and apalutamide were acknowledged to have the same mechanism of action as darolutamide, and clinicians mentioned prior studies showing non-durable responses in patients who received one anti-androgen after another. Chemotherapy was identified as the most appropriate treatment for nmCRPC patients after progression on darolutamide. Overall, darolutamide was considered to be a "nice to have" therapy in addition to apalutamide and enzalutamide. All three treatments were considered similar in efficacy. However, clinicians appreciated the option of darolutamide as it may have a favourable side effect profile that requires less monitoring and can be useful to patients with seizure history and comorbidities.

Summary of Supplemental Questions

The Sponsor-Provided ITC and NMA compared darolutamide to apalutamide and enzalutamide in patients with nmCRPC who are at high risk of developing metastases during continuous ADT and who have a good ECOG performance status. The results of the ITC and NMA suggest that darolutamide increases the risk of MFS as compared to apalutamide and enzalutamide. In addition, there was no statistical differences between darolutamide, apalutamide and enzalutamide for OS.

The Sponsor-Provided ITC and NMA was conducted using the relevant patient population (i.e., patients with high risk nmCRC). The patient populations of the ARAMIS, PROSPER and SPARTAN studies aligned with the indication under review (i.e., patients with nmCRPC). The indirect comparisons included relevant efficacy outcomes, such as MFS and OS but there were no analyses conducted for any safety endpoints or HRQoL. The Sponsor-Provided NMA was limited to the use of fixed-effects models. However, given the lack of trials included in the NMA this was deemed appropriate.

There are a few limitations of the Sponsor-Provided ITC and NMA that warrant discussion. First, there was no literature search strategy or study selection process provided. Similarly, there were no methodological details reported regarding data extraction and it was not reported if a risk of bias assessment was performed by the Sponsor. Therefore, there are some concerns regarding missing studies from this analysis and the absence of formal risk of bias assessment. However, the Sponsor stated that to date there are only three phase 3, randomized, placebo controlled clinical trials that have assessed the efficacy and safety of androgen receptor-axis-targeted therapies, which include: SPARTAN, PROSPER and ARAMIS.[3] Secondly, there was a high degree of heterogeneity among the ARAMIS, PROSPER and SPARTAN trials. This implies that there may be systematic differences between the patient populations among the three included studies. Although the Sponsor did adjust for differences in censoring across the three trials, the other sources of known heterogeneity may potentially confound the outcomes of interest because they were not captured in the prediction models. It should be noted that the bias resulting from missing prognostic factors is very difficult to quantify, and as a result, it is unclear what impact the missing prognostic factors have on the results of the ITC and NMA. In fact, given the heterogeneity among the trials, the Sponsor has stated the estimates from the ITC and NMA should be considered unreliable. Additionally, the Sponsor-Provided ITC and NMA was completed by external consultancy groups hired by the submitter. As a result, the information provided in the reports should be viewed considering this potential conflict of interest and lack of peer-review. Due to the above limitations, the comparative efficacy estimates obtained are likely biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with darolutamide.

The CADTH Methods Team identified four additional abstracts that reported on indirect treatment comparisons of darolutamide versus apalutamide and enzalutamide.[11-14] Due to the limited information available from the abstracts, the CADTH Methods Team was not able to perform a critical assessment and to provide detailed summaries. The efficacy results appeared to be similar to those reported in the Sponsor-Provided ITC and NMA[11-13] but the safety results appear to be variable.[11-14] This variability may be due to differences in what studies were included in the ITC or NMA and the methodologies that were implemented to build the network. The abstract by Altavilla et al (2019) will be described in more detail.[15]

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2: Assessment of generalizability of evidence for darolutamide for non-metastatic castration resistant prostate cancer

Domain	Factor	Evidence (ARAMIS trial)	Generalizability Question	CGP Assessment of Generalizability
Population	Performance status	The included trial limited eligibility to patients with an ECOG performance status of 0 or 1.	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The benefit for patients with ECOG 2 cannot be formally concluded from the study, however it would be reasonable to expand darolutamide to patients with a good performance status, based on clinical experience and the manageable side-effect profile of similar drugs as seen in the metastatic CRPC setting.
	Definition of castration resistant prostate cancer	ARAMIS required that patients have three PSA rises at least one week apart with the last PSA more than 2 ng/ml.	If different criteria are used to define castration resistance in the Canadian practice, are the results of the trial applicable in the Canadian setting?	The CGP feels that the definition of castration resistant prostate cancer used in the ARAMIS trial is clinical reasonable, based on available evidence, and applies to the Canadian practice setting. The prostate cancer working group (PCWG) is the generally accepted definition and ARAMIS used that definition and then selected the high-risk group. Hence, the results of the ARAMIS trial can be generalized to the PCWG definition.
	Risk of metastasis	ARAMIS required study participants to be at high risk for development of metastases, defined as PSADT≤ 10 months, during continuous ADT.	Are the results of the trial generalizable to patients with PSADT>10 months or patient with other high risk features (high Gleason score or baseline PSA levels) who have had no PSA progression in the non-metastatic setting?	Interpretation of the trial results applies to patients at high risk for progression as defined in the ARAMIS trial (PSADT≤ 10 months). There are no data to support use of darolutamide in patients with PSADT > 10 months. Patients without the high-risk features as defined in the ARAMIS trial can have prolonged, indolent course of disease and it is unclear how much benefit they would derive from darolutamide. As such the ARAMIS results cannot be generalized to high risk patients (e.g., Gleason score 8-10, high PSA at diagnosis, etc.) who have not had a PSA

Domain	Factor	Evidence (ARAMIS trial)	Generalizability Question	CGP Assessment of Generalizability
				progression in the non-metastatic setting.
Intervention	Prior treatments	ARAMIS excluded patients who received prior chemotherapy for prostate cancer, except if administered in the adjuvant/neoadjuvant setting.	Are the results of the trial generalizable to patients who received prior chemotherapy?	The CGP feels that these are reasonable exclusion criteria, based on available evidence. Prior chemotherapy (except in the adjuvant/neoadjuvant setting) was not permitted in the ARAMIS trial and these patients should be excluded from darolutamide treatment. However, the CGP felt that darolutamide would be a reasonable treatment option for patients who received chemotherapy in the adjuvant/neoadjuvant setting.
		The trial also excluded patients with a history of treatment with second generation anti-androgens (e.g., enzalutamide).	Are the results of the trial generalizable to patients who received prior treatment with second generation anti-androgens?	History of treatment with second generation anti-androgens was not permitted in ARAMIS and these patients should be excluded from darolutamide treatment.
		ARAMIS included patients who already receive a first generation anti-androgen (e.g. bicalutamide, flutamide, nilutamide) if they had at least a 28-day washout prior to randomization and showed continuing disease (PSA) progression (an increase in PSA) after washout. The majority of patients in the ARAMIS trial (in both treatment groups) had already received a combination of ADT and at least two or more previous hormonal agents.	Are the results of the trial generalizable to patients who had already started ADT plus an anti-androgen?	All of these patients had to have been on androgen deprivation therapy either with a LHRH antagonist alone or a LHRH plus an antiandrogen. If they had been on both the antiandrogen was to be stopped and PSA observed. That reflects a clinical standard. Hence it is fully generalizable.
		The majority of patients in the ARAMIS trial (in both treatment groups) had received two or more prior hormonal therapies.	Are the results of the trial generalizable to patients who are undergoing secondary hormonal manipulation (e.g., changing bicalutamide to megestrol acetate, or	The results are fully generalizable to patients undergoing secondary hormonal manipulation. These secondary hormone maneuvers are part of standard therapy for hormone sensitive disease and can be tried. They are usually not very effective and the CGP considered that the introduction of darolutamide will

Domain	Factor	Evidence (ARAMIS trial)	Generalizability Question	CGP Assessment of Generalizability
			antiandrogen withdrawal)?	decrease the use of these secondary maneuvers.
Comparator	Standard of care	In the ARAMIS trial, placebo was used as a comparator. In order to assess the comparative efficacy of darolutamide plus ADT compare with apalutamide plus ADT and enzalutamide plus ADT in patients with nmCRPC, the pCODR Methods Team reviewed an indirect treatment comparison. Refer to section 7 for more details.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	The current standard of care for patients with non-metastatic castration resistant prostate cancer (nmCRPC) is androgen deprivation therapy (ADT). Enzalutamide and apalutamide for nmCRPC were recently (in 2018 and in 2019, respectively) reviewed at pCODR and received conditionally positive reimbursement recommendations; price negotiations for apalutamide have concluded. This product is now considered 'under provincial consideration' which means that provinces are considering a listing. Once apalutamide plus ADT and/or enzalutamide plus ADT are reimbursed in Canada, they will be the most relevant comparators to darolutamide plus ADT in this setting (i.e. same use of ADT, and similar mechanism of action between darolutamide and enzalutamide or apalutamide). Please refer to the CGP interpretation in section 1.2.4 for more information on the CGP's assessment of the ITC.
Outcomes	Appropriateness of Primary and Secondary Outcomes	**Primary Outcomes** -MFS **Secondary Outcomes** -OS -Time to pain progression -Time to initiation of first cytotoxic chemotherapy for prostate cancer -Time to first SSE	Were the primary and secondary outcomes appropriate for the trial design?	For non-metastatic castration resistant prostate cancer, MFS is a meaningful endpoint for patients because it delays the onset of metastatic disease which is associated with more fatigue, pain, less wellbeing and potential bone complications such as fractures and need for radiation. The primary endpoint is supported by secondary outcomes in favour of darolutamide. The trial also showed that darolutamide plus ADT does not seem worsen/shorten the time to pain progression compared to ADT alone (the time to progression estimates are

Domain	Factor	Evidence (ARAMIS trial)	Generalizability Question	CGP Assessment of Generalizability
				considered exploratory due to the hierarchical gatekeeping procedure used in the trial).
Setting	Trial centres	The trial was conducted in 409 sites in 36 countries, including: Argentina (7), Australia (6), Austria (2), Belgium (5), Bulgaria (2), Belarus (2), Brazil (21), Canada (10), Colombia (3), Czech Republic (8), Germany (23), Spain (27), Estonia (1), Finland (5), France (27), United Kingdom (17), Hungary (10), Israel (1), Italy (15), Japan (41), South Korea (11), Lithuania (5), Latvia (6), Peru (4), Poland (11), Portugal (10), Romania (10), Russian Federation (23), Serbia (4), Slovakia (4), Sweden (4), Turkey (6), Taiwan (Province Of China) (5), Ukraine (8), United States (56), South Africa (9).	Do the trial results apply to patients from Canadian centres? Are there any known differences in practice patterns between the countries listed and Canada?	Overall, most patients were from Europe or the US, where practice patterns are similar to Canada.
Notes: ADT = androgen deprivation therapy; CRPC = Castration Resistant Prostate Cancer; ECOG = Eastern Cooperative Oncology Group; LHRH = Luteinizing hormone–releasing hormone; MFS = metastasis-free survival; nmCRPC = nonmetastatic castration-resistant prostate cancer; OS = overall survival; PCWG = Prostate cancer working group; PSA = Prostate specific antigen; PSADT = Prostate specific antigen doubling time; SEE = symptomatic skeletal event				

1.2.4 Interpretation

Burden of Illness and Need

As per the 2019 Canadian Cancer statistics, prostate cancer is the fourth most commonly diagnosed cancer with a projected incidence of 22,900 cases and the third leading causing of death in men with an expected mortality of 4,100 cases.[16]

nmCRPC is defined as serum testosterone at castrate level (less than 1.73 nmol/L) in a setting of rising PSA with no evidence of metastatic disease by conventional imaging such as CT or MRI or bone scan.[17]

Despite the early-stage diagnosis and high cure rates with surgery or radiotherapy, 28% of patients develop recurrent disease, as evidenced by a biochemical recurrence (elevation in PSA) with or without metastases.[18] These patients will relapse and receive salvage therapy (androgen deprivation therapy, antiandrogens) for rising PSA in the absence of metastatic disease and most often it takes two years from rising PSA to the development of metastases. However, patients with high-risk features (higher baseline PSA, higher PSA velocity (nanograms/ml/months), PSA doubling time (<8–10 months) have shorter metastasis-free survival and overall survival.[19]

Historically, the optimal management in the setting of nmCRPC had not been clearly established as previous trials with bisphosphonates and secondary hormone therapies failed their primary end-point.[20-24] The FDA identified the transition of non-metastatic to metastatic as a clinically relevant event and often heralds the development of symptoms (pain, fatigue, and a decline in quality of life) and additional intervention.[25,26] For MFS to be a reasonable endpoint, a significant clinical benefit will need to be realized with a favorable benefit-risk ratio for toxicity and cost evaluation. For example, the phase III trial of denosumab showed modest improvement in bone metastatic-free survival at risk of osteonecrosis of the jaw with no increase in overall survival.[5]

Most recently, the phase III SPARTAN (apalutamide versus placebo) and PROSPER (enzalutamide versus placebo) clinical trials showed an improvement in MFS (primary endpoint) with a trend towards improvement in overall survival survival and with no apparent detrimental effect on quality of life.[27,28] The Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) study and exploratory analysis from the SPARTAN trial suggest that MFS can be a surrogate marker for overall survival.[9,26]

Both apalutamide and enzalutamide are approved by Health Canada and received conditional positive final pCODR recommendations for funding in the treatment of patients with nmCRPC at high risk of progression to metastatic disease (PSA doubling time less than 10 months).[29,30]

The present pCODR review addresses a similar patient population and reviews data from the ARAMIS (darolutamide versus placebo) study.[31]

Effectiveness

The ARAMIS trial is a double-blind, randomized, placebo-controlled trial evaluating darolutamide in patients who are at high risk of developing metastatic disease with nmCRPC. The key inclusion criteria were men with histologically confirmed prostate adenocarcinoma, rising PSA despite castration level serum testosterone, baseline PSA of 2

ng per ml, PSA doubling time of ≤ 10 months while on continuous androgen deprivation therapy (ADT), ECOG PS 0 or 1 and absence of metastatic disease by conventional imaging (bone scan and CT chest, abdomen and pelvis for soft tissue or MRI if indicated). Patients were stratified based on the PSA doubling time (<6 months or >6 months) and use of bone-targeted agents at baseline (yes or no) and randomized in 2:1 ratio to receive either darolutamide or placebo. The primary endpoint of this study was MFS, while overall survival was a secondary endpoint.

Patient characteristics were balanced between the two groups and consistent with the characteristics of patients commonly seen in Canadian clinical practice. The median age was 74 years, median serum PSA level was 9-10 ng/mL, median PSA doubling time was 4.4 months (approximately 70% of the trial population), less than 5% of patients were treated with bone resorption inhibitors and 76% of patients received two or more hormonal therapy agents.

The trial met its primary endpoint; the median metastatic-free survival was 40.4 months with darolutamide versus 18.4 months in the placebo group. There was a statistically significant reduction in the hazard for metastases or death when compared with placebo (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.34 to 0.50; P<0.001) which is considered to be clinically meaningful.

With regards to the secondary endpoints, at the time of the interim analysis, use of darolutamide was associated with a favourable trend in overall survival (HR 0.71, CI 0.5-0.99, P=0.045) while the median overall survial was not reached in either group. At the final OS analysis, 15.5% of patients treated with darolutamide died (N = 148) while 19.1% treated with placebo died (N=106).[7] The median OS in the darolutamide and the placebo groups were not reached.[7] Treatment with darolutamide was associated with statistically significant prolonged OS as compared to placebo (HR: 0.685, 95% CI: 0.533 to 0.881; P=0.003) (Figure 6.7).[7]

At the time of the interim analysis, there were also a trend towards improvement in time to pain progression (HR 0.65, 95% CI, 0.53-0.79, p<0.001), time to cytotoxic chemotherapy (HR = 0.43,95% CI, 0.31-0.60, p < 0.001), time to first symptomatic skeletal event (HR 0.43, 95 CI 0.22-0.84, p=0.01), progression-free survival (HR 0.38, 95% CI 0.31-0.45, p<0.001), time to PSA progression (HR 0.13, 95% CI 0.11-0.16, p<0.001), time to first prostate cancer-related invasive procedure (HR: 0.39, 95% CI, 0.25 to 0.61; p < 0.001) and time to initiation of subsequent antineoplastic therapy (HR: 0.33, 95% CI, 0.23 to 0.47; p < 0.001). Secondary endpoints (time to initiation of first cytotoxic chemotherapy and time to first symptomatic skeletal event also showed statistical significant results in favour of darolutamide at the time of the final OS analysis.[7]

Safety

Darolutamide was well tolerated and no new toxicities were encountered in the ARAMIS trial when compared to other agents in a similar class. The treatment-emergent adverse events (TEAEs) of any grade occurred in 83.2% and 76.9% of patients in the darolutamide and placebo groups, respectively.

The proportion of patients who discontinued the study drug due to adverse events of any grade was 8.9% and 8.7%, in the darolutamide and placebo groups, respectively. Serious adverse events occurred in 24.8% and 20% of patients in the darolutamide and placebo

groups, respectively. One death in the darolutamide and two deaths in the placebo group were attributed to treatment.

The common toxicities were fatigue, back pain, arthralgia, diarrhea, hypertension, constipation, pain in extremity, anemia, hot flush, nausea, urinary tract infection, urinary retention, falls, fracture, dizziness and cardiovascular disorder. Overall fatigue/asthenic conditions occurred in 15.8% and 11.4% of patients in the darolutamide and placebo groups, respectively. The occurrence of CNS toxicities (cognitive disorder, memory impairment, change in mental status, cerebral ischemia, seizure) and fall/fracture appeared similar across both groups.

Given the small number of patients with CNS toxicity (e.g., seizure, mental impairment disorder) across all three trials (ARAMIS, PROSPER, SPARTAN), it is not possible to draw firm conclusions from these results about the use of these agents in patients with either a history of seizure or who are at high risk for seizure. CGP suggests caution in the use of darolutamide in patients with a history of seizures or who are on drugs which can lower the seizure threshold. CGP agrees that it should be at the discretion of the treating physician to consider darolutamide in these patients.

There appears to be no substantial improvement/ deterioration in quality of life as a result of treatment with darolutamide. This seems reasonable in the nmCRPC setting, where patients' quality of life is expected to be relatively high and stable.

Unfortunately, no predictive biomarker is available or identified for selecting patients for darolutamide.

Choice of anti-androgen agent: Apalutamide, Darolutamide, Enzalutamide

In order to assess the comparative efficacy of darolutamide to apalutamide and enzalutamide in patients with nmCRPC, the CADTH Methods Team reviewed a sponsor submitted indirect treatment comparison (ITC) and a network-meta analysis (NMA). The results of the ITC and NMA were similar suggesting that the risk of having metastatic disease or death was higher for patients treated with darolutamide as compared to those treated with apalutamide (NMA: MFS HR [95% CrI]: 1.46 [1.10 to 1.94]) or enzalutamide (NMA: MFS HR [95% CrI]: 1.41 [1.08 to 1.85]). There were no significant differences on OS for patients treated with darolutamide relative to those treated with apalutamide (NMAC: OS HR [95% CrI]: 1.02 [0.60 to 1.71]) or enzalutamide (NMA: OS HR [95% CrI]: 0.89 [0.56 to 1.42]).

The quality assessment performed by the CADTH Methods Lead concluded that due to high heterogeneity between the three clinical trials (the difference in number of patients who initiated new anti-cancer therapy prior to metastasis in ARAMIS, PSA being unblinded in ARAMIS, patients with metastasis at baseline, treatment effect modifiers [ECOG performance status and receipt of bone targeting agents at baseline], patients with a history of seizures), the comparative effectiveness estimates from the ITC and NMA are likely biased, and the magnitude or the direction of the bias cannot be established. This aligned with the Sponsors conclusions with respect to the ITC and NMA. Also, since the median OS had not been reached in any of the included studies, there is uncertainty about how the intervention will compare using matured data. The CGP agreed with the CADTH Methods Team and cautioned against drawing conclusions from the ITC or NMA on the magnitude of effect of darolutamide compared with either apalutamide or enzalutamide. The CGP noted that, for the proposed target population, it seemed likely that in clinical

practice similar MFS benefits would be observed between the three novel androgen-receptor-axis targeted therapies (ARATS) (darolutamide, apalutamide, and enzalutamide).

In addition, the CGP noted that recently several abstracts[11,15,32-34] have been published of indirect treatment comparisons evaluating the efficacy and safety of apalutamide, enzalutamide, and darolutamide. The efficacy results are broadly in line with the results of the submitted NMA and ITC. In terms of safety, the findings were variable. This variability may be due to differences in what studies were included in the ITC or NMA and the methodologies that were implemented to build the network. However, in the absence of full publications, the CADTH Methods Team was unable to conduct a rigorous evaluation of the conduct and reporting of theses analyses.

Furthermore, the CGP noted that most recently, the secondary end-point results of OS reached statistical significance in the ARAMIS study[7] (darolutamide versus placebo) and the PROSPER study[35] (enzalutamide versus placebo) while the SPARTAN[36] study (apalutamide versus placebo) showed a trend towards improvement in OS and the pre-defined p-value did not reach statistical significance. The results from the above trials provide additional evidence and reassurance that MFS (the primary endpoint across all three trials) is a reasonable surrogate end-point for OS. Even though OS is an important endpoint in oncological trials, due to the differences in the hierarchical statistical order of the secondary end-points across the trials, it is difficult to conclude whether one ARAT is superior to another ARAT based on cross-comparison of the trials.

Overall, the CGP concluded that there is insufficient evidence to recommend one ARAT over another in patients with nmCRPC. Given the absence of more robust direct evidence from a randomized trial, there is insufficient evidence to determine the comparative effectiveness and safety of darolutamide compared to apalutamide or enzalutamide and therefore patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection. Refer to section 7 for the complete critical appraisal of the ITC and NMA.

1.3 Conclusions

- The Clinical Guidance Panel concluded that there is a net overall clinical benefit to darolutamide plus ADT compared with ADT alone in patients with high-risk nmCRPC based on one high-quality randomized controlled ARAMIS trial that demonstrated a clinically meaningful and statistically significant benefit in MFS. The secondary outcome OS also reached statistical significance in favour of darolutamide at the time of the final OS analysis. Darolutamide was associated with a favourable trend in other secondary endpoints including time to pain progression, progression-free survival, time to PSA progression, time to first prostate cancer-related invasive procedure, and time to initiation of subsequent antineoplastic. The secondary endpoints time to cytotoxic chemotherapy and time to first symptomatic skeletal event reached statistical significance in favour of darolutamide at the time of the final OS analysis. The grade 3 and 4 adverse events were low and clinically acceptable without worsening health-related quality of life. Currently, the standard treatment option for high-risk patients with nmCRPC is evolving with the recent approval of apalutamide and enzalutamide by Health Canada and conditional positive final recommendations by pCODR.

In making this recommendation, the Clinical Guidance Panel considered:

- The transition from non-metastatic CRPC to detectable metastatic CRPC is a clinically relevant event and often associated with the onset of pain, fatigue, weakness, a decline in overall quality of life, psychological burden and additional interventions.
- While significant advances have been achieved in recent years in the treatment of castration resistant prostate cancer, it remains an incurable disease. A significant portion of patients with prostate cancer will eventually relapse and progress to overt metastatic disease which is associated with a high burden of symptoms, decrease in quality of life and death.
- The identification of non-metastatic patients in ARAMIS was based principally on PSA and conventional imaging modalities of bone scan and CT. Advanced imaging techniques currently in development (e.g. PET scans) may have an ability to detect metastases earlier than current imaging techniques. As a result, more patients may be identified with evidence of early metastatic disease. The impact of treatments in this future cohort of patients has yet to be determined.

Provincial Advisory Group's (PAG) Related Implementation Questions:

- With respect to different definitions of CRPC, the CGP noted that the definition of CRPC in the ARAMIS trial is defined as "(…) *three rising PSA levels after the nadir taken at least 1 week apart during ADT. If the patient has a history of antiandrogen use, the most recent PSA value must be obtained at least 4 weeks after anti-androgen withdrawal*."[1] This definition was consistently used in previous trials as well (i.e., SPARTAN and PROSPER). CGP noted that this definition aligns with the PCWG2 criteria.
- CGP agreed that it would be appropriate that patients meeting the criteria for high-risk disease currently treated with ADT alone would be addressed on a time-limited basis.
- CGP noted that it would be appropriate to switch patients who experience intolerance to one anti-androgen agent to another anti-androgen agent as all three drugs have a similar mechanism of action with a slightly different toxicity profile and the patient may not experience the same toxicity.
- With regards to patient compliance (darolutamide is taken twice daily whereas apalutamide and enzalutamide are taken once daily), the CGP agreed with PAG on potential decreased compliance with a drug with twice a day dosing. However, the CGP noted that darolutamide is twice a day; the patient's on apalutamide with gastrointestinal toxicities could switch to twice a day dosing in the SPARTAN trial. GCP suggests an informed decision with the patient should occur on their preferences on the number of doses per day and the number of pills per dose to guide the selection of the drug.
- Regarding the frequency of clinic visits for monitoring of blood work and side effects compared to ADT alone the CGP noted that there is a difference on follow-up schedule in the clinic among the trials, the SPARTAN trial assessed patients every four weeks in the clinic, the PROSPER trial assessed patients at week 1, week 5, and week 17 and then every 16 weeks in the clinic and the ARAMIS trial evaluated patients at week 1, week 2, week 5 and week 16 and then every 16 weeks. All the trials obtained radiological imaging every 16 weeks. CGP agreed that there will likely be an increased number of visits in the first three months when compared to ADT alone. After the first 3 months it is likely patients will be seen at similar rates as per current practice (i.e., every 3 to 4 months).
- With respect to PAG seeking information on the appropriate treatment for metastatic disease after treatment with darolutamide in the non-metastatic setting, the CGP noted

that there is not sufficient data to make an evidence-based recommendation on sequencing. The use of darolutamide, apalutamide, or enzalutamide in these patients should be considered as first-line therapy in non-metastatic castrate-resistant disease.

Similar to the setting of mCRPC, for patients who progressed on enzalutamide, the next line of therapy could be abiraterone/prednisone, docetaxel, radium-223 or cabazitaxel. Since darolutamide is in the same class of drugs as apalutamide or enzalutamide, there is no clinical evidence to suggest efficacy or safety on switching to another ARAT (darolutamide to apalutamide, or enzalutamide or vice versa) upon radiological disease progression; CGP does not recommend this practice. Whether re-challenging with darolutamide is potentially reasonable after interim treatment with other options is currently unknown. The data available to date for the sequence of enzalutamide followed by abiraterone/prednisone demonstrate a very modest benefit for this sequence. There is insufficient evidence to recommend either abiraterone/prednisone or chemotherapy over the other following darolutamide use. However, there is mounting evidence that ARAT to ARAT sequencing yields worse oncological outcome when compared to sequencing ARAT to alternate mechanism of action therapy.[37,38]

The CGP suggests that patient values and preferences, co-morbidities, expected dug toxicities, and treatment availability (provincial reimbursement) should guide treatment selection in clinical practice.

- With respect to PAG seeking advice on whether patients who have been treated with abiraterone, enzalutamide, apalutamide or other second-generation anti-androgens (e.g., through a clinical trial or private drug insurance) should be offered darolutamide should these patients continue to remain non-metastatic, the CGP felt that darolutamide could be a treatment option for patients who received abiraterone, enzalutamide, apalutamide or other second-generation anti-androgens as part of a clinical trial.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Genitourinary Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Prostate cancer is the second most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers) and is the third leading cause of death from cancer. It is estimated that 22,900 men will be diagnosed with prostate cancer and 4,100 men will die from prostate cancer. The lifetime probability of developing prostate cancer is one in nine Canadian men and lifetime probability of dying from prostate cancer is one in 29 Canadian men.[16]

2.2 Accepted Clinical Practice

Treatment options for localized prostate cancer are based on risk stratification of the disease (clinical features: TNM Classification of Malignant Tumors (TNM) stage, PSA value and pathological features: Gleason grade group, percentage of positive biopsies) and life expectancy of the patient. The treatment options include active surveillance (based on risk of disease and life expectancy) or radical prostatectomy or radiation therapy (brachytherapy or external beam radiotherapy) +/- androgen deprivation therapy). Treatment decision is based on a shared decision aligning with the patient's values as there is no definitive evidence that one treatment modality is superior in efficacy.[39,40]

Despite the early-stage diagnosis and high cure rates with surgery or radiotherapy, most patients develop recurrent disease as evidenced by a biochemical recurrence (commonly defined as two consecutive rising PSA values >0.2 ng/mL following radical prostatectomy[41,42] or any PSA increase of 2 ng/mL higher than the PSA nadir value regardless of the serum concentration of the nadir after primary radiation therapy[43]) with or without metastases (bone lesions on bone scan or soft tissue lesion as per RECIST). Salvage therapies include observation or salvage radiation therapy after previous prostatectomy or salvage prostatectomy after prior radiation therapy or androgen deprivation therapy (ADT). Most patients initially respond to androgen deprivation therapy. However, almost all the patients will progress to develop castration-resistant prostate cancer (CRPC).
Non-metastatic castrate-resistant prostate cancer (nmCRPC) is defined as serum testosterone at castrate level (less than 1.73 nmol/L) in a setting of rising PSA with no evidence of metastatic disease by conventional imaging (CT or MRI or bone scan).[17] Generally it takes two years from rising PSA to the development of metastases. However, patients with high-risk features (higher baseline PSA, higher PSA velocity (nanograms/ml/months), PSA doubling time (<8–10 months) have shorter metastasis-free survival and overall survival.[26,44,45]
Historically, the optimal management in the setting of nmCRPC had not been clearly established since the clinical trials with bisphosphonates and older agents targeting the androgen pathway[20-24] failed their primary endpoint. If patients are treated with a first-generation anti-androgen agent, anti-androgen withdrawal, as well as low dose prednisone, are considered further options. A phase III trial with denosumab failed to show a significant benefit for its toxicity profile,[5] while chemotherapy with docetaxel is not recommended outside of a clinical trial. Most often, observation is preferred.
Since 2018, phase III clinical trial results from SPARTAN (apalutamide or placebo), PROSPER (enzalutamide or placebo) and ARAMIS (darolutamide or placebo) have provided level 1 evidence to consider newer generation anti-androgen agents in the treatment of high-risk nmCRPC patients (PSA doubling time less than 10 months).[27,28,31]

Apalutamide and enzalutamide are newer androgen-receptor ligand-binding domain inhibitors, prevent androgen-receptor translocation, inhibit DNA binding, and androgen receptor-mediated transcription. The SPARTAN trial demonstrated a significant improvement in the primary endpoint with a median metastasis-free survival (MFS) of 40.5 months in the ADT plus apalutamide group versus 16.2 months in the ADT plus placebo group (hazard ratio for metastasis or death, 0.28; P<0.001). The PROSPER trial also demonstrated a significant improvement in the primary endpoint with a median MFS of 36.6 months in the ADT plus enzalutamide group versus 14.7 months in the ADT plus placebo group (hazard ratio for metastasis or death, 0.29; P<0.001). Both these agents also showed a trend towards improvement in secondary endpoints such as overall survival and appeared to have no detrimental effect on quality of life. Apalutamide and enzalutamide received Health Canada approval and conditional positive final pCODR recommendations.[29,30] In the near future, these agents will be funded for use in high-risk nmCRPC patients.
Darolutamide is an androgen-receptor antagonist with a distinct structure, it has been developed to have low penetration of the blood-brain barrier and will potentially offer fewer toxic effects. Similarly, to the SPARTAN and PROSPER trials, the ARAMIS trial demonstrated a statistically significant improvement in the median MFS in favour of darolutamide in high-risk nmCRPC patients.

The present pCODR review addresses patients with non-metastatic castration-resistant prostate cancer at high risk of progression to metastatic disease. The evidence for this review is based on the ARAMIS trial which evaluated the use of darolutamide in patients with non-metastatic castration-resistant prostate cancer at high risk (PSA doubling time ≤10 months) of progression to metastatic disease.

2.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of darolutamide for patients with nmCRPC.

Patients with nmCRPC are characterized by an observed rising PSA despite androgen-deprivation therapy and castrate testosterone levels as well as no detectable bone or soft tissue distant metastases on imaging.

Currently, no clinically useful and reliable biomarkers exist for the prediction of response and/or benefit.

2.4 Other Patient Populations in Whom the Drug May Be Used

Darolutamide has been issued marketing authorization without conditions for the treatment of patients with nmCRPC. The Health Canada Product Monograph (PM) also notes that darolutamide has not been studied in patients with nmCRPC at low risk of developing metastatic disease. The benefit and risk profile in these patients is unknown.

The CGP agrees that there is insufficient evidence to determine how much benefit patients without the high-risk features as defined in the ARAMIS trial would derive from darolutamide.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, the Canadian Cancer Survivor Network (CCSN), provided input for darolutamide (Nubeqa) for non-metastatic castration resistant prostate cancer (nmCRPC). CCSN obtained responses from 98 patients and caregivers through a survey launched in August 2019. All respondents were Canadian. Most respondents were from Ontario (73%), followed by Alberta (9.3%), British Columbia (7.3%), Nova Scotia (5.2%), Quebec (3.1%), New Brunswick (1%) and Manitoba (1%). All respondents, except one, were male and patients; the only female respondent was a caregiver. Six respondents reported having experience with darolutamide, however none of them chose to answer questions specifically related to darolutamide. To obtain more information about experience with darolutamide, CCSN conducted qualitative interviews over the phone with five patients with prostate cancer who were either currently taking or had taken darolutamide in the past; these interviews were conducted between August 6, 2019 to August 31, 2019. Patients taking part in the interviews were from Nova Scotia (n=2), Ontario (n=2), and Alberta (n=1).

The symptom most affecting patient's quality of life due to prostate cancer was reported to be erectile dysfunction. Erectile dysfunction was also a reported side effect of treatments patients were currently taking. Some quotes suggest that patients wish to have been better informed about the issues with erectile dysfunction.

Of the five patients with direct experience with darolutamide that CCSN conducted qualitative interviews with, all reported that there were no side effects experienced while they were receiving darolutamide. Men commented on being able to engage in daily activities while taking darolutamide and maintain a good quality of life. In general, the men reported positive experiences with darolutamide and would recommend it as an option for other patients with prostate cancer. However, one patient did indicate feelings of nausea if they took darolutamide without food. One patient experienced issues with their cardiovascular health, CCSN stated that he still thought the benefits of darolutamide outweighed the side effects. Overall, from a patient's perspective, patients value treatments that allow them to maintain their quality of life, have reduced side effects (e.g., erectile dysfunction), and lead to a longer life.

Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient advocacy group.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Prostate Cancer

Table 1 reports the methods by which respondents received confirmation of their prostate cancer diagnosis. The most commonly reported tests respondents received were PSA testing, biopsies, and rectal examinations.

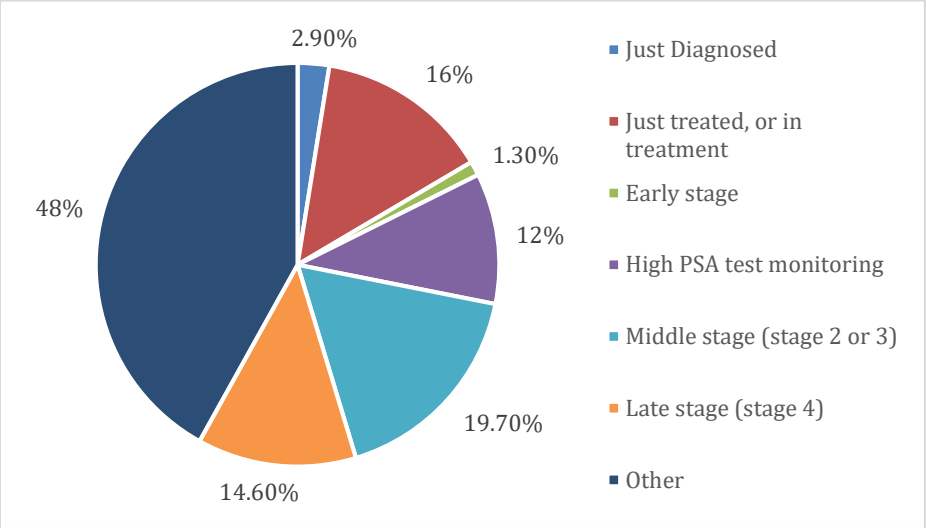
Table 1: Tests reported by respondents to confirm their cancer diagnosis

Test	N (%)
PSA testing	90 (91.8)
Biopsy	78 (80)
Rectal exam	56 (57.1)
Incidental finding/physical exam at family doctor	23 (23.5)
Blood work	19 (19.4)

Test	N (%)
A combination of any tests mentioned above	20 (20.4)
Other*	6 (6.1)
*including emergency room visits for acute urinary retention, MRI, family history, abdominal scan, bone scan, prostate biopsy, PSA numbers	

Seventy-five respondents also reported at what stage they received their diagnosis (Figure 1).

Figure 1: Stage of respondents' disease at diagnosis



Patients seemed to have been diagnosed at varying stages of prostate cancer. Not many patients reported being diagnosed at an early stage of their prostate cancer. Almost half of the 75 respondents reported 'other'; respondents who reported 'other' provided comments, which included having surgery or other treatment several years ago and not having had a recurrence.

- *"Had prostatectomy. PSA now about 0.1 and monitoring to decide on radiation treatment."*
- *"I have had three forms of treatment and now am on PSA monitoring with hormone treatment ongoing."*
- *"About to begin hormone injections."*
- *"11 years on HT."*
- *"Prostatectomy on May 29/2018, 4 PSA tests of 0.008 since operation."*
- *"Advanced PC that has been treated with radiation, chemo and hormone (Eligard) therapy."*

Table 2 includes symptoms/problems experienced by respondents that affected quality of life and/or day-to-day living (n=75). Erectile dysfunction was the most commonly reported symptom affecting respondent's quality of life.

Table 2: Prostate cancer symptoms affecting respondent's quality of life, n=75

Symptoms	%
Erectile dysfunction	76.0
Fatigue	46.7
Urinary incontinence	40.0
Loss of muscle mass	28.0
Hot flashes	28.0
Anxiety	20.0
Weight gain	20.0
Depression	18.7
Loss of bone mass	13.3
Constipation	9.3
Infertility	9.3
Pencil thin stool	8.0
Shortness of breath	8.0
Diarrhea	5.3
Bowel incontinence	4.0
Weight loss	4.0
Loss of appetite	4.0
Abdominal cramping	2.7
Bowel obstruction	2.7
Dizziness	2.7
Nausea and/or vomiting	1.3
Other	24.0

Eighteen respondents (24%) reported experiencing 'other' symptoms in relation to their prostate cancer, and provided comments, which are included below, to describe how their symptoms impacted their quality of life:

- *"Lost bowel function."*
- *"Suprapubic catheter, ongoing significant rectal bleeding for 4+ years after radiation treatment despite 4 argon coagulation treatments plus drug treatments."*
- *"Acute mental instability – I felt totally lost as a man."*
- *"Blood in my stool."*
- *"My symptoms are mostly from the treatments – chemotherapy and hormone therapy."*
- *"Climacturia."*
- *"Get up at night a couple times to pee."*
- *"An onset of arthritis during treatment. Chemotherapy, radiation and ADT."*
- *"I attribute most/all of the above* [referring to table 1] *to extended (4 years) intermittent ADT."*
- *"Radiation burns in bladder."*

3.1.2 Patients' Experiences with Current Therapy for Prostate Cancer

Out of 75 respondents, 54% reported they did not experience issues with accessing current therapies. However, 8% reported limited availability of treatment in their community, 7%

reported issues with travel costs related to access of therapy/treatment, 4% reported hardships due to cost, and 3% reported issues with supplies or issues with administration.

CCSN asked respondents whether there were any needs in their current therapies that were not being met; of the respondents who asked, 56% reported 'no' and 29% reported that they were not on therapy at the time of the survey. Fifteen respondents reported experiencing needs their treatments were not meeting. Quotes were provided by the 15% of respondents whose needs were not being met by treatments and are included below. The quotes reflect patient's desires for therapies with improved side effects, and better communication about the treatments they are taking, and possible short- and long-term side effects; specifically, some respondents commented on the lack of communication about erectile dysfunction and possible management strategies. Quotes also discussed the use of alternative therapies, and a need for more frequent scanning and quicker communication of test results.

- *"I am currently on Eligard which produces weight gain around the stomach, hot flashes and ED; would like to try an alternate therapy."*
- *"I have been on Eligard for 4 years. I am concerned about long term impacts and effects on my health."*
- *"I should have been better informed about ED and immediately after Zoladex ended, put on to penile injections as these are better than pills like Viagra."*
- *"Post ADT/post radiation – unanswered questions and a lack of guidance. You need to be an aggressive advocate and do your own research to seek relief and info."*
- *"Waiting to be assessed for hyperbaric treatment."*
- *"Coordination between doctors discussion of alternatives, esp. new therapies and long term projections"*
- *"Theranostic approach should be discussed. Use more advanced scanning technology."*
- *"Not enough scanning to see if it has spread. Radiation treatments are over. I receive a radiation injections every 6 months. Cat scans and MRO not done very often. Worried."*
- *"Proton beam therapy not available in Canada."*
- *"I'd like to be given my blood test results ASAP."*
- *"Want to access darolutamide."*

When asked about what respondents would like to see in a new treatment, 73 respondents provided input. Most respondents hope that new treatments will maintain quality of life (80.8%). Other expectations for new treatments included a delayed need for chemotherapy (46.9%), access to a new option for treatment (46.9%), reduced side effects from current medications or treatments (42.3%), delayed onset of symptoms (41.1%), ease of use (28.8%), and other (20.6%). Respondents who reported 'other' provided comments which are included below. The quotes convey a need for treatment options alternative to hormone therapy, avoidance of erectile dysfunction, and improved survival.

- *"ADT is a horrible treatment option for many men, although it is necessary in some cases. Post ADT treatment, I am reluctant to ever do it again (Lupron), I'd rather be dead!!!"*
- *"Delay need for hormone therapy and reduce hot flashes."*
- *"Delay need for salvage radiation."*
- *"Avoid erectile dysfunction."*
- *"Regain continence and erectile function."*
- *"GIVE ME MORE YEARS TO LIVE."*
- *"Live longer…"*

- *"Should provide a reason for optimism."*

CCSN also asked patients which side effects they considered were unacceptable on a new drug, the responses are captured in Table 3. Side effects considered the unacceptable by most respondents include feelings of depression worsened after taking medication, nausea and vomiting, bowel incontinence, diarrhea, dizziness, feelings of anxiety worsened after takin medication, loss of bone mass and development of breasts or having breast tenderness.

Table 3: Side effects respondents consider unacceptable for new treatments for prostate cancer

Side effect	%
Feelings of depression worsened after taking medication	95.3
Nausea & vomiting	93.4
Bowel incontinence	92.0
Diarrhea	86.4
Dizziness	84.4
Feelings of anxiety worsened after taking medication	83.8
Loss of bone mass	82.8
Develop breasts or have tenderness	81.5
Urinary incontinence	79.4
Loss of muscle mass	72.3
Weight gain	62.9
Hormonal changes	55.0
Hot flashes	50.4
Erectile dysfunction	48.5
Weight loss	48.5
Fatigue	36.9
Infertility	23.3

Respondents were asked how much improvement would be needed from a new drug to be considered better than current treatment options; quotes are included below. Responses discussed reduction of side effects (e.g., erectile dysfunction, hot flashes, muscle atrophy, and changes in weight), disease control, longevity and improved quality of life.

- *"A reduction in typical side effects would be a good start."*
- *"Reduction in the severity of the side effects."*
- *"Not have hot flashes and not have loss of muscle mass."*
- *"Less weight gain, less hot flashes, less ED."*
- *"Less incontinence and some control over ED."*
- *"I'm dealing with incontinence and erectile dysfunction. I would like a new drug to minimize these 2 issues."*
- *"Improve too much weight gain, easier on the kidneys and liver, bring back testosterone."*
- *"Effectiveness in reducing PSA with few side effects."*
- *"Current impact of ADT on cancer progression will fail. New drug must be effective in stalling cancer progression/metastases for significant time. Any reduction in side effects is a (very positive) bonus."*

- *"Ensure new drug works to stop growth of prostate cancer."*
- *"Much improvement required."*
- *"Increased longevity."*
- *"Elimination long term risks."*
- *"Better quality of life. Longer life."*
- *"Less emotional disturbance."*
- *"Need a cure, not a treatment."*
- *"I need hope!"*

Impact of Prostate Cancer and Current Therapy on Caregivers

One caregiver responded to CCSN's survey. The main concerns of the caregiver were reported to be fatigue, emotional drain, anxiety/worrying, management of medications, management of side effects, lifestyle changes, and an inability to plan ahead. The caregiver also mentioned a lack of time to do things for herself.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Darolutamide

All of the six respondents to CCSN's survey who reported having experience with darolutamide chose not to answer questions specifically related to their experiences with darolutamide in the survey. Therefore, CCSN obtained direct patient experiences with darolutamide through qualitative phone interviews with five prostate cancer patients who were currently taking or had taken darolutamide. Two of the patients had stage 4 disease, one respondent was cancer free (PSA=0), one respondent was unsure of his status and the final patient referred to his stage as *"stable"*. None of the men reported having experienced any symptoms prior to their diagnosis of prostate cancer. Of the five men, three reported having discovered their diagnosis through a routine physical checkup, one patient had their prostate cancer discovered only after PSA tests were covered in their province, and the fifth patient did not provide a response. Please see below for quotes:

- *"My cancer was discovered during a routine annual checkup. I had asked my doctor about PSA test, but he said not to worry about it."*
- *"I didn't have a PSA test because at the time it was $60 and I didn't have that kind of money. Eventually though, it was paid for and I had the test then."*

CCSN asked the patients how long they had been taking darolutamide. One patient reported taking darolutamide for four years; two men reported taking darolutamide for three years (one had recently stopped taking darolutamide due to rising PSA levels); another patient received darolutamide for two years; and the fifth patient did not specify. Aside from the one patient who recently stopped taking darolutamide, the other four patients continue to receive the therapy. When asked what other treatments the patients were currently using or had used in the past, three men indicated currently taking goserelin (Zoladex) injections every three months, one was currently taking escitalopram (Cipralex) and leuprorelin (Eligard), and one had previously taken degarelix (Firgmagon).

When asked about side effects related to darolutamide, all five men stated they did not experience any side effects while receiving the treatment. However, one patient experienced cardiovascular issues that required a triple bypass after he stopped taking darolutamide. Another patient stated experiencing nausea if they did not take darolutamide with food. One patient stated they experienced breast growth, loss of hair and weakness, but attributed these side effects to degarelix (Firmagon), another therapy

they were also taking. CCSN provided a number of quotes on behalf of the five patients. In general, the quotes confirm that patients did not experience side effects, or, if they did, they attributed the side effects to other causes. Patients were able to maintain some quality of life and engage in their regular routines and travel.

- *"No one tells you most men don't die from prostate cancer but from cardiovascular disease. They didn't stress the risk of darolutamide enough; with limited options, though, I can understand that it's a hard choice. My doctor told me to "pick my poison", to decide what will kill me – prostate cancer or cardiovascular disease. But darolutamide brought me three years; I just didn't realize what it was doing to other parts of my body."*
- *"My quality of life been great; darolutamide hasn't prevented me from doing any of the things I've wanted. We've don't lots of travelling and it hasn't upset my normal routine. There was no change in my activity – it was if I didn't have prostate cancer." (also from gentleman with CV issues)*
- *"Darolutamide hasn't stopped or interfered with my quality of life. I like to ravel and can still do that. I still do stuff around the house. In fact, I just got back from golf."*
- *"Before darolutamide, my PSA was going up but it dropped down to a safe level, and I am happy on it."*
- *"For what I can feel, darolutamide hasn't bothered me at all, my quality of life is the same as always. I was working in my garden this morning; I do my thing; it didn't affect me at all. I am always looking forward; I am happy to be around and hope to be for many years… In fact, recent scans have found no cancer at all and my PSA is 0."*
- *"I really found no problems at all."*
- *"I'm trying to buy enough time to stay alive and see a more permanent treatment."*
- *"The only thing I have noticed is that I seem a bit more lethargic than before, but I think that might be more age related than anything having to do with the drug."*

According to CCSN, four of the five men interviewed believed unequivocally that the benefits of darolutamide outweighed the side effects, particularly three of the men who stated they did not experience any side effects. Due to their experience with cardiovascular disease, CCSN stated the fourth patient hesitated when answering this question. However, even with the cardiovascular related issues, CCSN stated the patient believed they would still have opted for treatment with darolutamide.

- *"I don't know. If I hadn't taken it, I might be metastatic. Thinking back, even with my CV issues, I probably still would have taken it."*
- *"My brother died four years ago and I'm still here. We had the exact same cancer so I assume darolutamide is keeping me alive."*
- *"Yes. I don't know exactly what it's doing but I also don't know what would happen if I wasn't on it."*

CCSN asked the five men if they believed darolutamide should be available to all patients with prostate cancer; all five men agreed. The following quotes were provided by CCSN:

- *"I would recommend it. Right now, I am still around because of darolutamide."*
- *"Based on my experience, the sooner, the better. Darolutamide worked well for me right away. I feel I am in good hands."*

- *"Absolutely. What do you have to lose? I've seen other people go through all kinds of things like leaking and if that had happened to me, I wouldn't be able to swim. It's not really worth living if I can't swim. It's miraculous – I am walking around because of [darolutamide]."*
- *"Yes. I can't tell what it's doing but my doctors seem satisfied. There doesn't seem to be any kind of panic. If [my doctors] don't seem very concerned, then I'm not."*

3.3 Additional Information

N/A

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Comparative information with apalutamide or enzalutamide

Economic factors:

- Twice daily whereas apalutamide and enzalutamide are taken once daily

Please see below for more details.

4.1 Currently Funded Treatments

The current standard of care for patients with non-metastatic castration resistant prostate cancer (nmCRPC) is androgen deprivation therapy (ADT).

Enzalutamide and apalutamide for nmCRPC were recently reviewed at pCODR and received positive reimbursement recommendations; apalutamide is currently under negotiations.

Although the comparator of ADT in the ARAMIS trial is a funded option, PAG is also seeking comparative information on darolutamide compared with apalutamide or enzalutamide.

4.2 Eligible Patient Population

PAG noted that there are different definitions of castration-resistance and it would be important for pERC to note that the definition of castration-resistance in the ARAMIS trial was according to the PCWG2 criteria.

PAG is seeking clarity on whether the following patients would be eligible for treatment with darolutamide:

- Patients who received prior chemotherapy or immunotherapy for prostate cancer (in the ARAMIS trial, these patients were excluded except for adjuvant/neoadjuvant treatment completed >2 years before randomization)
- Patients with PSA doubling time greater than 10 months,
- Patients with ECOG performance status of 2 or greater.

If recommended for reimbursement, PAG noted the following groups of patients would need to be addressed on a time-limited basis:

- Patients currently treated with ADT alone
- Patients that experience intolerance to apalutamide or enzalutamide and appropriateness of switching to darolutamide

PAG noted that there is potential for indication creep to use darolutamide in high risk patients (e.g., Gleason score 8-10, high PSA at diagnosis, etc.) who have not had a PSA

progression in the non-metastatic setting or to non-metastatic hormone sensitive prostate cancer.

4.3 Implementation Factors

Darolutamide is available in one tablet strength and the dose is four tablets daily. Dose adjustments are made by adjusting the number of tablets and there would be minimal drug wastage.

Darolutamide is taken twice daily whereas apalutamide and enzalutamide are taken once daily. PAG noted some patients may find the twice daily dosing inconvenient compared to apalutamide and enzalutamide and there are concerns for patient compliance.

PAG noted that darolutamide is an oral treatment that can be administered at the patient's home and chemotherapy chair time is not required. However, PAG identified that there may be more frequent clinic visits for monitoring of blood work and side effects compared to ADT alone. There would also be additional pharmacy resources required to dispense darolutamide.

PAG noted that darolutamide is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home, and no chemotherapy chair time would be required. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on what clinical scenarios darolutamide, apalutamide or enzalutamide would be the preferred treatment for patients with non-metastatic castration-resistant prostate cancer in this setting.

PAG is seeking information on the appropriate treatment for metastatic disease after treatment with darolutamide in the non-metastatic setting. Treatments available for castration resistant metastatic disease include abiraterone, enzalutamide and chemotherapy. PAG noted that darolutamide and enzalutamide are the same class of drug and seeking information on the use of enzalutamide in the metastatic, castration resistant setting after darolutamide or whether patients previously treated with darolutamide should be treated with abiraterone or chemotherapy in the castration resistant metastatic setting.

PAG identified that there may be a small number of patients who have been treated with abiraterone, enzalutamide, apalutamide or other second generation anti-androgens (e.g., through a clinical trial or private drug insurance) for non-metastatic castration-resistant prostate cancer. PAG is seeking guidance on the appropriateness of using darolutamide following abiraterone, enzalutamide, apalutamide or other second generation anti-androgens after failure of these drugs in this therapeutic space should these patients continue to remain non-metastatic.

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Input was received from 10 individual clinicians and two joint clinician inputs on behalf of Prostate Cancer Canada (PCC, representing four clinicians) and Cancer Care Ontario (CCO, representing three clinicians) for the review for darolutamide (TBD) for non-metastatic castration resistant prostate cancer (nmCRPC). Overall, input was received from 17 clinicians from Alberta, Ontario, Nova Scotia, New Brunswick, and British Columbia. Their input is summarized below.

Eligibility criteria of the ARAMIS trial were considered as being clinically relevant and applicable to practice. Unmet need for nmCRPC patients was highlighted as they represent a relatively new patient group with minimal available treatment options. Apalutamide and enzalutamide were stated to be the most appropriate comparators to darolutamide, although neither treatment is currently funded in Canada; only ADT is currently funded for patients with nmCRPC. Patients may access apalutamide and enzalutamide through compassionate access programs. Compared to apalutamide and enzalutamide, darolutamide was stated to show similar efficacy but a potentially favourable side effect profile. However, it was acknowledged that no direct comparative evidence between apalutamide, enzalutamide and darolutamide exists.

Clinicians agreed that generalization of evidence for darolutamide to patients who had received prior chemotherapy was acceptable. Clinicians expressed mixed opinions regarding generalization to patients who had received prior immunotherapy; a lack of evidence to support the use of darolutamide for these patients was acknowledged, however some clinicians highlighted that patients who received immunotherapy would be unfairly disadvantaged for participating in a clinical trial. All clinicians agreed that a PSA doubling time of ≤ ten months and an ECOG performance status of 0 or 1 were acceptable eligibility criteria for darolutamide. One clinician stated that androgen receptor inhibitors are generally benign and may be worth using on patients with poorer ECOG performance status.

Should patients progress on darolutamide, clinicians did not support the use of another anti-androgen therapy as a subsequent treatment. Enzalutamide and apalutamide were acknowledged to have the same mechanism of action as darolutamide, and clinicians mentioned prior studies showing non-durable responses in patients who received one anti-androgen after another. Chemotherapy was identified as the most appropriate treatment for nmCRPC patients after progression on darolutamide. Overall, darolutamide was considered to be a “nice to have” therapy in addition to apalutamide and enzalutamide. All three treatments were considered similar in efficacy. However, clinicians appreciated the option of darolutamide as it may have a favourable side effect profile that requires less monitoring and can be useful to patients with seizure history and comorbidities.

Please see below for a summary of specific input received from the registered clinicians.

5.1 Current Treatments for this nmCRPC

All inputs noted that apalutamide and enzalutamide, while currently not funded, are the two most appropriate treatments for patients with nmCRPC. Clinicians stated that they can put their patients on apalutamide or enzalutamide through compassionate access programs through the drug companies Janssen and Astellas, respectively. One clinician stated that the ARAMIS trial demonstrated similar efficacy with darolutamide as apalutamide or enzalutamide, with darolutamide showing a more favourable side effect profile; however, the clinician noted that there are no head to head trials of these treatments. Clinicians from PCC highlighted metastasis-free survival (MFS) as a reasonable

surrogate endpoint for OS in prostate cancer, and that no currently funded treatments in Canada show a significant MFS benefit to nmCRPC patients.

The only currently funded treatment for patients with nmCRPC was identified to be ADT. Clinicians from CCO acknowledged that the evidence space for nmCRPC population is fairly new, and that these patients have limited standard treatment options beyond ADT. Patients with nmCRPC are maintained on ADT and then observed for signs of metastatic disease. One clinician highlighted that ADT is not the best treatment for nmCRPC patients, since being castration resistant means they are already failing ADT; this clinician stated that these patients are maintained on the monotherapy while they experience both biochemical and local progression. Once patients become metastatic, the clinician stated that patients may become eligible for additional treatments, including abiraterone, enzalutamide, docetaxel or radium 223. Another clinician also acknowledged that nmCRPC patients will eventually progress where they will be faced with chemotherapy. A clinician further highlighted that while guidelines suggest the use of ADT with high risk nmCRPC patients, medical literature shows that development of metastases may, on average, be delayed by two years with the use of apalutamide, enzalutamide or darolutamide.

5.2 Eligible Patient Population

In general, clinicians agreed that the reimbursement request, and inclusion and exclusion criteria of the clinical trial were generalizable to current clinical practice, and similar to trials with comparator agents. Patients with high risk nmCRPC who meet the following criteria were agreed upon by clinicians as the target population for treatment with darolutamide: rising PSA levels despite castrate testosterone levels, PSA doubling time of less than or equal to 10 months, ECOG performance status of 0 or 1, chemotherapy naïve, and no evidence of metastatic disease on conventional imaging (abdomen/pelvis CT and bone scan). One clinician stated that the inclusion criteria of the clinical trial were actually quite restrictive but did not provide further details.

Unmet need was highlighted for patients with nmCRPC, as this is a relatively new subgroup of patients who make up a minority of prostate cancer patients. In addition, there are no currently available treatments funded for nmCRPC patients beyond ADT. As there are no funded treatments for nmCRPC patients, an individual clinician commented that patients have to wait until they develop metastatic disease to receive treatment. Although apalutamide and enzalutamide were identified as treatments available through compassionate access programs, the clinician stated that relying on the pharmaceutical funded programs is not a secure long-term plan for nmCRPC patients.

One clinician stated that most urologists would identify only a few patients within their practice that meet this indication. nmCRPC patients were stated to be difficult to identify as they progress rapidly to metastatic disease. No other subgroups of interest were identified in any of the clinician inputs.

5.2.1 In clinical practice, is there evidence to extend the use of darolutamide to (provided all other eligibility criteria are met):

Patients who received prior chemotherapy or immunotherapy for prostate cancer (in the ARAMIS trial, these patients were excluded except for adjuvant/neoadjuvant treatment completed >2 years before randomization)

Regarding patients who have received prior chemotherapy, all clinicians noted that, while the evidence to extend to this population is limited, generalizing use of darolutamide to

this group would be acceptable. One clinician commented that there is biological plausibility of using darolutamide for patients with prior history of chemotherapy. Especially for patients with adjuvant/neoadjuvant chemotherapy greater than two years prior, clinicians from CCO stated there is reason to believe biological benefit as these patients were included in the ARAMIS trial.

Three individual clinician inputs stated that patients who have received prior chemotherapy would not be relevant to patients in the nmCRPC setting as chemotherapy is only indicated in patients in the metastatic setting; it would be unusual to use chemotherapy in patients who do not have metastatic disease. Clinicians from the joint input from PCC agreed that darolutamide should be extended to patients who received prior chemotherapy if they received it for metastatic castration-sensitive prostate cancer. For example, patients that achieve a complete radiological response to docetaxel plus ADT that subsequently progress to nmCRPC.

One clinician did not support the exclusion of patients who received either immunotherapy or chemotherapy. The clinician pointed out that the development of nmCRPC occurs, in general, sequentially; patients begin with localized disease, are then treated with surgery or radiation therapy some of whom will experience disease recurrence and exhibit rising PSA levels. The patients who experience disease recurrence will be treated with ADT. When patients become resistant to ADT, as indicated by rising PSA levels despite castrate levels of testosterone, they will be termed “castrate resistant.” If, in addition to being castrate resistant, patients show no evidence of metastasis during imaging, then they are termed to have nmCRPC. Essentially, the development of nmCRPC occurs after progression of localized disease followed by biochemical recurrence to nmCRPC. Therefore, the clinician suggested that a patient would not be exposed to chemotherapy or immunotherapy unless it was as part of a clinical trial. The clinician did not agree with excluding patients who had previously received chemotherapy or immunotherapy from receiving darolutamide; the clinician described such an exclusion as being punitive, as patients would be disadvantaged for taking part in a clinical trial at an earlier time point in their disease progression. Similarly, clinicians from PCC stated it was unreasonable to exclude such patients, as patients may volunteer for clinical trials involving immunotherapy that would disadvantage them if they are considering treatment with darolutamide. Clinicians from PCC also acknowledged that immunotherapy is not a currently funded treatment for prostate cancer patients in Canada. Due to lack of data, other individual clinician inputs and the joint input from CCO expressed uncertainty about extending use of darolutamide to patients who received prior immunotherapy.

Patients with PSA doubling time greater than 10 months

Both joint clinician inputs and eight of the ten individual clinician inputs supported that the use of darolutamide should be restricted to patients with a PSA doubling time of 10 months. Darolutamide was suggested to be used among patients with a high risk of developing metastases, which tends to be among patients with a PSA doubling time of less than 10 months. A clinician from the joint input on behalf of PCC stated that, specifically, patients with high risk nmCRPC defined by PSA doubling time of less than or equal to 10 months without evidence of metastasis on conventional imaging should be eligible. Many clinician inputs identified a PSA doubling time of less than or equal to 10 months as a good criterion for eligibility, as the use of darolutamide for patients with a longer PSA doubling time would not be evidence based. In addition to acknowledging the lack of evidence to support a longer PSA doubling time, one of the clinician inputs stated that data for comparator agents has always favoured use earlier in the disease process. Clinicians on the joint input from PCC also acknowledged the lack of evidence for use of darolutamide

among patients with longer PSA doubling times. Only input from one individual clinician stated seeing no reason why use of darolutamide could not be extended to patients with longer PSA doubling times.

Patients with ECOG performance status of 2 or greater

All inputs except one individual clinician input highlighted that darolutamide should not be extended to patients with an ECOG performance status of 2 or greater. Clinicians identified the lack of evidence to support the use of darolutamide among patients with an ECOG performance status of 2 or greater. One individual clinician expressed concern for patients with ECOG performance status of 3 or higher due to issues with fatigue. However, clinicians from PCC stated that an ECOG performance status of 2 or greater should not be an exclusion criterion if the cause of a poor performance status was not related to prostate cancer, but to comorbidities. The individual clinician that thought extension of darolutamide to patients with poor performance status was reasonable as androgen receptor inhibitors are generally benign, and it might be worth trying darolutamide among patients with poorer performance status even if they were not included in the ARAMIS trial. If patients with poorer performance status cannot tolerate darolutamide, then treatment should be stopped. However, if patients with poor performance status can tolerate darolutamide, the clinician assumed that similar efficacy might be observed.

5.3 Relevance to Clinical Practice

Both joint clinician inputs and six of ten individual clinician inputs identified having experience prescribing darolutamide. Clinicians agreed that darolutamide would be used among high risk nmCRPC patients with rapid PSA doubling times. Darolutamide showed superior MFS compared to placebo and ADT. Apalutamide and enzalutamide were also stated to show superior MFS compared to placebo and ADT; a clinician suggested that darolutamide be considered similarly to apalutamide and enzalutamide depending on funding/cost. Compared to apalutamide and enzalutamide, clinicians agreed darolutamide showed similar efficacy as all drugs delayed development of clinically significant metastatic disease by approximately two years (22 months for darolutamide, 24 months for apalutamide, and 22 months for enzalutamide).

While no direct comparative evidence exists, the safety profile of darolutamide was suggested to be superior to apalutamide and enzalutamide. Clinicians reported fewer drug-drug interactions, fatigue, rash, falls, fracture risk, hypertension, and reduced rate of discontinuation. It was highlighted that darolutamide exhibits reduced crossing of the blood brain barrier leading to reduced neurocognitive effects. Specifically, several clinicians highlighted the advantage of being able to use darolutamide among patients with seizure history. History of seizures, liver toxicity, medication interactions, and thyroid interactions were identified as contraindications to apalutamide or enzalutamide among patients with nmCRPC, however darolutamide may be able to reduce or eliminate most of these.

One clinician stated that while darolutamide is indicated for patients with nmCRPC, they would be interested in using darolutamide in metastatic CRPC and earlier stage cases. Overall, darolutamide was identified as a “nice to have” drug with similar efficacy as apalutamide and enzalutamide, but with an improved tolerability and safety profile. Darolutamide was referred to by a clinician from PCC as a welcome addition to the treatment space, as it has fewer side effects which may make it easier to prescribe in an already population receiving multiple medications for comorbidities. Aside from the safety

profile, one clinician stated there were no specific contraindications that would lead them from choosing darolutamide over apalutamide or enzalutamide.

5.4 Sequencing and Priority of Treatments with Darolutamide

5.4.1 Please consider if there is evidence to support the optimal treatment sequencing of darolutamide with other treatment options (e.g., apalutamide, enzalutamide, abiraterone, and chemotherapy), for the treatment of prostate cancer:

In what clinical scenarios would darolutamide or apalutamide or enzalutamide be the preferred treatment for patients with non-metastatic castration-resistant prostate cancer in this setting? Please comment on the preference considering patient preference, efficacy, safety, and administration.

Clinicians highlighted that currently neither enzalutamide nor apalutamide are standard of care in the nmCRPC setting. While darolutamide, enzalutamide and apalutamide show similar efficacy, darolutamide may have improved safety. Seizure and rash were specified by clinicians, as darolutamide showed lower risk for both adverse events than enzalutamide and apalutamide, respectively. Although no trials exist to directly compare darolutamide to apalutamide or enzalutamide, one clinician stated that tolerability is often an issue for enzalutamide which can result in discontinuation. One clinician input stated that clinical assessments in the ARAMIS trial occurred less frequently than in the SPARTAN trial, complicating the comparison of darolutamide to enzalutamide or apalutamide. The PCC joint clinician input and other individual clinician inputs suggested that darolutamide may be the preferred treatment choice for patients with pre-existing fatigue, seizure disorders, hypothyroidism, or those in whom drug-drug interactions are a concern or who are at risk for falls. The reduced drug-drug interactions and cognitive side effects was highlighted by one clinician, as they highlighted that the nmCRPC population of patients tends to be elderly.

All three drugs are oral therapies and were considered to be reasonable options for nmCRPC patients. All drugs were stated to be administered similarly, with dosing frequency being the only difference between them. The lack of data to support the choice of one anti-androgen over another was highlighted. Each drug was stated to have its own nuances, side effect profile and related trial eligibility (such as, inclusion of patients with seizure history) that will allow physicians to choose the optimal therapy for each nmCRPC patient. As one drug will likely not be best for all patients, choice of agent would be highly subject to clinician experience and tolerability of the drug with the patient.

What is the preferred treatment (e.g., abiraterone, enzalutamide and chemotherapy) for metastatic disease after treatment with darolutamide in the non-metastatic setting?

As darolutamide, apalutamide ad enzalutamide share the same mechanism of action, one clinician suggested the drugs should not be funded in succession. Therefore, if a patient progresses on one of darolutamide, apalutamide or enzalutamide, clinicians did not support the use of another anti-androgen for subsequent therapy. Clinicians also stated they would never sequence enzalutamide or apalutamide to darolutamide, or vice versa, as prior studies showed poor response rates and non-durable response in those with initial response to such a sequence. One clinician highlighted data from the

BC Cancer Agency showing that response rates in the metastatic CRPC setting on patients with enzalutamide converting to abiraterone at PSA progression are only about 6%, with median time to progression of about 1.6 months. Similar response rates to sequencing from darolutamide to abiraterone were stated to be expected due to having the same mechanism of action as enzalutamide. Darolutamide was stated not to replace any current treatment available, but rather be a potential substitution for apalutamide or enzalutamide.

All clinician inputs agreed that the preferred treatment upon progression of darolutamide would be chemotherapy; clinicians suggested treatment with a taxane chemotherapy or possibly radium 223 in men with bone-predominant progression to metastatic CRPC without visceral metastases. Similarly, if patients with nmCRPC progress on enzalutamide or apalutamide, chemotherapy would also be the preferred treatment of choice. Clinicians from CCO stated that abiraterone is likely not to have a role in the nmCRPC setting as it has not formally been evaluated. Clinicians from CCO agreed that patients are left with chemotherapy or clinical trials upon progression with darolutamide. A clinician from Alberta identified sequencing to begin with abiraterone with prednisone or enzalutamide in the first line, docetaxel upon progression, and abiraterone or enzalutamide upon failure (whichever was not used in the first line).

The appropriateness of using darolutamide following abiraterone, enzalutamide, apalutamide or other second generation anti-androgens after failure of these drugs in this therapeutic space should these patients continue to remain non-metastatic.

Clinicians highlighted the lack of data regarding sequencing with darolutamide following progression on abiraterone, enzalutamide or apalutamide. One clinician questioned the utility of switching to darolutamide for patients progressing on enzalutamide or apalutamide given they all have the same mechanism of action. Other clinician inputs including both joint inputs agreed that use of darolutamide following enzalutamide or apalutamide would not be expected to significantly benefit nmCRPC patients. However, a clinician from the joint PCC clinician input and another individual clinician input supported the switching to darolutamide should patients experience severe side effects related to apalutamide, enzalutamide or abiraterone. In addition, the clinician commented on darolutamide following abiraterone being a moot point; abiraterone is not approved for use in stages of disease leading up to nmCRPC.

5.5 Companion Diagnostic Testing

Clinicians agreed that no new diagnostic testing is required. Darolutamide was stated to require minimal clinical monitoring. One clinician compared darolutamide to other agents requiring serial examination for fluid retention, congestive heart failure and hypertension. Current standard of care includes a CT scan of a patient's chest, abdomen, and pelvis, and a nuclear medicine bone scan to rule out metastatic disease. Patients were stated to be followed-up with bloodwork, including tests for PSA, testosterone, alkaline phosphatase (ALP), and lactate dehydrogenase (LDH), and CT imaging and bone scans, which are routine in these patients. Clinicians from PCC stated that tests for PSA doubling time were stated to be reliable, cheap, easy to calculate, and is already used in clinical practice. Usage of these tests is mandatory in non-metastatic hormone refractory prostate cancer patients to screen for clinical progression, and the tests were stated not to be expected to change; therefore, no additional strain on healthcare system resources is expected.

Clinicians from PCC also identified the Memorial Sloan Kettering Cancer Center (MSKCC) online prediction tool that can be used to help clinicians calculate PSA doubling times. A

time frame within which patients have had a negative CT and bone scan to qualify for funding was suggested. Prostate-specific membrane antigen and positron emission tomography (PSMA-PET) scans were identified by one clinician as a new imaging tool for patients with nmCRPC. The clinician expressed uncertainty whether PSMA-PET scans qualified as a companion diagnostic test, but stated that, if so, it would not result in an increase in use of darolutamide. The clinician suggested that PSMA-PET scans may potentially decrease the use of darolutamide. PSAM-PET scans would allow for detection of patients with remote metastatic disease; metastatic disease status already exists but it is not visible on conventional imaging with CT and Tc^{99} Bone Scans.

5.6 Additional Information

One of the clinicians from PCC expressed strongly that each Canadian man with advanced prostate cancer should, during the course of their disease, have at least one second generation androgen receptor signalling inhibitor, such as, abiraterone, apalutamide, enzalutamide or darolutamide. The clinician stated that the clinical benefit and quality of life improvement on such drugs is more pronounced in earlier stages of advanced prostate cancer. Therefore, the clinician stated that patients should have funded access to second generation androgen receptor signalling inhibitors when they present with a disease stage supporting their use.

One clinician commented on the market share competition darolutamide may face with comparator agents. As the third agent to enter the market after enzalutamide and apalutamide, to gain market share, the clinician stated darolutamide would need to demonstrate significantly improved tolerability and decreased need for physician monitoring. Direct medication costs were suggested to likely be similar to competitor agents, but there may be modest cost saving achieved through fewer physician visits and decreased need for laboratory monitoring. Another clinician stated that while treatments such as darolutamide can be costly, the delaying of metastases should be considered as the cost of managing symptomatic metastatic disease, and that consequences of metastases in prostate cancer can be substantial.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of darolutamide in combination with ADT for patients with nmCRPC who are at high risk of developing metastases (high risk defined as PSA doubling time ≤ 10 months) during continuous ADT and who have a good ECOG performance status.

Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below (Table 6.1). Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of darolutamide should be included.	Patients with nmCRPC who are at high risk of developing metastases (high risk defined as PSA doubling time ≤ 10 months) during continuous ADT and who have a good ECOG performance status. Subgroups: • Age (<65 years vs ≥ 65 years) • Baseline ECOG performance status (0-1 vs ≥ 2) • Baseline serum PSA level (≤median vs ≥ median) • Baseline PSA doubling time (>6 months vs ≤6 months) • Use of bone sparing agents (yes vs no) • Local or regional nodal disease at baseline (NO vs N1) • Previous prostate cancer treatments (type of treatment) • Ethnicity (White vs Black vs Asian vs Hispanic or Latino vs Other)	Darolutamide (600 mg twice daily) and ADT	Enzalutamide (160 mg once daily) + ADT Apalutamide (240 mg one daily) + ADT Placebo + ADT	Primary • **MFS** Secondary • Time to PSA progression • Time to first use of new antineoplastic therapy • **OS** • Time to pain progression • Time to first use of cytotoxic chemotherapy • Chemotherapy-free disease-specific survival • Chemotherapy-free survival • PSA response rates • **HRQoL** • **PFS** **Safety** • AEs • SAEs • WDAEs

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
				• Dose adjustment, interruption and/or discontinuation • Time to discontinuation
Abbreviations: AE=adverse events; ECOG = Eastern Cooperative Oncology Group; HRQoL=Health related quality of life; MFA = metastasis-free survival; nmCRPC = non-metastatic castration resistant prostate cancer; OS = overall survival; PSA = prostate-specific antigen; RCT=randomized controlled trial; SAE=serious adverse events; WDAE=withdrawals due to adverse events;				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).				

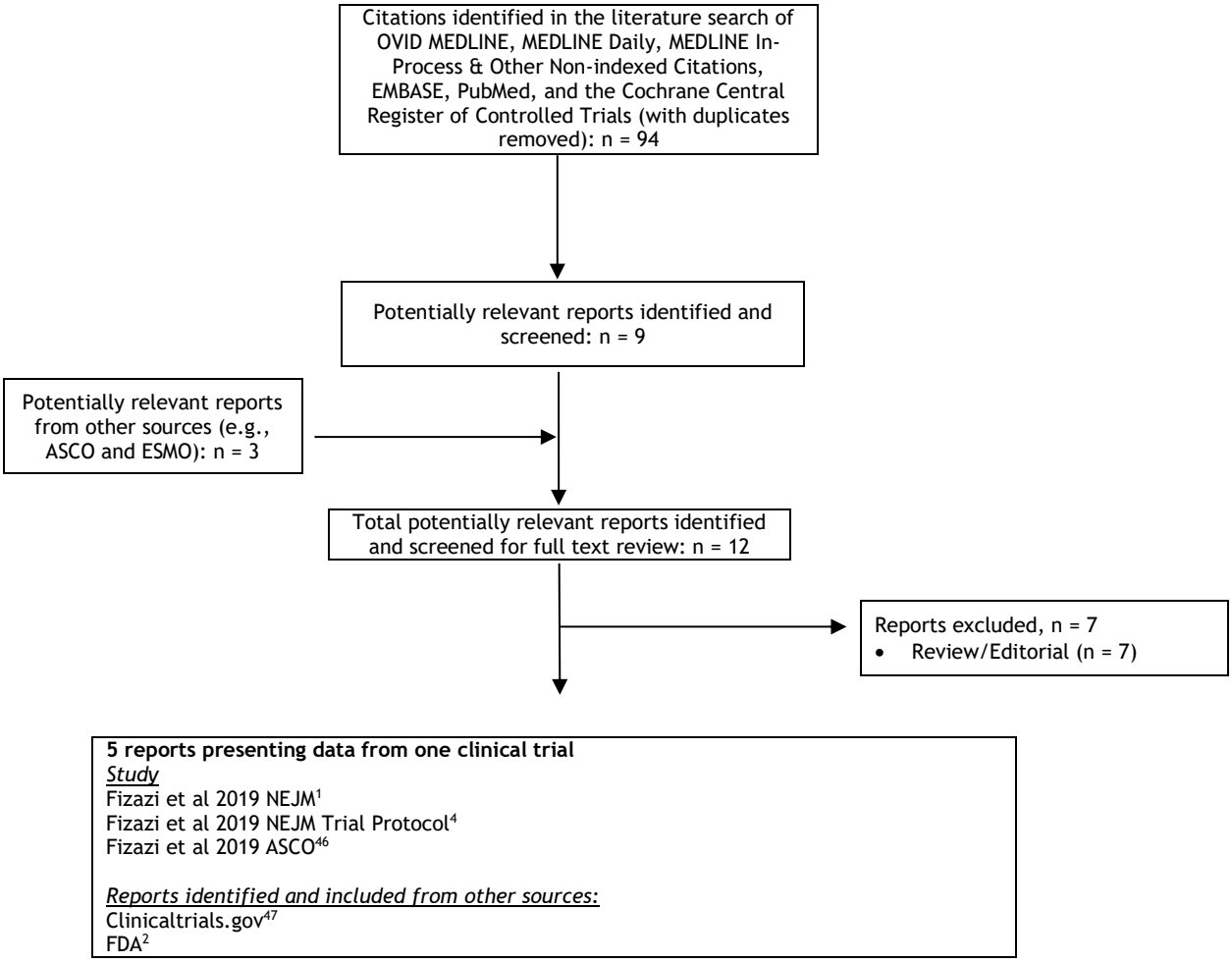
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 94 potentially relevant reports identified, one study (ARAMIS), reported in five citations, was included in the pCODR systematic review (Figure 6.1).[1,2,4,46,47] Seven reports were excluded because they were either a review or an editorial. Additional reports related to the ARAMIS trial were obtained from the Sponsor.[3,7,48]

Figure 6.1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the ARAMIS trial were also obtained through requests to the Sponsor by pCODR [Clinical Rationale,[7] Indirect Treatment Comparison,[7] Clinical Summary Report,[7] Checkpoint Responses on 11-November-2019,[3] Fizazi et al (2019) ASCO[48]]

6.3.2 Summary of Included Studies

The pCODR systematic review included one ongoing, randomized, double-blind, placebo-controlled, phase III trial (ARAMIS) that assessed the safety and efficacy of darolutamide as compared to placebo in 1,509 men with nmCRPC and a PSA doubling time of 10 months or less.

6.3.3 Detailed Trial Characteristics

The summary of the trial and select quality characteristics are presented in Tables 6.2 and 6.3.

Table 6.2: Summary of ARAMIS trial

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
Study ARAMIS **Trial Characteristics** Ongoing, randomized, double-blind, placebo-controlled phase III trial **Number Randomized** N= 1509 **Number Treated** N= 1508 **Number of centres and countries** 409 centers in 36 countries **Patient Enrolment Dates** Sep-2014 to Mar-2018 **Primary Analysis Database cut-off** 3-Sep-2018 **Final Analysis Database cut-off** 15-November-2019[7] **Funding** Bayer Healthcare and Orion Pharma	Key Inclusion Criteria: • Males aged ≥ 18 years • Histologically or cytologically confirmed adenocarcinoma of prostate without neuroendocrine differentiation or small cell features. • CRPC defined as three rising PSA levels after the nadir taken at least 1 week apart during ADT. If the patient has a history of antiandrogen use, the most recent PSA value must be obtained at least 4 weeks after anti-androgen withdrawal. • Castrate level of serum testosterone (<1.7 nmol/l [50 ng/dl]) on GnRH agonist or antagonist therapy or after bilateral orchiectomy at screening or Day 1 visit. Patients who have not undergone bilateral orchiectomy must continue GnRH therapy during the study. • PSADT of ≤10 months and PSA ≥2 ng/ml at screening. • ECOG performance status of 0–1. • Blood counts at screening: hemoglobin ≥9.0 g/dl, absolute neutrophil count ≥1500/µl (1.5Å~109/l), platelet count ≥100,000/µl (100Å~109/l) (patient must not have received any growth factor or blood transfusion within 7 days of the hematology laboratory obtained at screening). • Screening values of serum alanine transaminase (ALT) and aspartate transaminase (AST) ≤2.5 x upper limit of normal (ULN), total bilirubin ≤1.5 x ULN (except patients with a diagnosis of Gilbert's disease), creatinine ≤2.0 x ULN. Key Exclusion Criteria: • History of radiographically documented metastatic disease at any time or presence of detectable metastases by blinded central reading within 42 days prior to start of study treatment. Presence of pelvic lymph nodes <2 cm in short axis below the aortic bifurcation is allowed.	Intervention *Darolutamide* 600 mg given as two 300-mg tablets twice daily with food (a daily dose of 1200 mg) Control *Placebo*	Primary: • MFS Secondary: • OS • Time to first SSE • Time to initiation of first cytotoxic chemotherapy for prostate cancer • Time to pain progression Exploratory: • PFS • Time to first prostate cancer-related invasive procedure • Time to initiation of subsequent antineoplastic therapy • Time to PSA progression • Percent of patients with PSA response • Percent of patients with ECOG performance status deterioration • Time to ECOG performance status deterioration • Changes in HRQoL assessed by FACT-P, EORTC-QLQ-PR25 and EQ-5D-3L

Trial Design	Inclusion Criteria	Intervention	Trial Outcomes
	• Symptomatic local-regional disease that requires medical intervention including moderate/severe urinary obstruction or hydronephrosis due to prostate cancer. • Prior treatment with: (1) second-generation androgen receptor (AR) antagonists such as enzalutamide and apalutamide, or darolutamide or other investigational AR antagonists; (2) CYP17 enzyme inhibitors, such as abiraterone acetate, TAK-700; or (3) oral ketoconazole for longer than 28 days. • Use of estrogens or 5-α reductase inhibitors (finasteride, dutasteride) within 28 days before randomization and AR antagonists (bicalutamide, flutamide, nilutamide, cyproterone acetate) at least 28 days before screening. • Prior chemotherapy or immunotherapy for prostate cancer, except adjuvant/neoadjuvant treatment completed >2 years before randomization. • Use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/day within 28 days before randomization. • Radiation therapy (external beam radiation therapy, brachytherapy, or radiopharmaceuticals) within 12 weeks before randomization. • Treatment with an osteoclast-targeted therapy (bisphosphonate or denosumab) to prevent skeletal-related events within 12 weeks before randomization. Patients receiving osteoclast-targeted therapy to prevent bone loss at a dose and schedule indicated for osteoporosis may continue treatment at the same dose and schedule. • Prior malignancy. • Treatment with any investigational drug within 28 days before randomization.		

Abbreviations: ADT = androgen deprivation therapy; ALT = alanine transaminase; AST = aspartate transaminase; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-PR25 = European Organization for Research and Treatment of Cancer Quality of life Questionnaire – Prostate Cancer Module; EQ-5D-3L = European QoL 5-domain scale; FACT-P = Functional Assessment of Cancer Therapy-Prostate; GnRH = gonadotrophin releasing hormone; HRQoL = health-related quality of life; MFS = metastasis-free survival; PFS = progression-free survival; PSA = prostate specific antigen; PSADT = prostate specific antigen doubling time; SSE = symptomatic skeletal event; ULN = upper limit of normal

Source: ARAMIS Trial Protocol and FDA[2,4]

Table 6.3: Select quality characteristics of included studies that assessed the efficacy and safety of darolutamide in combination with ADT for patients with nmCRPC who are at high risk of developing metastases during continuous ADT and who have a good ECOG performance status

Study	ARAMIS
Treatment vs. Comparator	Darolutamide (600 mg [two 300-mg tablets] twice daily) or placebo while continuing androgen-deprivation therapy
Primary outcomes	MFS
Required sample size	The power calculation for MFS was based on a sample size of 1,500 patients. Three hundred and eighty five events were required in order for the trial to have 91% power to detect a HR of 0.71 using a two-sided alpha of 0.05.[4] A diluted HR of 0.71 was chosen to account for the 5% of patients with baseline metastasis.[2]
Sample size	The final sample size included 1,509 patients with nmCRPC and a PSA doubling time of 10 months or less.
Randomization method	Randomization was stratified according to PSA doubling time (≤6 months or >6 months) and the use of osteoclast-targeted therapy at randomization (yes or no).[4]
Allocation concealment	Yes. The randomization schedule was created using randomly permuted blocks and patients were randomized using interactive response technology.
Blinding	ARAMIS was a double-blind, placebo-controlled, phase 3 RCT. All patients, study personnel and the sponsor's personnel directly involved in the conduct of the trial were blinded to treatment assignment. An independent DSMB was employed to safeguard patients randomized to the study. The DSMB could perform unblinded analyses on the data.[4][protocol pg 101] The FDA noted that PSA levels were not blinded during the trial.[2]
ITT Analysis	Yes
Final analysis	Yes. The final analysis for OS was pre-specified and it was planned to occur when 240 OS events had occurred. The database cut-off for the final analysis was on 15-November-2019.[7]
Early termination	The ARAMIS was not terminated early and continued as per pre-specified study plan.
Ethics Approval	Yes

DSMB = Data and Safety Monitoring Board; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = Intention to Treat; MFS = metastasis-free survival; nmCRPC = nonmetastatic, castration-resistant prostate cancer; OS = overall survival; PSA = prostate-specific antigen; RCT = randomized controlled trial

a) Trials

Trial Characteristics

The ARAMIS trial is an ongoing, international, multicentre, randomized, double-blind, placebo-controlled, phase III trial that assessed the safety and efficacy of darolutamide as compared to placebo in 1,509 men with nmCRPC and a PSA doubling time of 10 months or less.[1] The trial was conducted in 409 centres within 36 countries, including Canada.[1] It was sponsored by Orion Pharma and Bayer HealthCare.

Patients were included in the trial if they met the following criteria: 18 years of age or older; histologically or cytologically confirmed adenocarcinoma of the prostate; castration-resistant prostate cancer; a baseline PSA level of at least 2 ng per milliliter; a PSA doubling time of 10 months or less; and an ECOG performance status of 0 to 1.[1] Patients were excluded if they had detectable metastases or a history of metastatic disease; however, patients with the presence of

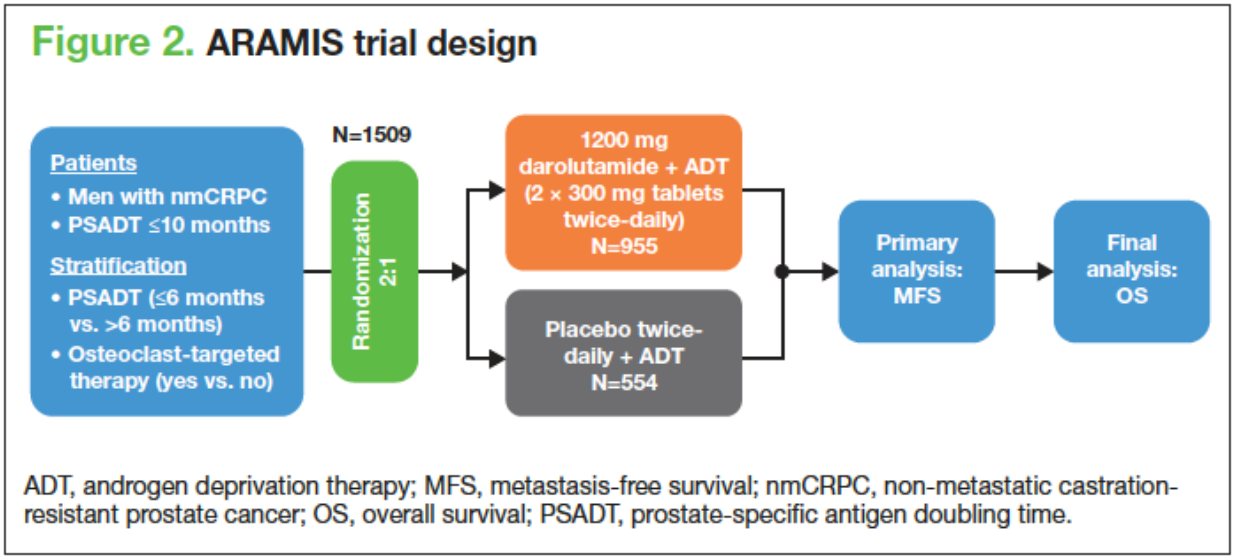
pelvic lymph nodes less than 2 cm in diameter in the short axis below the aortic bifurcation were included in the trial. Patients who had a history of previous seizure or conditions predisposing to seizure were not excluded from participating in the trial.[1] Further details on the inclusion criteria and exclusion criteria are provided in Table 6.2.[1]

Patients were randomized in a 2:1 ratio to receive either darolutamide (600 mg [two 300-mg tablets] twice daily) or placebo, using an interactive voice response system. The randomization was stratified by PSADT (>6 months vs. ≤ 6 months) and the use of bone sparing agents (yes vs. no).[4]

The study design is illustrated in Figure 6.2. As shown, the study consisted of two phases: the study treatment phase and the long-term follow-up phase.[46] In the first phase, patients received either oral darolutamide or a matching placebo using a continuous daily dosing schedule while continuing androgen-deprivation therapy. Patients continued taking their randomly assigned regimen until protocol-defined progression, discontinuation of the regimen because of adverse events or withdrawal of consent. In the second phase, patients initially randomized to the intervention group could continue receiving darolutamide while those randomized to the control group could cross-over and received open-label darolutamide. According to the FDA, cross-over was only allowed once the MFS analysis was completed. However, there is the potential that cross-over will confound the final OS analysis.[2]

Patients continued to receive androgen-deprivation therapy (luteinizing hormone–releasing hormone agonist or antagonist) throughout the trial.[1]

Figure 6.2: ARAMIS trial design



Fizazi, K, SHore, N, Tammela. TL, et al. ARAMIS: efficacy and safety of darolutamide in non-metastatic castration-resistant prostate cancer [poster]. ASCO GU 2019.[46]

Disease assessments, including CT and MRI, were performed by a BICR every 16 weeks from Cycle 1 Day 1 until confirmed metastasis. Assessments could be performed if distant metastases were suspected. PSA levels were measured at a central laboratory and it was assessed on Day 1 of

Cycles 1 to 6, on Day 1 every 2 cycles starting from Cycle 7 to Cycle 13, and at the end of treatment.[2] The FDA noted that PSA levels were not blinded during the trial.[2]

Patients who had documented locoregional-only progression were also allowed to remain on their assigned therapy at the investigator's discretion, even if this progression was symptomatic and/or required intervention. In addition, patients were allowed to continue study treatment if BICR reported metastasis during study treatment but the investigator provided an alternate explanation for the findings. In contrast, at the investigator's discretion, patients could discontinue study treatment for progressive locoregional or metastatic disease if not confirmed by the BICR.[2]

The primary endpoint in the ARAMIS trial was MFS. Secondary outcomes were OS, time to pain progression, time to cytotoxic chemotherapy and time to first SSE. The main exploratory outcomes were PFS, time to PSA progression, PSA response rate, HRQoL and safety.

The trial was designed to have 91% power to detect a HR of 0.71 for MFS with a two-sided significance level (α) of 0.05.[1] The assumed HR was 0.65 but a diluted HR of 0.71 was chosen to account for the 5% of patients with baseline metastasis.[2] Based on the results of a phase III study of denosumab versus placebo in high risk nmCRPC patients,[5] the median MFS was assumed to be 25 months in the placebo group. Approximately 1500 patients (1000 in the darolutamide group and 500 in the placebo group) were planned to be randomized and it was estimated that 385 MFS events were required for the primary analysis.[4] The trial was originally designed to detect a HR of 0.75 for MFS; however, based on the results from the PROPSER and SPARTAN trials, it was decided that the HR of 0.75 was too conservative. In June 2018, the FDA agreed to change the target HR from 0.75 to 0.65 thereby reducing the targeted number of MFS events from 572 to 385.[2] The FDA stated that this protocol amendment did not bias the interpretation of the results.[2]

The trial was composed of two analysis populations: the ITT population and the safety set population.[4] The efficacy analyses were conducted in the ITT population, which was composed of all randomized patients regardless of the actual treatment they received. The safety analyses were conducted in the safety set population, which was composed of all patients that received at least one dose of the study drug.[4]

The objective of the primary analysis for the AMARIS trial was to compare MFS between the two treatment groups using a two-sided log-rank test, stratified according to the pre-specified factors at α= 0.05 significance level.[4] A hierarchical, adaptive, group sequential procedure was used for the secondary outcomes in the following order: OS, time to pain progression, time to cytotoxic chemotherapy, time to SSE.[4] The Sponsor noted that the final time to pain progression was performed at the primary analysis for MFS (i.e. 03-September-2018 database lock). An interim analysis was planned to occur for OS and the other secondary outcomes at the time of the primary analysis. Additionally, the final analysis for OS was pre-planned and it will be conducted after 240 OS events.[4] For the final OS analysis, a similar hierarchical gatekeeping approach was used.

Subgroups analyses were planned a priori.[4] All subgroup analyses were descriptive and performed using non-stratified Cox model and a log-rank test.

Protocol and statistical analysis plan amendments were made to the ARAMIS trial (Table 6.4). The FDA stated that the protocol amendments did not bias nor confound interpretation of the results of the trial because it was not expected to influence the final effect estimates of the trial.[2]

Table 6.4: Summary of the major amendments that occurred in the ARAMIS trial

Amendment	Date	Changes
Protocol Amendment 1	24-November-2014	• Clarified the definition of progression in soft tissue to exclude progression in lymph nodes in the pelvis below the aortic bifurcation. • Amended the eligibility criterion related to PSA values to allow patients with 3 rising PSA values at least 1 week apart during ADT to enroll. The observation period of PSA values that could be used in the calculation of PSADT was extended from 6 to 12 months. • Extended the collection period of pain data from the end of the follow-up period to the time of documented pain progression. • Added "suspected disease progression" as a reason for an unscheduled visit, and chest, abdomen and pelvic CT/MRI or x-ray and bone scan were added as options for assessments that could be performed at the unscheduled visit. • Stipulated that another systemic antineoplastic therapy could be initiated no sooner than 7 days after the last dose of study treatment, and the end-of-study treatment visit was to take place 28 days after the last dose (instead of 7 days) for patients who discontinued study treatment and started subsequent antineoplastic therapy. • Limited the exclusion criterion for osteoclast-targeted therapy to patients using this therapy for prevention of SREs (not for osteoporosis at a dose and schedule indicated for osteoporosis).
Protocol Amendment 2	19-July-2016	• The protocol was updated to reflect the sponsorship change from Orion to Bayer, and to update information about the study number and study drug nomenclature. • Clarifications on inclusion and exclusion criteria were made. • Requirements for monitoring drug-drug interactions were revised.
Statistical Analysis Plan Amendment 1	15-March-2017	• Changes were made to the sample size and justification to reflect the higher estimation of the treatment effect (HR of 0.75 was changed to 0.70) and statistical considerations were condensed. • A safety analysis set was described. • Censoring rules were updated for secondary efficacy variables and the sensitivity analysis of MFS. • A description was added for placebo patients being allowed to receive open-label darolutamide treatment. • "Time to ECOG PS deterioration" was added as an exploratory endpoint. • Clarified that there was no planned formal interim analysis for the primary endpoint.
Statistical Analysis Plan Amendment 2	22-June-2017	• Updated the planned number of randomized patients from approximately 1200 to approximately 1300.
Protocol Amendment 3	26-February-2018	• Increased the assumed treatment effect size from a hazard ratio of 0.75 (requiring 572 MFS events) 0.65 (requiring approximately 385 MFS events). • Added an option for patients to receive open-label darolutamide at the time of study treatment code unblinding should the study results support a positive benefit/risk assessment for darolutamide.
Statistical Analysis Plan Amendment 3	12-March-2018	• Changes were made to the sample size and justification due to identification of patients with metastases at baseline, a secondary analysis of MFS was added with censoring rules adjusted accordingly, and several sensitivity analyses of MFS were added.

Amendment	Date	Changes
		• The hierarchical order of the analysis of secondary endpoints was updated to be: OS, time to pain progression, time to first symptomatic skeletal event, time to cytotoxic chemotherapy. The second sequential test of secondary endpoints was modified to occur when approximately 240 OS events have been observed. • The per protocol analysis set (PPS) was removed and the intent-to-treat analysis set (ITT) was named the full analysis set (FAS).
Statistical Analysis Plan Amendment 4	10-August-2018	• MFS and PFS analyses were updated for handling of patients with baseline metastasis. • The hierarchy of secondary analyses was updated to: OS, time to pain progression, time to cytotoxic chemotherapy, time to first symptomatic skeletal event. • Time to first opioid use for cancer pain was added as an additional endpoint. • In the section for patient disposition, the number of patients who discontinued study treatment due to increased PSA without documented metastasis was added. • Additional laboratory parameters to be analyzed in baseline characteristics were included. • Flags were added related to the independent central image reading process with a table showing all available flags. • Subgroups of interest were modified for MFS and OS and safety subgroups were updated. • Analysis of special topics TEAEs was added.

Data source: Clinical Summary Report by Bayer and FDA[2,7]

b) Populations

Overall, the baseline characteristics of patients in the ARAMIS trial were well balanced between the two treatment groups (Table 6.5).[1] The median ages in both treatment groups was 74 years (darolutamide range: 48-95 and placebo range: 50 to 92). The median PSA doubling time at baseline was 4.4 months (range: 0.7 to 11.0) in the darolutamide group and 4.7 months in the placebo group (range: 0.7 to 13.2).[1] The median time from initial prostate cancer diagnosis to randomization was 86.2 months in the darolutamide group and 84.2 months in the placebo group.[3] As compared to the darolutamide group, slightly more patients in the placebo group had a history of treatment with a bone sparing agent (6% vs 3%), presence of lymph nodes on central imaging review (<2cm) (10.5% vs 11.9%) and an ECOG performance status of 0 (71% vs 68%); however, patients in both groups had a similar proportion for those who have received two or more previous hormonal therapies (76% for both).[1] The incidence of seizures was 0.2% in both groups. None of the patients enrolled with a history of seizure (N = 12 in the darolutamide group) had experienced seizures while receiving darolutamide.[1]

The types and frequencies of prior prostate cancer treatments are presented in Table 6.6.[2] majority of patients in the darolutamide and placebo groups had received treatment for prostate disease at the baseline (95.9% and 95.7%, respectively). The most common prior medications for prostate cancer were bicalutamide, leuprorelin, goserelin, and triptorelin, flutamide and cyproterone.

Table 6.5: Baseline characteristics of patients enrolled in the ARAMIS Trial[&]

Characteristic	Darolutamide (N=955)	Placebo (N=554)
Median age (range) — yr	74 (48–95)	74 (50–92)
Geographic region — no. (%)		
North America	108 (11)	76 (14)
Asia-Pacific	119 (12)	67 (12)
Rest of the world†	728 (76)	411 (74)
Median time from initial diagnosis (range) — mo	86.2 (2.6–337.5)	84.2 (0.5–344.7)
Presence of lymph nodes on central imaging review — no. (%)		
Yes	163 (17)	158 (29)
No	792 (83)	396 (71)
Median serum PSA level (range) — ng/ml	9.0 (0.3–858.3)	9.7 (1.5–885.2)
PSA doubling time		
Median (range) — mo	4.4 (0.7–11.0)	4.7 (0.7–13.2)
≤6 mo — no. (%)	667 (70)	371 (67)
>6 mo — no. (%)	288 (30)	183 (33)
Median serum testosterone level (range) — nmol/liter‡	0.6 (0.2–25.9)	0.6 (0.2–7.3)
ECOG performance status — no. (%)§		
0	650 (68)	391 (71)
1	305 (32)	163 (29)
Use of bone-sparing agent — no. (%)		
Yes	31 (3)	32 (6)
No	924 (97)	522 (94)
Previous hormonal therapy agents received — no. (%)¶		
One	177 (19)	103 (19)
Two or more	727 (76)	420 (76)
Not applicable‖	51 (5)	31 (6)

* Percentages may not total 100 because of rounding. PSA denotes prostate-specific antigen.
† This category predominantly includes European countries (15% of these patients came from non-European countries).
‡ Testosterone levels from screening or day 1 could be used for eligibility, and all patients met the inclusion criterion of having a testosterone level lower than 1.7 nmol per liter.
§ Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with higher scores reflecting greater disability.
¶ Common previous hormonal therapies for prostate cancer (received by ≥10% of all patients) included leuprolide (52%), goserelin (32%), triptorelin (29%), bicalutamide (66%), flutamide (13%), and cyproterone (11%).
‖ This category includes patients who underwent surgical castration.

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[&] *Note: According to the sponsor, the following rates were subsequently correct during the Health Canada review, the presence of lymph nodes during the central imaging review was 10.5% in the darolutamide group and 11.9% in the placebo group.*

Table 6.6: Prior Prostate Cancer Drug Therapy (more than two patients in either group)

	Darolutamide N = 955	Placebo N = 554
Any	916 (95.9%)	530 (95.7%)
Bicalutamide	642 (67.2%)	358 (64.6%)
Leuprorelin, Leuprorelin acetate	483 (50.6%)	295 (53.2%)
Goserelin, Goserelin acetate	309 (32.4%)	174 (31.4%)
Triptorelin, Triptorelin acetate, Triptorelin embonate	286 (29.9%)	155 (28.0%)
Flutamide	121 (12.7%)	79 (14.3%)
Cyproterone, Cyproterone acetate	110 (11.5%)	60 (10.8%)
Degarelix, Degarelix acetate	61 (6.4%)	34 (6.1%)
Buserelin, Buserelin acetate	40 (4.2%)	29 (5.2%)
Diethylstilbestrol	11 (1.2%)	5 (0.9%)
Finasteride	10 (1.0%)	5 (0.9%)
Chlormadinone acetate	6 (0.6%)	5 (0.9%)
Histrelin, Histrelin acetate	6 (0.6%)	6 (1.1%)
Dexamethasone	5 (0.5%)	3 (0.5%)
Dutasteride	4 (0.4%)	2 (0.4%)
Gonadorelin, Gonadorelin diacetate tetrahydrate	4 (0.4%)	3 (0.5%)
Hexestrol	4 (0.4%)	0
Nilutamide	4 (0.4%)	5 (0.9%)
Octreotide	3 (0.3%)	0
Prednisone	3 (0.3%)	3 (0.5%)
Tamsulosin, Tamsulosin hydrochloride	3 (0.3%)	0

Source: dataset ADCM; variables CMCAT, TRTP, CMDECOD

Data source: FDA[2] pg 101

c) Interventions

Treatment Dosing Schedule

Patients in the darolutamide group received 600 mg (given as two 300-mg tablets) of darolutamide twice daily with food (a daily dose of 1200 mg) while patients in the placebo group received a matching placebo.[4] Patients continued taking their randomly assigned regimen until protocol-defined progression, discontinuation of the regimen because of adverse events or withdrawal of consent. Patients in both treatment groups continued to receive androgen-deprivation therapy (luteinizing hormone–releasing hormone agonist or antagonist) throughout the trial.[1]

Patients were prohibited from receiving concomitant treatment with another systemic antineoplastic therapy (except GnRH) or another investigational product, such as:[4]

- Radiopharmaceuticals
- Immunotherapy (e.g. sipuleucel-T)
- Cytotoxic chemotherapy and any other systemic antineoplastic therapy (modified by amendment 2)
- Enzalutamide, ARN-509, bicalutamide, flutamide, nilutamide
- Cyproterone acetate, estrogen
- 5 α-reductase inhibitor
- Abiraterone acetate, TAK-700 or other CYP17 inhibitors
- Systemic ketoconazole (as antineoplastic therapy) (modified by amendment 2)

- Osteoclast-targeted therapy such as bisphosphonate or denosumab. Patients receiving treatment with osteoclast-targeted therapy at a dose and schedule indicated for osteoporosis prior to study entry may continue treatment at the same dose and schedule.
- Continuous use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/prednisolone per day. Short-term use of systemic corticosteroids with higher doses up to 28 days during the study treatment period is allowed, but treatment should be kept as short as possible.

Dose modifications, interruptions or reductions

The study medication could be delayed or reduced when patients experienced a clinically significant toxicity that was associated with the study drug. Patients who experienced a treatment-related grade 3 or 4 AEs could have their assigned therapy interrupted until the AE improved to grade 2 or less. These patients could then be restarted on a 300 mg bid dosing schedule.[4]

Dose interruptions were permitted for a period of 28 consecutive days. Patients who exceeded this period were excluded from the study.

The dose of darolutamide could be reduced to 300 mg twice daily. However, patients were not permitted to receive darolutamide doses below 300 mg bid. Patients who experienced a grade 3 or higher treatment-related AE on a 300 mg bid dosing schedule were withdrawn from the study treatment.

d) Patient Disposition

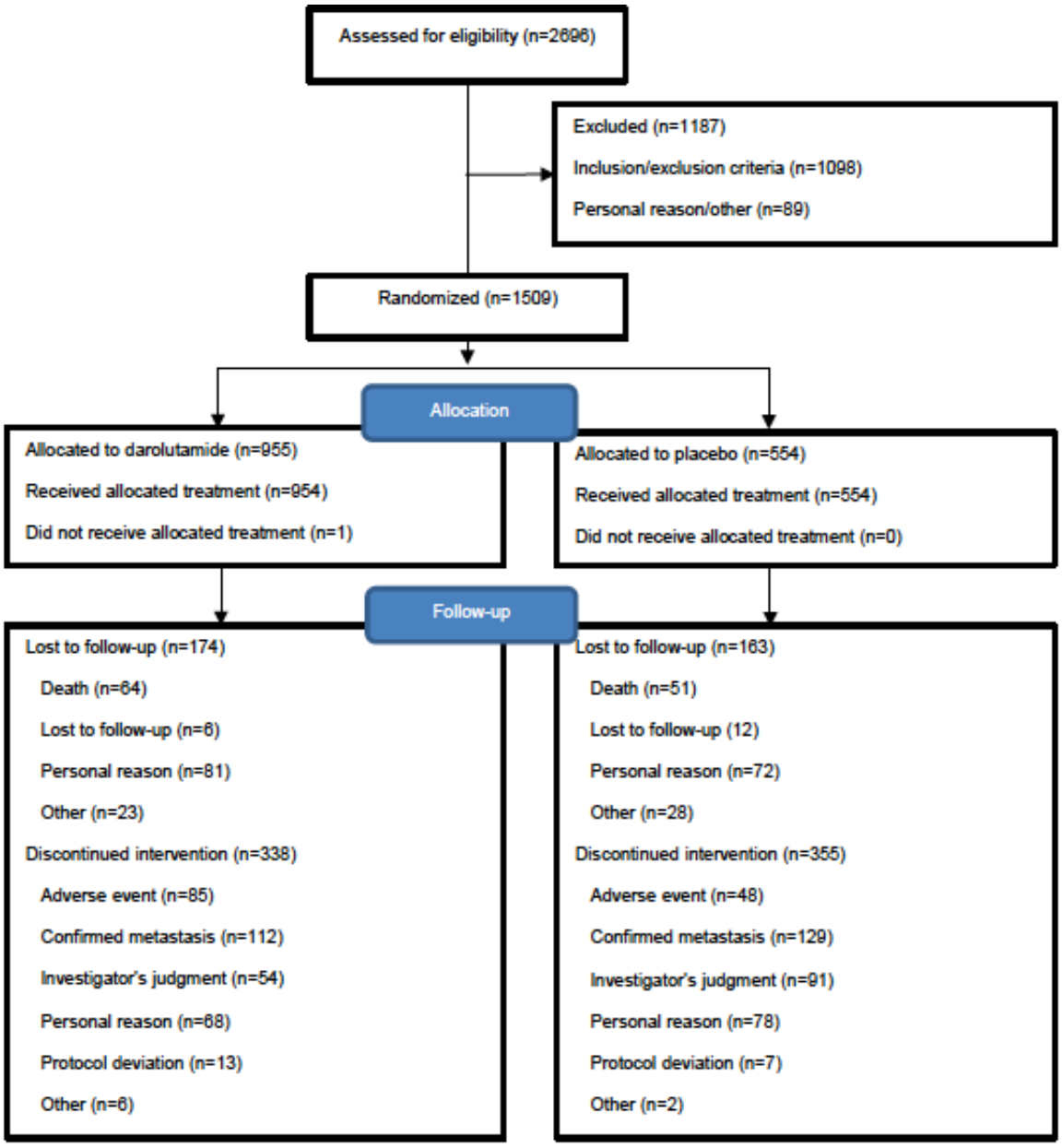
The patient disposition for the ARAMIS trial is presented in Figure 6.3. A total of 1,509 patients were randomized to receive either darolutamide (N = 955) or placebo (N = 554).[1] In the darolutamide group, 0.1% of patients did not receive their assigned treatment while all patients in the placebo group received their assigned treatment.[2]

At the 03-September-2018 data cut-off, 64% of patients (N = 615) were still receiving darolutamide and 36% of patients were still receiving placebo (N= 200).[1,2] In the darolutamide group, 35.5% of patients discontinued their assigned treatment (N = 339) while 63.9% of patients discontinued treatment with placebo (N=354).[2] The most common reason for discontinuation in the darolutamide group was confirmed metastasis, AEs, and personal reasons; while it was confirmed metastasis, judgement by the investigator, and personal reasons in the placebo group (Figure 6.3). The proportion of patients still receiving darolutamide or placebo was not reported at the 15-November-2019 database cut-off.[7]

There was only one major protocol deviation in the trial. Here, one patient randomized to the darolutamide groups did not receive their assigned therapy.[2] Overall, 68.1% of patients in the darolutamide and 72.7% in the placebo group had an important deviation and they were evenly distributed across treatment groups.[2]

The Sponsor provided details on the number of participants who received open-label darolutamide after end of observation period.[3] Overall, 95.1% of patients who were initially treated with darolutamide continued receiving open-label darolutamide while 85.0% of patients initially treated with placebo crossed-over and received open label darolutamide.[3] According to the FDA, cross-over was only allowed once the MFS analysis was completed. However, there is a potential that cross-over will confound the final OS analysis.[2]

Figure 6.3: Disposition of patients enrolled in the ARAMIS trial at the 03-September-2018 data cut-off.



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e) Limitations/Sources of Bias

Overall, ARAMIS was a well-designed and conducted RCT because it used several methods to minimize bias. The strengths of the trial are discussed in more detail, more specifically:

- The ARAMIS trial used a double-blind study design to minimize bias in the assessment of all study outcomes. Furthermore, the investigators, patients and sponsor were blinded to the results until the time of the primary analysis.

- A 2:1 randomization ratio was used to increase the probability that eligible patients would be randomized to receive darolutamide and to increase feasibility. In addition, a stratified randomization procedure was used based on known prognostic factors to minimize potential imbalances between the study groups that might lead to biased results.

- Analyses of efficacy endpoints were based on radiographic tumor assessments by BICR.

- The primary outcome in the ARAMIS trial was MFS. Several studies have demonstrated that MFS is a valid surrogate endpoint for OS in the localized setting and is a clinically meaningful endpoint for men with nmCRPC.[9,10]

There are also some limitations in the trial that warrant discussion, more specifically:

- In the ARAMIS trial, two independent BICR reader pools assessed patients for eligibility and efficacy. It was noted that during the central efficacy imaging review some patients were retrospectively classified as having metastases at baseline.[1] Here, 50 patients in the darolutamide group and 39 in the placebo group were classified as metastasis-free at baseline. These patients were included in the primary analysis of MFS; however, an additional sensitivity analysis was conducted, whereby events of baseline metastases were censored, to explore the effect of the trial design flaw. The results of this sensitivity analysis showed a consistent treatment benefit in favor of darolutamide.[2]

- The PSA and PSADT assessments were not blinded in the trial and more patients in the placebo group discontinued due to rising PSA as compared to those in the darolutamide group (24.5% vs 9.2%).[2] The FDA stated that sensitivity analyses adjusting for these dropouts were similar to the primary estimates of MFS, and therefore, it is unlikely that these unblinded measurements would impact the overall results.[2]

- Although the statistical analysis of secondary outcomes used a hierarchical gatekeeping procedure to control for type 1 error, OS was not statistically significant at this interim analysis because the prespecified alpha split (α =0.05) between the primary and secondary outcomes was not met.[1] Here, the alpha spending function was used for sequential testing of the secondary variables and a predefined interim alpha significance level of 0.0005 as used for OS.[1,2] Thus, the remaining key secondary endpoints in the testing hierarchy (i.e., time to pain progression, time to initiation of cytotoxic chemotherapy, and time to first SSE) are summarized descriptively and no statistical inferences should be made.

- Patients randomized to placebo in the treatment phase of the trial were permitted to cross-over and receive darolutamide during the open-label phase. However, this cross-over could confound the results of the final OS analysis and other secondary outcomes.

- Patient-reported and HRQoL outcomes were exploratory endpoints in the ARAMIS trial.
- All the subgroup analyses should be considered exploratory or hypothesis generating due to small sample sizes and the descriptive nature of the analysis.

Detailed Outcome Data and Summary of Outcomes

Metastasis-free Survival

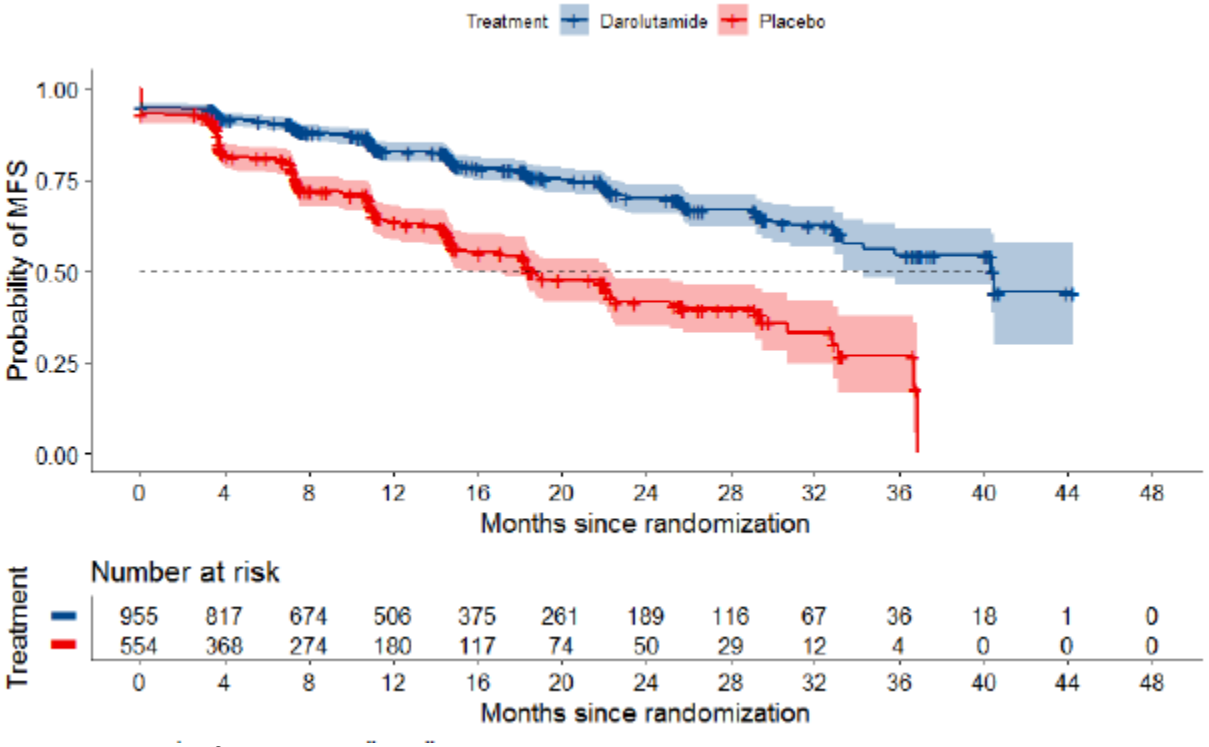
MFS was the primary outcome in the trial and it was defined as time from randomization to confirmed evidence of distant metastasis on imaging or death from any cause, whichever occurred first.[1] The MFS curves were estimated using the Kaplan-Meier method and treatment differences were determined using a two-sided log-rank test stratified by PSADT (≤6 vs. >6 months) and use of osteoclast-targeted at randomization.[4] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% confidence intervals (CIs).[4]

In the ARAMIS trial, two independent BICR reader pools assessed patients for eligibility and efficacy. It was noted that during the central efficacy imaging review some patients were retrospectively classified as having metastases at baseline.[1] Here, 50 patients in the darolutamide group and 39 in the placebo group were misclassified as metastasis-free at baseline.[2] These patients were included in the primary analysis of MFS; however, an additional sensitivity analysis was conducted to explore the effect of the trial design flaw (results reported further down).[2]

The primary analysis for MFS occurred on 03-September-2018. The Kaplan-Meier curves for MFS are presented in Figure 6.4. At the 03-September-2018 data cut off, 23.1% of patients in the darolutamide group had a metastasis or died (N = 221) as compared to 39.0% of patients in the placebo group (N=216).[1] The median MFS in the darolutamide group was 40.4 months (95% CI: 34.3 to not reached [NR]) and it was 18.4 months (95% CI: 15.5 to 22.3) in the placebo group.[1] [redacted].[7] *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).*

Fizazi et al (2019) reported that treatment with darolutamide was associated with statistically significant prolonged MFS as compared to placebo (HR: 0.41, 95% CI: 0.34 to 0.50; P<0.001).[1] The majority of patients were censored at the time of the primary analysis in both study groups (darolutamide: 78.9% vs. placebo: 61.0%, respectively).[2] The main reason for censoring in both groups was “censored at last MFS-free tumour assessment”(see Table 6.7).[2]

Figure 6.4: Kaplan-Meier survival curves of MFS as assessed by BICR for all patients in the ITT population at the 03-September-2018 data cut-off.



Data Source: FDA[2]

Table 6.7: Primary MFS Analysis

	Darolutamide N = 955	Placebo N = 554
Patients with event, n (%)	221 (23.1%)	216 (39.0%)
Death	41 (4.3%)	19 (3.4%)
Metastasis post-baseline	130 (13.6%)	158 (28.5%)
Metastasis at baseline	50 (5.2%)	39 (7.0%)
Patients censored, n (%)	734 (76.9%)	338 (61.0%)
Censored at last MFS-free tumor assessment	673 (70.5%)	226 (40.8%)
Censored at last tumor assessment before death	0	2 (0.4%)
Censored at last tumor assessment before new anticancer therapy	39 (4.1%)	86 (15.5%)
Censored on randomization date	22 (2.3%)	24 (4.3%)
Median[1] MFS (95% CI), months	40.4 (34.3, NE)	18.4 (15.5, 22.3)
Stratified[2] HR (95% CI)	0.413 (0.341, 0.500)	
Two-sided stratified[2] log-rank p-value	<0.0001	

NE=Not Estimable

[1] Based on Kaplan-Meier estimates

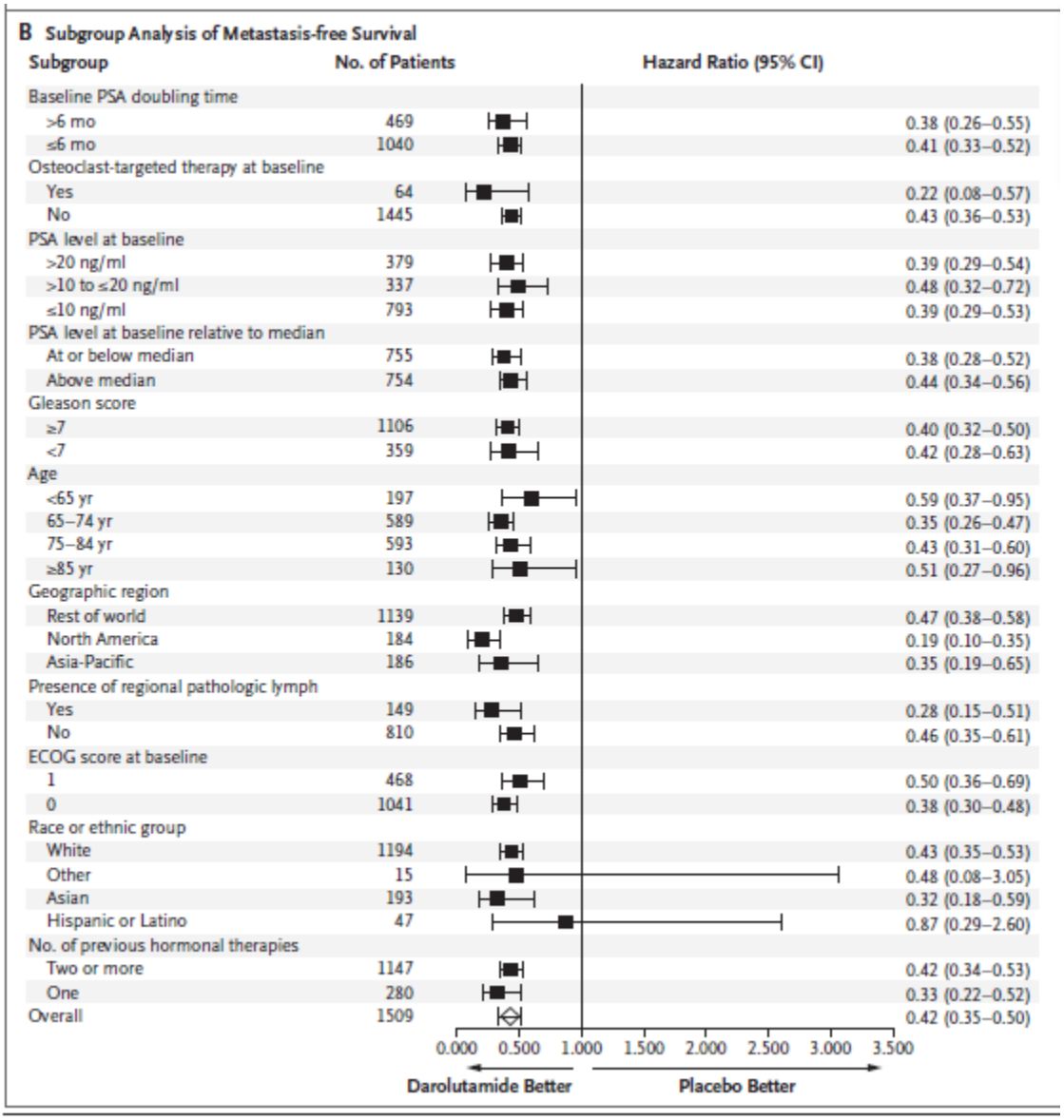
[2] Stratified by PSADT (≤6 months vs. >6 months) and use of osteoclast-targeted therapy (yes vs. no)

Source: dataset ADTTE; variables PARAM, AVLC, CNSR, EVNTDESC, CNSDTDSC, and TRT01P

Data Source: FDA[2]

The subgroup analysis for MFS were performed using non-stratified Cox HRs with corresponding 95% CI are presented in Figure 6.5.[4] It was reported that darolutamide appeared to be associated with a protective effect against the risk of MFS as compared to placebo across all subgroups (Figure 6.5).[1] However, these results should be interpreted with caution because they are considered exploratory and not adjusted for multiplicity.

Figure 6.5: Subgroup analysis of MFS as assessed by BICR for all patients in the ITT population at the 03-September-2018 data cut-off.



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As previously mentioned, a sensitivity analysis was conducted to explore the effect of including patients in the primary analysis of MFS with baseline metastasis. Here, the 89 patients with baseline metastases were censored at the date of randomization.[2] The median MFS in the darolutamide group was 40.5 months (95% CI: 35.8 to NR) and it was 22.1 months (95% CI: 18.3 to 25.8) in the placebo group.[2] The sensitivity analysis demonstrated a similar protective treatment effect of darolutamide on MFS as compared to placebo (HR: 0.356, 95% CI: 0.287 to 0.441).[2]

Overall Survival

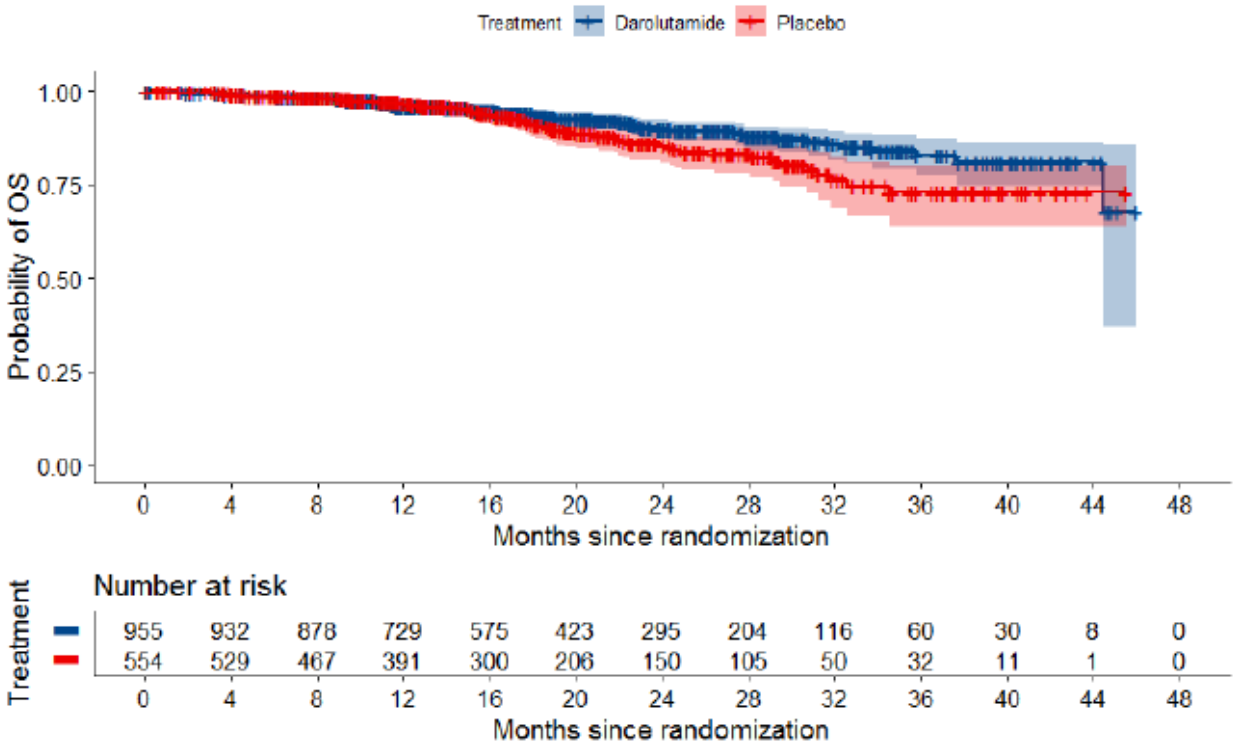
OS was a secondary outcome in the trial and it was defined as the time from randomization to death due to any cause.[4] The OS curves were estimated using the Kaplan-Meier method and treatment differences were determined using a two-sided log-rank test stratified by PSADT and use of osteoclast-targeted at randomization.[4] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[4] As previously mentioned, the trial implemented a hierarchical gatekeeping procedure. Thus, an alpha spending function was used for sequential testing of the secondary variables and a predefined alpha significance level of 0.0005 was used for OS.[1,2]

The interim analysis for OS occurred on 03-September-2018 and the pre-planned final analysis was on 15-November-2019. The OS Kaplan-Meier curves for the interim analysis are presented in Figure 6.6. Approximately, eight percent of the patients in the darolutamide group died (8.2%; N = 78) while 10.5% of patients in the placebo group died (N=58).[2] The median OS in the darolutamide and the placebo groups were not reached.[1] [redacted].[7] *Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this efficacy information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.*

There was no statistically significant differences between darolutamide and placebo on the effect of OS (HR: 0.71, 95% CI: 0.50 to 0.99; P= 0.045).[1] Since OS was not statistically significant, the remaining key secondary endpoints in the testing of the hierarchical gatekeeping procedure (i.e., time to pain progression, time to initiation of cytotoxic chemotherapy, and time to first SSE), were summarized descriptively and no statistical inference could be made. The majority of patients were censored at the time of the interim analysis in both study groups (darolutamide: 91.8% vs. placebo: 89.5%, respectively) (see Table 6.8).[2]

At the 15-November-2019 database cut-off, 15.5% of patients treated with darolutamide died (N = 148) while 19.1% treated with placebo died (N=106).[7] The median OS in the darolutamide and the placebo groups were not reached.[7] Treatment with darolutamide was associated with statistically significant prolonged OS as compared to placebo (HR: 0.685, 95% CI: 0.533 to 0.881; P=0.003) (Figure 6.7)[7]

Figure 6.6: Kaplan-Meier survival curves of OS for all patients in the ITT population at the 03-September-2018 data cut off.



Data Source: FDA[2]

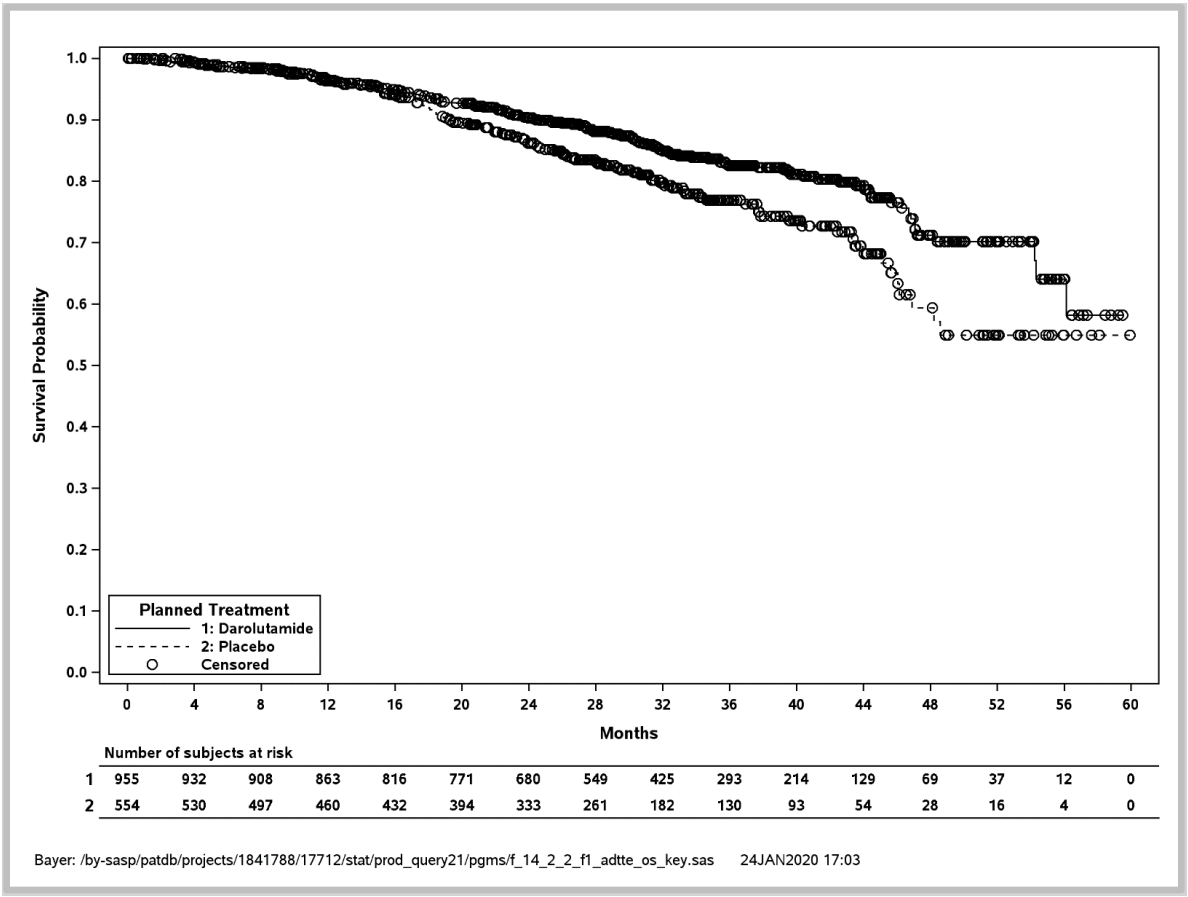
Table 6.8: Interim OS results

	Darolutamide N = 955	Placebo N = 554
Patients with event, n (%)	78 (8.2%)	58 (10.5%)
Patients censored, n (%)	877 (91.8%)	496 (89.5%)
Median[1] OS (95% CI), in months	NE (44.4, NE)	NE (NE, NE)
Stratified[2] HR (95% CI)	0.706 (0.501, 0.994)	
Two-sided stratified[2] log-rank p-value	0.045	

NE=Not Estimable
[1] Based on Kaplan-Meier estimates
[2] Stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no)
Source: dataset ADTTE; variables PARAM, AVLC, CNSR, and TRT01P

Data Source: FDA[2]

Figure: 6.7 Kaplan-Meier survival curves of OS for all patients in the ITT population at the 15-November-2019 database cut-off.



Source: Checkpoint responses[7]

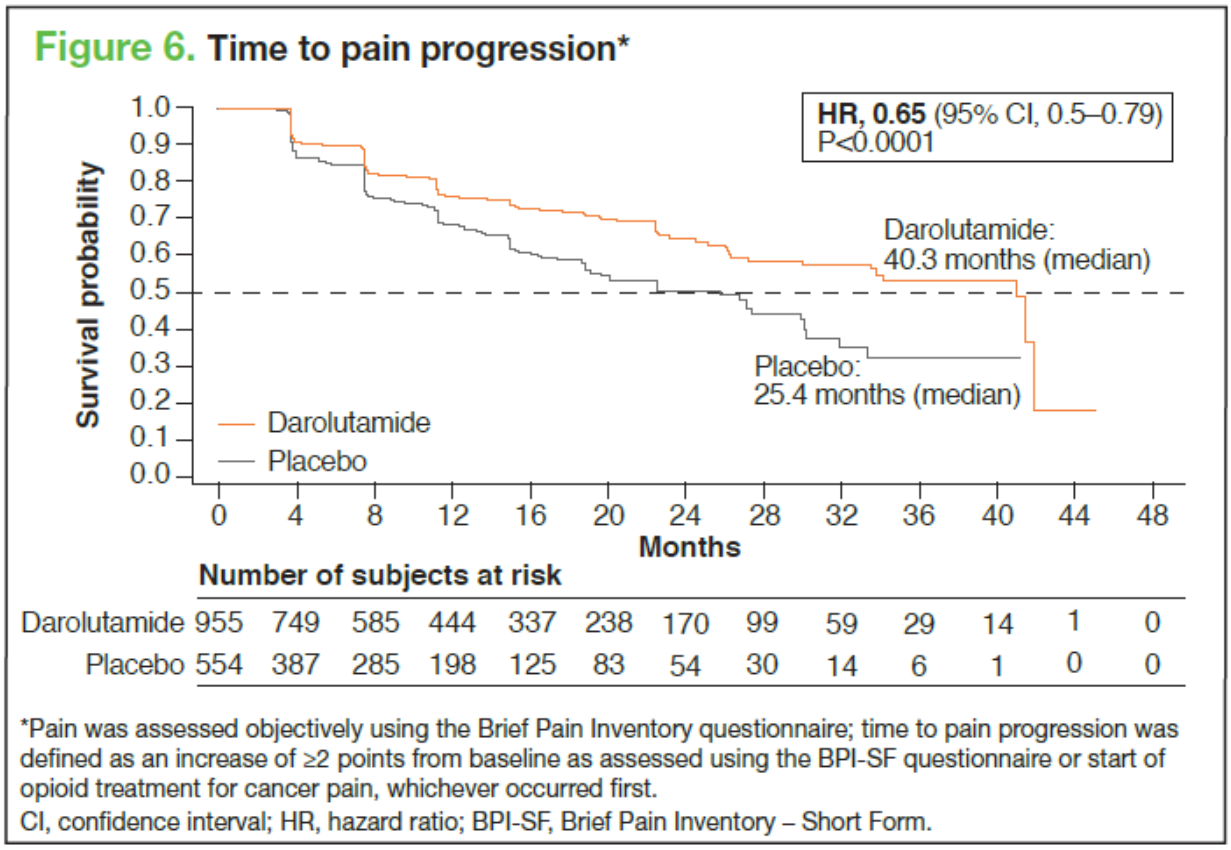
Time to pain progression

Time to pain progression was a secondary outcome and it was defined as the time from randomization to pain progression. Progression was classified as an increase of two or more points from baseline in question 3 of the Brief Pain Inventory-Short Form questionnaire (BPI-SF) related to the worst pain in the last 24 hours taken as a 7-day average for post-baseline scores or the initiation of short or long acting opioids for pain, whichever comes first.[4] The time to pain progression curves were estimated using the Kaplan-Meier method and treatment differences were determined using a two-sided log-rank test stratified by PSADT and use of osteoclast-targeted at randomization.[4] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[4]

The final analysis for time to pain progression was performed at the 03-September-2018 database cut-off. The Kaplan-Meier curves for time to pain progression are presented in Figure 6.8. Here, 26.3% of patients in the darolutamide group had pain progression (N = 251) as compared to 32.1% of patients in the placebo group (N=178).[1] The median time to pain progression in the darolutamide group was 40.3 months (95% CI: 33.2 to 41.2) and it was 25.4 months (95% CI: 19.1 to 29.6) in the placebo group.[2] Treatment with darolutamide was associated with prolonged time

to progression as compared to placebo (HR: 0.65, 95% CI: 0.53 to 0.79).[1] The time to progression estimates are considered exploratory due to the hierarchical gatekeeping procedure at the 03-September-2018 database cut-off, and therefore, the p-values should be interpreted with caution.

Figure 6.8: Kaplan-Meier survival curves of time to progression for all patients in the ITT population at the 03-September-2018 data cut off.



Fizazi, K, SHore, N, Tammela. TL, et al. ARAMIS: efficacy and safety of darolutamide in non-metastatic castration-resistant prostate cancer [poster]. ASCO GU 2019.[46]

Time to first use of cytotoxic chemotherapy

Time to first use of cytotoxic chemotherapy was a secondary outcome and it was defined as time from randomization to the start of the first cytotoxic chemotherapy cycle. The time to first use of cytotoxic chemotherapy curves were estimated using the Kaplan-Meier method and treatment differences were determined using a two-sided log-rank test stratified by PSADT and use of osteoclast-targeted at randomization.[4] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[4]

At the 03-September-2018 data cut off, 7.6% of patients in the darolutamide group (N = 73) used cytotoxic chemotherapy relative to 14.3% of patients in the placebo group (N=79).[1,2] The median time to first use of cytotoxic chemotherapy in the darolutamide group was NR and it was 38.2 months (95% CI: 35.5 to 41.9) in the placebo group.[2] Treatment with darolutamide was associated with prolonged time to first use of cytotoxic chemotherapy as compared to placebo (HR: 0.43, 95% CI: 0.31 to 0.60).[1] The time to first use of cytotoxic chemotherapy estimates are considered exploratory due to the hierarchical gatekeeping procedure at the 03-September-2018 database cut-off, and therefore, the p-values should be interpreted with caution.

The 15-November-2019 database cut-off represents the final analysis for time to first use of cytotoxic chemotherapy.[7] Here, 13.3% of patients in the darolutamide group (N = 127) used cytotoxic chemotherapy relative to 17.7% of patients in the placebo group (N=98).[7] The median time to first use of cytotoxic chemotherapy was not reached for either group.[7] Treatment with darolutamide was associated with prolonged time to first use of cytotoxic chemotherapy as compared to placebo (HR: 0.579, 95% CI: 0.444 to 0.755; p-value = 0.0004).[7]

Time to first symptomatic skeletal event

Time to SSE was a secondary outcome and it was defined as time from randomization to the occurrence of the first SSE. SSE was defined as external beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor related orthopedic surgical intervention.[4] The time to first SSE curves were estimated using the Kaplan-Meier method and treatment differences were determined using a two-sided log-rank test stratified by PSADT and use of osteoclast-targeted at randomization.[4] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[4]

At the 03-September-2018 data cut off, 1.7% of patients in the darolutamide group (N = 16) had a first SSE relative to 3.2% of patients in the placebo group (N=18).[2] The median time to first SSE was NR for either treatment group.[1] Darolutamide was associated with prolonged time to first SSE as compared to placebo (HR: 0.43, 95% CI: 0.22 to 0.84).[1] The time to first SSE estimates are considered exploratory due to the hierarchical gatekeeping procedure at the 03-September-2018 database cut-off, and therefore, the p-values should be interpreted with caution.

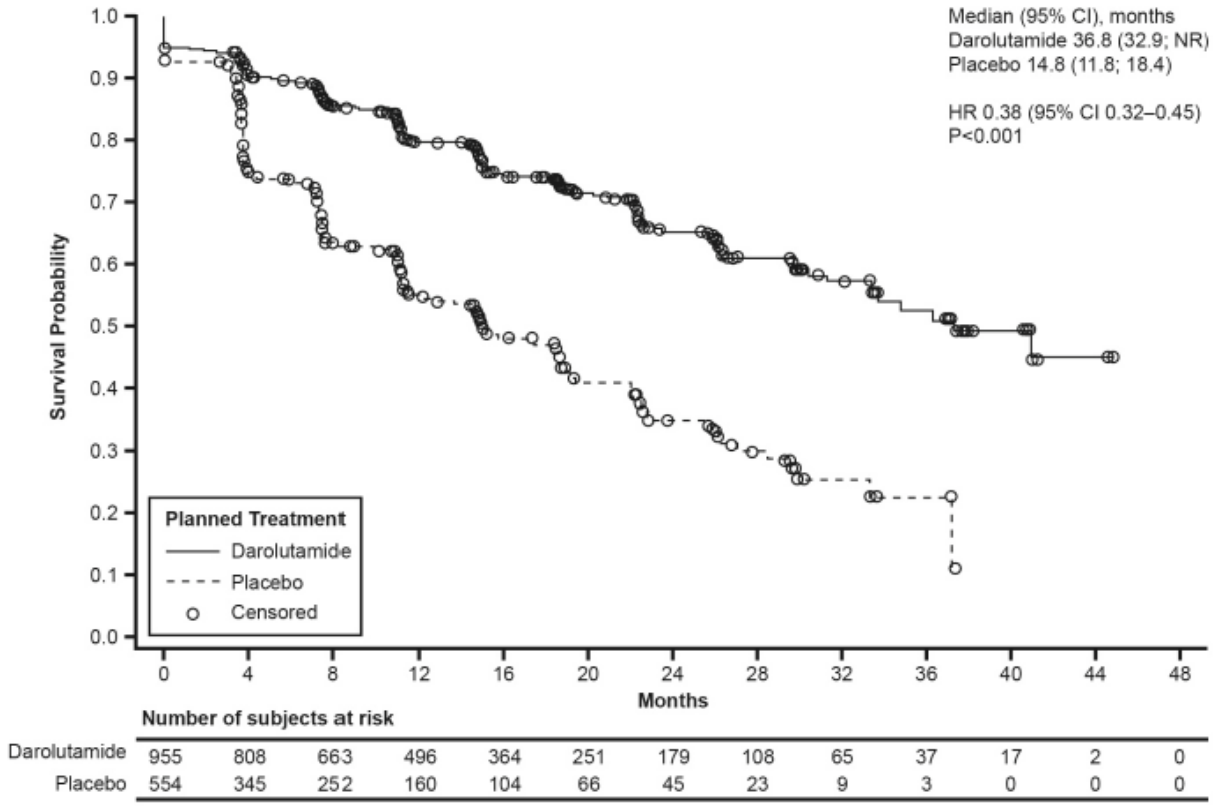
The 15-November-2019 database cut-off represents the final analysis for time to SSE.[7] Here, 3.0% of patients in the darolutamide group (N=29) had an SSE compared to 5.1% of patients in the placebo group (N=28).[7] The median time to SSE was not reached for either group.[7] Treatment with darolutamide was associated with prolonged time to SSE as compared to placebo (HR: 0.484, 95% CI: 0.287 to 0.815; p-value = 0.0053).[7]

Progression-free survival

PFS was an exploratory outcome and it was defined as the time in days from the date of randomization to the date of radiological disease progression based on independent blinded central reading, including progressing pelvic lymph nodes and new pathologic lymph nodes identified above or below the aortic bifurcation or death due to any cause, whichever occurs first.[4] PFS curves were estimated using the Kaplan-Meier method and treatment differences were determined using a stratified two-sided log-rank test of 0.05.[4] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[4]

At the 03-September-2018 data cut off, 26.7 of patients in the darolutamide group (N = 255) had a progression or died as compared to 46.6% of patients in the placebo group (N=258) (Figure 6.9).[2] The median time to PFS was 36.8 months (95% CI: 32.9 to NR) and it was 14.8 months (95% CI: 11.8 to 18.4 in the placebo group (Figure 6.8).[2] Darolutamide was associated with a prolonged PFS as compared to placebo (HR: 0.38, 95% CI: 0.32 to 0.45).[1] The results of PFS should be interpreted with caution because they are considered exploratory.

Figure 6.9: Kaplan-Meier survival curves of progression-free survival for all patients in the ITT population at the 03-September-2018 data cut off.



CI, confidence interval; HR, hazard ratio; NR, not reached.

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Time to PSA progression

Time to PSA progression was an exploratory outcome and it was defined in accordance with Prostate Cancer Working Group 2 (PCWG2) criteria.[1] Here, a decline from baseline at week 16 was defined as ≥25% increase in PSA and increase in absolute PSA of ≥2 ng/ml above the nadir, confirmed by a second consecutive value obtained 3 or more weeks later. In contrast, no decline from baseline at week 16 was defined as ≥25% increase in PSA and increase in absolute PSA levels of ≥2 ng/ml above baseline, confirmed by a second consecutive value obtained 3 or more weeks later.[1] It was measured as the time in days from the date of randomization to the date of first PSA progression.[4] Time to PSA progression curves were estimated using the Kaplan-Meier method and treatment differences were determined using a stratified two-sided log-rank test of 0.05.[4] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[4]

At the 03-September-2018 data cut off, 23.7% of patients in the darolutamide group (N = 226) had a PSA progression as compared to 66.4% of patients in the placebo group (N=368).[2] The median time to PSA progression was 33.1 months (95% CI: 25.9 to NR) and it was 7.3 months (95% CI: 3.9

to 7.4) in the placebo group.[2] Darolutamide was associated with a prolonged time to PSA progression as compared to placebo (HR: 0.13, 95% CI: 0.11 to 0.16; P<0.001).[1] The results of time to PSA progression should be interpreted with caution because they are considered exploratory.

Time to initiation of subsequent antineoplastic therapy

Time to initiation of subsequent antineoplastic therapy was an exploratory outcome and it was defined as the time from randomization to initiation of first antineoplastic therapy.[4] Time to initiation of subsequent antineoplastic therapy curves were estimated using the Kaplan-Meier method and treatment differences were determined using a stratified two-sided log-rank test of 0.05.[4] Additionally, stratified Cox proportional hazard models were used to calculate HRs with corresponding 95% CIs.[4]

At the 03-September-2018 data cut off, 5.0% of patients in the darolutamide group (N = 48) had a subsequent antineoplastic therapy as compared to 12.6% of patients in the placebo group (N=70).[1] The median time to initiation of subsequent antineoplastic therapy was NR for either treatment group.[1] Darolutamide was associated with a prolonged time to initiation of subsequent antineoplastic therapy as compared to placebo (HR: 0.33, 95% CI: 0.23 to 0.47; P<0.001).[1] These results should be interpreted with caution because they are considered exploratory.

Table 6.9 shows the type of subsequent therapy patients received after discontinuing their assigned therapy. More patients in the placebo group received a subsequent therapy as compared to those in the darolutamide group (23.5% vs 10.5%).[1] Regardless of assigned therapy, the majority of patients were treated with docetaxel (darolutamide: 49.0% and placebo: 50.8%).

Table 6.9: First subsequent anticancer therapy for all patients who discontinued their assigned therapy at the 03-September-2018 data cut off.

Patients, n (%)	Darolutamide (N=955)	Placebo (N=554)
Discontinued study treatment	339 (35.5)	354 (63.9)
Received cytotoxic chemotherapy or antineoplastic therapy	100 (10.5)	130 (23.5)
Abiraterone, abiraterone acetate	13 (13.0)	23 (17.7)
Docetaxel	49 (49.0)	66 (50.8)
Enzalutamide	18 (18.0)	19 (14.6)
Other[a]	13 (13.0)	16 (12.3)

[a]'Other' includes all treatments given to ≥2% of patients who received subsequent therapies (bicalutamide, flutamide, carboplatin, cisplatin, and estramustine).

Percentages for individual treatments are based on the total number of patients who received at least one antineoplastic therapy and/or cytotoxic chemotherapy after treatment discontinuation (N=100 for the darolutamide group and N=130 for the placebo group).

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Percent of patients with PSA response

Percent of patients with PSA response was an exploratory outcome and it was defined as the proportion of patients achieving a decline of ≥ 50% from baseline.[4] The PSA response rates with corresponding 95% CI were compared using the Cochran-Mantel-Haenszel test.[4]

More patients in the darolutamide group had a PSA response compared to the placebo group (83.6%, 95% CI: [81.1%; 85.9%] vs 7.6%, 95% CI: [5.5%; 10.1%]).[7]

Quality of Life

In the ARAMIS trial, HRQoL was measured using the following instruments: Brief pain inventory – short form (BPI-SF), European Organization for Research and Treatment of Cancer Quality of life Questionnaire - Prostate Cancer Module (EORTC-QLQ-PR25), European Quality of Life 5-Domain Scale (EQ-5D-3L), Functional Assessment of Cancer Therapy-Prostate (FACT-P) and the FACT-P Prostate cancer subscale (PCS).

The BPI-SF assesses clinical pain related to cancer. It is measured on a 10-point scale, where higher numbers reflect greater pain.[1] Two scores can be derived from this instrument: pain

severity and pain interference. The pain severity score is obtained from the mean score of the 4 questions related to pain, which is measured by "worst" "least" "average" and "right now" (current pain). The pain interference score is obtained from the mean of the following seven daily activities: general activity, walking ability, normal work, mood, enjoyment of life, relations with others, and sleep.[4] The minimally clinically important difference (MCID) for the BPI-SF was a 2-point difference.[1] In the trial, the BFI-FS was evaluated at screening, day 1, week 16, and at every subsequent visit until the end of the trial or death.[1]

The EORTC-QLQ-PR25 assesses prostate cancer-related QoL and it has been validated in prostate cancer patients.[4] It is a 25-item questionnaire that includes subscales on urinary symptoms (8 items), bowel symptoms (4 items), hormonal treatment-related symptoms (6 items), incontinence aid (1 item), sexual activity (2 items) and sexual functioning (4 items).[4] Functional scales are obtained from sexual activity and sexual functioning scales while symptom scales are obtained from urinary symptoms, bowel symptoms, hormonal treatment-related symptoms and incontinence aid.[4] Higher scores indicate a greater effect of symptoms on QoL and the MCID was an 8-point difference.[1] In the trial, the EORTC-QLQ-PR25 was evaluated at screening, day 1, week 16 and every 16 weeks until the end of the treatment period.[1]

The EQ-5D-3L assesses general health status and health utility measure and it has been validated in cancer populations. It measures five dimensions of health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[4] EQ-5D-3L index score is the sum of the five health dimensions and the scale ranges from -0.59 to 1, where higher scores represent better health states.[4] The MCID for the EQ-5D-3L was a 0.1-point difference and it was a 7-point difference for the EQ-5D-3L VAS.[7] In the trial, the EQ-5D-3L was evaluated at screening, day 1, week 16 and at the end of the treatment period.[1]

FACT-P assesses prostate cancer-related QoL and it has been validated in prostate cancer patients. The instrument measures five domains of health: Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-being (EWB), Functional Well-Being (FWB) and Additional Concerns (also called PCS). The total score is the sum of the scores of 39 items and the scale ranges from 1 to 156, where higher scores represent better health states. The MCID for the FACT-P and the FACT-P PCS were a 10-point difference and a 3-point difference, respectively.[1] In the trial, the FACT-P was evaluated at screening, day 1, week 16 and at the end of the treatment period while the FACT-P PCS was given every 16 weeks until the end of the trial or death.[1]

The descriptive HRQoL analyses were conducted in the ITT population.[2] In the trial, the completion rates were calculated for the HRQoL instruments[2],considering questionnaires that met at least minimum requirements for scoring questionnaire completion at the corresponding time point.[3] Completion rates were calculated among those study participants who were expected to complete a HRQoL assessment.[2] The Sponsor further clarified the denominator of the calculation of completion rate as *"the number of patients who continue on the study treatment at the point of assessment and are expected to complete the questionnaire."* [3] These analyses included only patients with baseline assessments. The mean difference in the time-adjusted area under the curve between the two treatment groups were estimated using an analysis of covariance model with covariates for baseline PRO scores and stratification factors. The least-square mean change from baseline to week 16 estimate, standard errors, and 95% CIs were estimated for each treatment group and the difference in treatment groups.[2] The Sponsor provided a rationale for the 16 week cut-off date.[3] First, week 16 aligns with the timing of taking measures of other clinical endpoints in the trial and it was common across the SPARTAN and PROSPER trials. Secondly, week 16 is also used by clinicians to perform radiographic imaging and hence reflects typical real-life clinical practice and since disease progression for the majority of nmCRPC is not rapid, capturing HRQoL at 16 weeks would be appropriate to document disease progression.[3] It should be noted

that the HRQoL analysis was not included in the testing hierarchy, and therefore, no adjustments were made for type 1 error.

Table 6.10: Summary of the HRQoL estimates in the trial

LSM Time-Adjusted AUC (95% CI)	Darolutamide	Placebo	Difference	MID
BPI-SF Pain Interference[a]	1.1 (1.0, 1.3)	1.3 (1.2, 1.4)	−0.2 (−0.3, −0.1)	2
BPI-SF Pain Severity[a]	1.3 (1.1, 1.4)	1.4 (1.3, 1.6)	−0.2 (−0.3, −0.1)	2
FACT-P (total)[b]	112.9 (111.8, 114.0)	111.6 (110.5, 112.7	1.3 (0.4, 2.1)	10
FACT-P PCS[b]	32.4 (31.9, 32.9)	31.8 (31.3, 32.2)	0.6 (0.3, 1.0)	3
EORTC-QLQ-PR25[c] (urinary symptoms subscale)	23.7 (22.4, 25.0)	26.4 (25.1, 27.8)	−2.7 (−3.8, −1.7)	8
EQ-5D-3L Index Score[d]	0.8 (0.8, 0.8)	0.8 (0.8, 0.8)	0.01 (−0.00, 0.02)	–
EQ-5D-3L Visual Analogue Scale[d]	73.3 (72.1, 74.4)	72.7 (71.5, 73.9)	0.6 (−0.3, 1.5)	–

AUC, area under the curve; BPI-SF, Brief Pain Inventory Short-Form; CI, confidence interval; EORTC-QLQ-PR25, European Organisation for Research and Treatment of Cancer Quality of Life; EQ-5D-3L, EurQol 5-dimensions 3-levels; FACT-P, Functional Assessment of Cancer Therapy-Prostate; LSM, least-squares mean; MID, minimally important difference; PCS, prostate cancer subscale.

Note that 95% CIs are not adjusted for multiplicity.

[a]Higher scores represent more pain or interference, ranging from 0–10; a negative difference favors darolutamide. Patients were defined as having increasing severity of pain/greater pain interference if they experienced an increase of ≥2 points from baseline.
[b]Higher scores represent better health-related quality of life, ranging from 1–156; a positive difference favors darolutamide. Patients were defined as having total quality of life deterioration if they experienced a decrease of ≥10 points in FACT-P total score at 16 weeks compared with baseline; deterioration in the PCS subscale was defined as having a decrease of ≥3 points.
[c]Higher scores reflect greater symptom impact, ranging from 0–100; a negative difference favors darolutamide. Patients were defined as having deterioration in the urinary symptoms subscale if they experienced an increase of ≥8 points.
[d]Higher scores represent better health-related quality of life, ranging from −0.59 to 1; a positive difference favors darolutamide. Patients were considered to have deterioration in overall quality of life if they experienced a deterioration of ≥0.06 points at 16 weeks compared with baseline.
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The 100% completion rates for BPI-SF were high (> 90% for both groups) until the end of the study treatment visit.[2] The baseline BPI-SF scores were similar across treatment groups and remained stable over time (Table 6.10). Although there was a significant decrease in the difference between darolutamide and placebo for the BPI-SF pain interference and pain severity scores at Week 16, the MCID was not reached.[1] More specifically, the pain interference score and pain severity score results favoured darolutamide (lower scores represent less pain) and were

statistically significant but were not clinically meaningful, as the difference in least squares mean between the MID threshold (MID=2 points).[7]

The 100% completion rates for FACT-P were low (< 50%) but the FACT-P PCS subscale had a higher 100% completion rate for both treatment groups until the end of the study treatment visit (> 80%).[2] The baseline FACT-P total score was similar for both treatment groups and remained stable over time (Table 6.10). There was a significant increase in the difference between darolutamide and placebo for the FACT-P total score at Week 16; however, the MCID was not reached.[1] Similar results were observed for the FACT-P PCS score.[1]

The 100% completion rates for EORTC-QLQ-PR25 were high (> 85% for both groups) until the end of the study treatment visit.[2] The baseline EORTC-QLQ-PR25 urinary symptoms score was similar for both treatment groups and remained stable over time (Table 6.10). There was a significant increase in the difference between darolutamide and placebo for the EORTC-QLQ-PR25 urinary symptoms scale at Week 16; however, the MCID was not reached.[1]

The 100% completion rates for the EQ-5D-3L were high (> 90% for both groups) until the end of the study treatment visit.[2] The baseline EQ-5D-3L was similar for both treatment groups and remained stable over time. There was no difference between the two treatment groups and the MCID was not reached (Table 6.10).[1] Similar results were observed for the EQ-5D-3L VAS.[1]

Overall, it would appear that darolutamide is unlikely to have a detrimental effect on patients' HRQoL compared to placebo. However, HRQoL outcomes were exploratory endpoints in the ARAMIS trial and should be interpreted with caution.

Harms Outcomes

The safety set in the ARAMIS trial consisted of patients who had received at least one dose of the study treatment.[4] There was a total of 1,498 patients in the safety set, with 954 patients in the darolutamide group and 554 patients in the placebo group.[1] At the 03-September-2018 data cut-off, the median duration of therapy was 14.8 months (range: 0 to 44.3) in the darolutamide group and 11.0 months (range: 0.1 to 40.5) in the placebo group.[1,2] In the darolutamide group, 39% of patients were treated for less than 12 months (N = 374), 38% were treated for 12 to 24 months (N=360) and 23% were treated for more than 24 months (N=220).[2] In contrast, 60% of patients in the placebo group were treated for less than 12 months (N = 332), 30% were treated for 12 to 24 months (N=160) and 11% were treated for more than 24 months (N=62).[2] The Sponsor reported that treatment compliance was high in both groups (darolutamide : 98.88% ± 5.39% [median 100.00%] and placebo: 99.37% ± 4.13% [median 100.00%]).[7]

Dose discontinuation, reduction and interruptions

Nine percent of patients in the darolutamide and placebo treatment groups discontinued their assigned therapies due to an AE (darolutamide N = 85 and placebo N = 48).[2] More patients in the darolutamide group (6%; N = 52) had an AEs that led to a dose reduction as compared to those in the placebo group (1.3%; N=7).[2] Moreover, 13% of patients in the darolutamide group had a dose interruption due to an AEs relative to 9% of patients in the placebo group (darolutamide N = 119 and placebo N = 48).[2]

Adverse Events

Treatment-emergent AEs (TEAEs) for all patients enrolled in the ARAMIS trial at the 03-September-2018 data cut are presented in Table 6.11.[1] Overall, slightly more TEAEs of any grade occurred in the darolutamide as compared to the placebo group (83.2% versus 76.9%).[1] Similar patterns were observed for grade 3 or 4 TEAEs (darolutamide: 24.7% versus placebo: 19.5%).[1] Grade 5 TEAEs

occurred at the same frequency among those treated with darolutamide or placebo (3.9% versus 3.2%).[1]

Patients who had a history of previous seizure or conditions predisposing to seizure were not excluded from participating in the trial. The incidence of seizures was 0.2% in both groups. None of the patients enrolled with a history of seizure (12 in the darolutamide group) had experienced seizures while receiving darolutamide.[1]

Table 6.11: Incidence of treatment-emergent adverse events in ≥ 5% of Patients in the ARAMIS trial

	Darolutamide, N=954		Placebo, N=554	
	All Grades N (%)	Grade 3-4 N (%)	All Grades N (%)	Grade 3-4 N (%)
Fatigue	151 (16%)	6 (0.6%)	63 (11%)	6 (1.1%)
Musculoskeletal and Connective Tissue Disorders				
Back pain	84 (8.8%)	4 (0.4%)	50 (9.0%)	1 (0.2%)
Arthralgia	77 (8.1%)	3 (0.3%)	51 (9.2%)	2 (0.4%)
Pain in extremity	57 (6.0%)	0	17 (3%)	1 (0.2%)
Gastrointestinal Disorders				
Diarrhea	66 (6.9%)	0	31 (5.6%)	1 (0.2%)
Constipation	60 (6.3%)	0	34 (6.1%)	0
Nausea	48 (5.0%)	2 (0.2)	32 (5.8%)	0
Vascular Disorders				
Hypertension	63 (6.6%)	30 (3.1%)	29 (5.2%)	12 (2.2%)
Hot flush	50 (5.2%)	0	23 (4.2%)	0
Blood and Lymphatic System Disorders				
Anemia	53 (5.6%)	8 (0.8%)	25 (4.5%)	2 (0.4%)
Infections and Infestations				
Urinary tract infection	47 (4.9%)	6 (0.6%)	28 (5.1%)	3 (0.5%)
Source: ADAE dataset				

Data source: FDA[2]

Serious Adverse Events

More patients in the darolutamide group had a serious adverse event (SAE) as compared to the placebo group (24.8% [N=237] vs 20.0% [N=111=) (Table 6.11). The incidence of treatment-related SAE was similar between both treatment groups (1.0% [N=10] vs 1.1% [N=6]).[7]

Adverse Events of Special Interest

TEAEs of special interest for all patients enrolled in the ARAMIS trial at the 03-September-2018 data cut off are presented in Table 6.11.[46] The FDA stated that TEAEs of special interest were

defined as "*…events/disorders representing potential or known risks associated with ADT or with novel anti-androgens. These included events associated with ADT such as bone fracture, fall, fatigue/asthenic conditions, weight decreased, cardiovascular disorders, hypertension, vasodilatation and flushing, diabetes mellitus and hyperglycemia, mental impairment disorders, depressed mood disorders, and breast disorders/gynecomastia.*"[2][FDA pg 136]

Overall, more patients in the darolutamide group had a TEAE of special interest (43%; N = 407) as compared to the placebo group (33%; N = 184).[2] Similar results were observed for Grade 3 or 4 events TEAE of special interest (darolutamide: 10% [N=93] and placebo: 6% [N=33]).[2] The most common TEAE of special interest was fatigue (darolutamide: 15.8% and placebo: 11.4%) (Table 6.12).[46]

Table 6.12: Treatment emergent adverse events of special interest*

Adverse event, all grades, n (%)	Darolutamide (N=954)	Placebo (N=554)
Fatigue/asthenic conditions	151 (15.8)	63 (11.4)
Dizziness (including vertigo)	43 (4.5)	22 (4.0)
Cognitive disorder	4 (0.4)	1 (0.2)
Memory impairment	5 (0.5)	7 (1.3)
Seizure (any event)	2 (0.2)	1 (0.2)
Bone fracture	40 (4.2)	20 (3.6)
Fall (including accident)	40 (4.2)	26 (4.7)
Hypertension	63 (6.6)	29 (5.2)
Coronary artery disorders	31 (3.2)	14 (2.5)
Heart failure	18 (1.9)	5 (0.9)
Rash	28 (2.9)	5 (0.9)
Weight decreased (any event)	34 (3.6)	12 (2.2)
Hypothyroidism	2 (0.2)	0 (0)

*Coronary artery disorders, heart failure, and rash were grouped terms.

Fizazi, K, SHore, N, Tammela. TL, et al. ARAMIS: efficacy and safety of darolutamide in non-metastatic castration-resistant prostate cancer [poster]. ASCO GU 2019.[46]

Deaths

Overall, 3.9% of patients in the darolutamide group (N = 37) and 3.2% in the placebo group died (N=18).[2] Fizazi et al (2019) reported that one death in the darolutamide group and two deaths in the placebo group were drug-related.[1]

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of an indirect treatment comparison

Critical appraisal of an indirect treatment comparison comparing the efficacy and safety of anti-cancer therapies for the treatment of non-Metastatic Castration Resistant Prostate Cancer

7.1.1 Background

The pCODR-conducted literature search identified only one ongoing, randomized, double-blind, placebo-controlled, phase 3 trial that assessed darolutamide in combination with ADT in patients with nmCRPC who are at high risk of developing metastases during continuous ADT and who have a good ECOG performance status.[1] Thus, there is a lack of direct evidence comparing darolutamide to other active therapies. Given the absence of head-to-head trials, the Sponsor provided an unpublished indirect treatment comparison (ITC) and network meta-analysis (NMA) that indirectly compared darolutamide to apalutamide and enzalutamide.[7] In addition, the CGP identified one published abstract of an NMA by Altavilla et al (2019) that indirectly compared the safety of darolutamide to apalutamide and enzalutamide.[15] The objective of this section is to summarize and critically appraise the submitted ITC and NMA and to review the NMA by Altavilla et al (2019) based on available information published in the abstract.

The CADTH Methods Team identified four additional abstracts that reported on indirect treatment comparisons of darolutamide versus apalutamide and enzalutamide.[11-14] Due to the limited information available from the abstracts, the CADTH Methods Team was not able to perform a critical assessment and to provide detailed summaries. The efficacy results appeared to be similar to those reported in the Sponsor-Provided ITC and NMA[11-13] but the safety results appear to be variable.[11-14] This variability may be due to differences in what studies were included in the ITC or NMA and the methodologies that were implemented to build the network. The abstract by Altavilla et al (2019) will be described in more detail.[15]

7.2.1 Objectives of ITC and NMAs

Review of Sponsor-provided ITC and NMA and published abstract

The objectives of the included indirect comparisons were reported as follows:

- The submitter-provided an ITC and NMA that investigated the clinical efficacy of darolutamide to other anticancer agents in patients with nmCRPC who are at high risk of developing metastases during continuous ADT and who have a good ECOG performance status.
- The published NMA abstract was conducted to compare the safety of darolutamide to apalutamide and enzalutamide.[15]

7.1.2 Methods

Submitter-Provided NMA

Search and Study Selection

In the 12-November-2019 Checkpoint Response, the Sponsor reported that they did not conduct a systematic review or quality assessment of the trials included in the ITC.[3]

Indirect Treatment Comparison Methodology

Feasibility Assessment

Prior to conducting the ITC and the NMA, the Sponsor conducted a feasibility assessment to ensure that the included trials provided sufficient evidence to form a network for the target population and outcomes of interest. Moreover, this assessment also explored whether the distribution of study, patient, treatment and outcome characteristics were balanced across the included studies in the ITC and NMA.

Indirect Treatment Comparison and Network Meta-Analysis Methodology

The Sponsor performed a Bucher ITC and an NMA. The ITC indirectly compares more than one RCT through a common comparator while still maintaining the randomisation between the treatment groups in each study. The Sponsor performed an ITC because there were only three studies included in the network and there were no direct comparisons (i.e. closed loops) between darolutamide, enzalutamide or apalutamide. In contrast, the NMA uses both direct and indirect evidence to compare all of the treatments of interest in a single coherent analysis for each endpoint. For this analysis, the Sponsor used a fixed effects model because there were only a few studies included in the network.

The NMA was performed using a Bayesian approach in order to capture all of the uncertainty in model parameters while still preserving the correlation arising from multi-arm trials. The relative treatment effects from the Bayesian NMA were obtained using the Markov Chain Monte Carlo (MCMC) methods. The MCMC combines the prior distributions with the trial data to construct a posterior distribution upon which to base summary results. Initially, a burn-in of 50,000 samples was used and a further 50,000 samples were generated from the posterior distribution to estimate treatment effects and 95% credible intervals (CrIs).

Altavilla et al (2019) NMA[15]
The NMA conducted by Altavilla et al (2019) has been published only as a conference abstract and the methods used in the NMA were sparsely reported. There were no details regarding the methodology for selecting studies for inclusion or for the NMA.

7.1.4 Results

Included studies

The Sponsor reported that they did not conduct a systematic review or quality assessment of the trials included in the ITC.[3]

Patient Populations

The patient characteristics are presented in Table 7.1. Additional information was provided by the Sponsor on the baseline median time from initial diagnosis to start of study treatment for the ARAMIS and SPARTAN trials only.[3] Finally, the Sponsor identified several effect modifiers across the trials included in the ITC. Here, a higher proportion of patients in the ARAMIS trial had an ECOG status of 1 and a lower proportion of those who received bone targeting agents at baseline as compared to the PROPSER and SPARTAN trials (Table 7.1). There were also differences in the baseline PSDAT across trials.

Table 7.1: Study characteristics of the studies included in ITC and NMA

Characteristics		PROSPER		SPARTAN		ARAMIS	
		Enzalutamide N=933	Placebo N=468	Apalutamide N=806	Placebo N=401	Darolutamide N=955	Placebo N=554
Median age in years (range)		74 (50-95)	73 (53-92)	74 (48-94)	74 (52-97)	74 (48-95)	74 (50-92)
ECOG, N (%)	0	747 (80)	382 (82)	623 (77.3)	311 (77.8)	650 (68.06)	391 (70.58)
	1	185 (20)	85 (18)	183 (22.7)	89 (22.3)	305 (31.94)	163 (29.42)
Baseline use of bone targeting agent. N (%)	No	828 (89)	420 (90)	724 (89.8)	362(90.3)	924 (96.8)	522 (94.2)
	Yes	105 (11)	48 (10)	82 (10.2)	39 (9.7)	31 (3.2)	32 (5.8)
Prior hormonal therapy. N (%)	1	NR	NR	156 (19.4)	84 (20.9)	177 (18.5)	103 (18.6)
	≥2	NR	NR	645 (80.0)	316 (78.8)	727 (76.1)	420 (75.8)
	Missing	NR	NR	5 (0.6)	1 (0.25)	51 (5.3)	31 (5.6)
Median serum PSA (range) ng/mL		11.1 (0.8-1071.1)	10.2 (0.2-467.5)	7.78 (0.1-294.8)	7.96 (1.1-291.8)	9.03 (0.31 - 858.3)	9.67 (1.46 - 885.21)
Median PSA doubling time, months (range)		3.8 (0.4-37.4)	3.6 (0.5-71.8)	4.40 (0.8-10)	4.50 (0.7-10)	4.389 (0.744-10.991)	4.65 (0.662- 3.194)
PSA doubling time <6 months, N (%)		715 (77)	361 (77)	576 (71.5)	284 (70.8)	667 (69.84)	371 (66.97)
PSA doubling time >6 months, N (%)		217 (23)	107 (23)	230 (28.5)	117 (29.2)	288 (30.15)	183 (33.03)
Gleason score	<7 =	NR	NR	152 (19.4)	72 (18.6)	217 (22.7)	142 (25.6)
	≥7 =	NR	NR	632 (78.4)	315 (78.6)	711 (74.5)	395 (71.3)
	Missing	NR	NR	22 (2.7)	14 (3.5)	27 (2.8)	17 (3.1)

*ARAMIS measured Median serum PSA in ug/L units
Abbreviations: ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen

Data source: NMA Document prepared by Bayer[7]

Feasibility Assessment

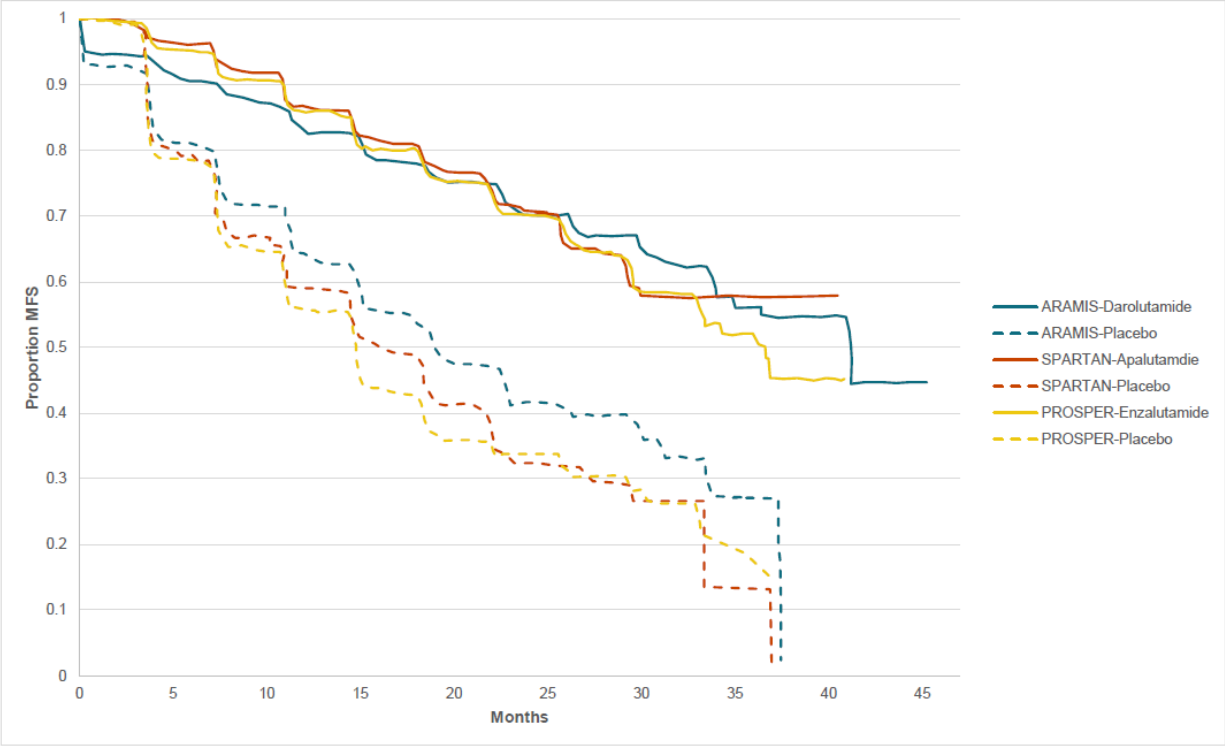
The Sponsor stated that there were key fundamental design differences and heterogeneity among the ARAMIS, PROSPER and SPARTAN trials that could not be adjusted for analytically. These differences may make it difficult to compare the three trials included in the ITC and NMA.

First, the Sponsor conducted a sensitivity analysis to explore the impact of MFS censoring in order to maintain comparability of MFS benefit among all the included trials. The purpose of this sensitivity analysis was to ensure that the censoring used in the ARAMIS trial for darolutamide and the PROSPER trial for enzalutamide aligned with the censoring rules used in the apalutamide Canadian regulatory submissions.[7] According to censoring rules in the Canadian regulatory submission for apalutamide events of new anticancer treatment started prior to documented metastases or documented metastasis after two or more consecutively missed tumor assessments were counted as events upon confirmation of progression.[7] The censoring method used in the apalutamide Canadian regulatory submission was different from what was used in the SPARTAN trial. In the enzalutamide Canadian regulatory submission, the censoring rules were similar to what was used in the trial; however, in order to align with the apalutamide Canadian regulatory submission censoring method, the enzalutamide Sponsor provided additional sensitivity analyses in their pCODR Submission, that best aligned with the censoring rules used in the apalutamide Canadian regulatory submission.[7]

Second, the Sponsor explored whether the definition of MFS was comparable across studies. It was concluded that the definitions were relatively similar for both the ARAMIS and SPARTAN trials. Here, the ARAMIS trial defined MFS as the time between randomisation and evidence of metastasis or death from any cause (whichever occurs first) while the SPARTAN trial defined it as the time from randomization to the time of first evidence of BICR-confirmed bone or soft tissue distant metastasis or death due to any cause (whichever occurred first). However, the definition was slightly different for the PROSPER trial, which defined MFS as the time from randomization to radiographic progression or death within 112 days of treatment discontinuation.

Third, the Sponsor identified some key differences across the placebo groups. Here, the median MFS in the placebo group of the ARAMIS trial was longer (median MFS: 18.4 months [95% CI: 15.5 to 22.3]) relative to the PROSPER and SPARTAN trials (median MFS: 14.7 months [95% CI: 14.2, 15.0] and median MFS: 16.20 months [95% CI: 14.6, 18.4], respectively) (Figure 7.1). Another source of heterogeneity is the application of different censoring rules for patients who had baseline metastases.[7] The ARAMIS trial counted these events at time zero while these events were censored in the PROSPER trial. There was also a lower metastatic event rate in the ARAMIS placebo group as compared to the placebo groups in the PROPSER and SPARTAN trials (Table 7.2).[7] This difference adds to the level of cross-study heterogeneity.

Figure 7.1: Kaplan-Meier curves for the ARAMIS, SPARTAN and PROSPER trials.



Source: Bayer Data on File

Data Source: NMA Document prepared by Bayer[7]

Table 7.2: The number of metastatic event rates in the ARAMIS, SPARTAN and PROSPER Trials

	% Metastatic Event Rate (# of Events / Total patients in study arm)		
	ARAMIS[1]	SPARTAN[2]	PROSPER[3]
ARAT arm	23.1% (221/955)	22.8% (184/806)	23.5% (219/933)
Placebo arm	39.0% (216/554)	48.4% (194/401)	48.7% (228/468)

Source: 1. Fizazi et al. 2019; 2. Smith et al. 2018; 3. Hussain et al 2018

Data Source: NMA Document prepared by Bayer[7]

There were also differences in the proportion of patients who started a new anti-cancer therapy prior to metastasis across the trials included in the ITC. Here, more patients in the ARAMIS trial switched to a new anti-cancer therapy prior to metastasis in the placebo group than in the darolutamide group ([redacted]). (*Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this clinical information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed).* In contrast, 4.0% of patients in the placebo group of the SPARTAN trial and 3.1% in the apalutamide group switched therapies.[7] The Sponsor defined this as the percent of cases who initiated new systemic anti-cancer therapy prior to metastasis or have two or more consecutive missed or unevaluable tumour assessments in the SPARTAN trial. There was no information available for the PROSPER trial. Since switching to a new anti-cancer therapy prior to metastasis will censor the patient, it will prevent a potential MFS event from occurring.[7] Therefore, it was concluded that switching to a new anti-cancer therapy may result in a potential lower number of MFS in the ARAMIS placebo group and would potentially inflate the HR for MFS as compared to the PROSPER and SPARTAN trials.

Fourth, the Sponsor also explored the differences in PSA and PSADT assessment in the included trials. Here, PSA and PSADT assessment was not blinded in the ARAMIS trials while it was in the PROSPER and SPARTAN trials.[7]

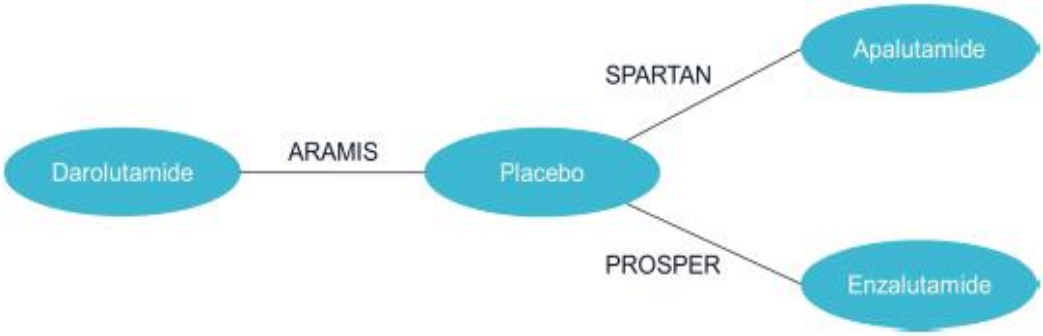
Fifth, some of the trials included patients who had metastasis at baseline after randomization. In the ARMAIS trial, 89 patients had metastasis at baseline after randomization as compared to 37 patients in the PROSPER trial. The number of patients, in the SPARTAN trial, who had metastasis at baseline after randomization is unknown.

Finally, the Sponsor identified several effect modifiers across the trials included in the ITC. Here, a higher proportion of patients in the ARAMIS trial had an ECOG status of 1, ARAMIS was the only trial that enrolled patients with history of seizures, and a lower proportion of those who received bone targeting agents at baseline as compared to the PROPSER and SPARTAN trials (Table 7.1). There were also differences in the baseline PSDAT across trials.[7]

Indirect Treatment Comparison Methodology

A graphical representation of the NMA is presented in Figure 7.2.

Figure 7.2. Graphical representation of the ITC comparing darolutamide to apalutamide and enzalutamide.



Data source: NMA Document prepared by Bayer[7]

Efficacy Outcomes

Metastasis Free-Survival

The direct estimates of MFS from the trials are presented in Table 7.3. Table 7.4 shows the HRs based on ARAMIS data of MFS after adjusting to better align with the censoring MFS rules used in the Canadian regulatory application for apalutamide and exploratory adjustments for switching to a new anti-cancer therapy prior to metastases as event, and baseline metastasis. The exploratory analyses in Table 7.4 demonstrate the potential impact that inter-trial differences may have by showing their effect on the MFS HR of darolutamide vs. ADT.

Table 7.5 shows the HRs of MFS after adjusting for MFS censoring rules only in the ARAMIS, PROSPER and SPARTAN trials.

Table 7.3: MFS HRs from the ARAMIS, SPARTAN and PROSPER trials.

Study	Treatment	MFS events N (%)	Median MFS, months (95% CI)	HR (95% CI), P
ARAMIS	Darolutamide (N=955)	221 (23.1)	40.4 (34.3, NR)	0.413 (0.341, 0.500), P <0.000001
	Placebo (N=554)	216 (39)	18.4 (15.5, 22.3)	
PROSPER	Enzalutamide (N=933)	219 (23)	36.6 (33.1, NR)	0.29 (0.24, 0.35), P < 0.0001
	Placebo (N=468)	228 (49)	14.7 (14.2, 15.0)	
SPARTAN	Apalutamide (N=806)	184 (22.8)	40.51 (NE, NE)	0.28 (0.23, 0.35), P <0.0001
	Placebo (N=401)	194 (48.4)	16.20 (14.6, 18.4)	
Abbreviations: **CI** = confidence interval; **HR** = Hazard ratio; **MFS** = metastasis-free survival; **NE** = not evaluable				

Data source: NMA Document prepared by Bayer[7]

Table 7.4: HRs for MFS based on ARAMIS trial data after adjusting for censoring* rules and exploratory scenarios

	HR	95% CI Lower bound	95% CI Upper bound
Primary Analysis	0.41	0.34	0.50
Adjustment for MFS censoring rules (Time of progression [metastasis] determined based on the date of progression, regardless of change of therapy or missed or unevaluable tumour assessments)	0.413	0.343	0.497
Hazard Ratios of MFS after Exploratory Adjustments*			
Switch to new anti-cancer therapy prior to metastases as event**	0.346	0.292	0.409
Baseline metastasis censored***	0.359	0.292	0.441
Switch to new anti-cancer therapy prior to metastases as event and baseline metastasis censored***	0.300	0.250	0.361

Source: Bayer Data on File; *Includes adjustment for MFS censoring rules; **Bayer Data on File, ARAMIS Clinical Study Report *** Bayer Data on File

***** Application of similar censoring rules as applied in the Canadian regulatory approval for apalutamide.

Data source: NMA Document prepared by Bayer[7]

Table 7.5: Sensitivity Analysis: MFS HRs based on ARAMIS, SPARTAN and PROSPER data after adjusting for censoring[§] in these trials.

Trial	HR (95% CI)
ARAMIS*	0.413 (0.343, 0.497)
SPARTAN**	0.30 (0.24, 0.36)
PROSPER***	0.30 (0.25, 0.36)

Time of progression (metastasis) determined based on the date of progression, regardless of change of therapy or missed or unevaluable tumour assessments. For enzalutamide, used Sensitivity Analysis 1 (inclusion of 'progression after alternative treatment')
Source: 1. Fizazi et al. 2019; 2. Smith et al. 2018; 3. Hussain et al. 2018; *Bayer Data on File; **Apalutamide Canadian Product Monograph; *** pCODR Final Recommendation for enzalutamide-Sensitivity Analysis 1
Abbreviations: CI = confidence interval; HR = Hazard ratio; MFS = metastasis-free survival; NE = not evaluable
[§]Application of similar censoring rules applied in the Canadian regulatory approval for apalutamide.

Data source: NMA Document prepared by Bayer[7]

The results of the ITCs and fixed effects NMA for MFS are presented in Table 7.6. The HRs for MFS were similar for both the ITC and the fixed effects NMA. The ITC analysis shows that the risk of having metastatic disease or death was higher for patients treated with darolutamide as compared to those treated with apalutamide or enzalutamide. Similar estimates for the ITC and NMA were obtained after adjusting the MFS censoring (adjustment made to better align with the censoring MFS rules used in the Canadian regulatory application for apalutamide). However, given the heterogeneity among the trials that could not be adjusted for (i.e., the difference in number of patients who initiated new anti-cancer therapy prior to metastasis in ARAMIS, PSA being unblinded in ARAMIS, patients with metastasis at baseline, treatment effect modifiers, patients with a history of seizures), the Sponsor has stated that the comparative estimates from the ITC and NMA should be considered unreliable.

Table 7.6: Summary of unadjusted indirect comparison and fixed effects NMA results for MFS

Endpoint	Intervention (Study)	Comparator (Study)	Censoring rules	Unadjusted indirect comparison HR (95% CI)	Unadjusted fixed effect NMA HR (95% CrI)
MFS	Darolutamide (ARAMIS)	Apalutamide (SPARTAN)	Original	1.46 (1.10 to 1.95)	1.46 (1.10 to 1.94)
MFS	Darolutamide (ARAMIS)	Enzalutamide (PROSPER)	Original	1.41 (1.08 to 1.85)	1.41 (1.08 to 1.85)
MFS (sensitivity)	Darolutamide (ARAMIS)	Apalutamide (SPARTAN)	Adjusted*	1.38 (1.05 to 1.81)	1.38 (1.05 to 1.82)
MFS (sensitivity)	Darolutamide (ARAMIS)	Enzalutamide (PROSPER)	Adjusted*	1.38 (1.06 to 1.79)	1.38 (1.06 to 1.78)

Abbreviations: **CI** = confidence interval; **CrI** = credible interval; **HR** = hazard ratio; **ITT** = intention-to-treat; **MFS** = metastasis-free survival; **NMA** = network meta-analysis

Note: * partial adjustment related to the application of different MFS censoring rules across trials (adjustment made to better align with the censoring MFS rules used in the Canadian regulatory application for apalutamide). It does not account for other cross-trial differences and sources of heterogeneity identified such as: the difference in number of patients who initiated new anti-cancer therapy prior to metastasis in ARAMIS, PSA being unblinded in ARAMIS, patients with metastasis at baseline, treatment effect modifiers, patients with a history of seizures.

Data source: NMA Document prepared by Bayer[7]

Overall Survival

The direct estimates of OS from the trials are presented in Table 7.7. The Sponsor commented that none of the studies included in the ITC had reached the predefined level of statistical significance.[7]

Table 7.7: OS estimates based on ARAMIS, SPARTAN and PROSPER trial data.

Study	Treatment	OS events N (%)	Median OS	HR (95% CI)	OS Log HR (SE)	Source
ARAMIS	Darolutamide (N=955)	78 (8.2%)	NE	0.706 (0.501; 0.994)	-0.342 (0.174)	CSR Table 9-7; Study publication
	Placebo (N=554)	58 (10.5%)	NE			
PROSPER	Enzalutamide (N=933)	103 (11%)	NE	0.80 (0.58; 1.09)	-0.223 (0.161)	Study publication
	Placebo (N=468)	62 (13%)	NE			
SPARTAN	Apalutamide (N=806)	62 (7.7%)	NE	0.700 (0.472; 1.038)	-0.357 (0.201)	CSR (FDA website)
	Placebo (N=401)	42 (10.5%)	39.03			

Data Source: Checkpoint materials[3]

The results of the ITCs and fixed effects NMA for OS are presented in Table 7.8. The HRs for OS were similar for both the ITC and the fixed effects NMA. There were no significant differences on OS for patients treated darolutamide relative to those treated with enzalutamide or apalutamide.

Table 7.8: Summary of the indirect comparison and fixed effects NMA results

Endpoint	Intervention (Study)	Comparator (Study)	Indirect comparison HR (95% CI)	Fixed effect NMA HR (95% CrI)
OS	Darolutamide (ARAMIS)	Apalutamide (SPARTAN)	NA	1.02 (0.60 to 1.71)
	Darolutamide (ARAMIS)	Enzalutamide (PROSPER)	NA	0.89 (0.56 to 1.41)
Abbreviations: **CI** = confidence interval; **CrI** = credible interval; **HR** = hazard ratio; **ITT** = intention-to-treat; **NMA** = network meta-analysis; **OS** = overall survival				

Data source: NMA Document prepared by Bayer[7]

Altavilla et al (2019) NMA[15]

Overall, the NMA included 4,104 patients across the three RCTs (i.e. SPARTAN, ARAMIS and PROSPER). The authors reported that there was significant heterogeneity for falls, fatigue of all grades, severe fatigue, hypertension and mental impairment. For falls, darolutamide was more protective as compared to enzalutamide (odds ratio (OR): 0.29, 95% CI: 0.14 to 0.60) and apalutamide (OR: 0.48, 95% CI: 0.25 to 0.91). For fatigue of all grades, darolutamide was more protective as compared to enzalutamide (OR 0.59, 95% CI: 0.39 to 0.88) but apalutamide was more protective than enzalutamide (OR: 0.61, 95% CI:0.44 to 0.84). Darolutamide was more protective against severe fatigue as compared to enzalutamide (OR 0.10, 95% CI: 0.02 to 0.60). Darolutamide was more protective for hypertension as compared to enzalutamide (0.51, 95% CI: 0.27 to 0.98) but apalutamide was more protective than enzalutamide (OR 0.53, 95% CI: 0.31 to 0.92). Finally, for mental impairment, darolutamide was more protective as compared to enzalutamide (OR: 0.15, 95% CI: 0.04 to 0.58) and apalutamide (OR: 0.24, 95% CI: 0.06 to 0.90).

7.1.5 Critical Appraisal of the Indirect Comparisons

The methods and reporting of the indirect comparisons were assessed according the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[49]

Table 7.9: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Sponsor-Provided ITC and NMA	Altavilla et al (2019) NMA[15]
1. Is the population relevant?	**Yes**. The study populations included in the Sponsor-Provided ITC and NMA and the Altavilla et al (2019) NMA matched the indication under review, which was to evaluate the efficacy and safety of darolutamide in patients with nmCRPC who are at high risk of developing metastases during continuous ADT and who have a good ECOG performance status.	
2. Are any critical interventions missing?	**Yes**. The Sponsor-Provided ITC and NMA and the Altavilla et al (2019) NMA assessed all the relevant comparators for MFS, OS and safety, which include: enzalutamide and apalutamide.	
3. Are any relevant outcomes missing?	**Yes, in part.** The following outcomes were identified as important during the pCODR protocol stage: MFS, OS, safety outcomes and HRQoL. However, given the lack of data, the Submitter was only able to assess MFS and OS. Thus, there is a lack of information on other relevant outcomes.	**Yes, in part.** The study authors only assessed safety outcomes.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes.** The clinical setting of both the Sponsor-Provided ITC and NMA and the Altavilla et al (2019) NMA were considered to be appropriate and generalizable to the Canadian context.	
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Unclear**. The methodology used to identify studies was poorly reported in the both the Sponsor-Provided ITC and NMA and the Altavilla et al (2019) NMA; however, there does not appear to be any relevant studies missing based on the systematic reviews conducted by the pCODR Methods Team.	
6. Do the trials for the interventions of interest form one connected network of RCTs?	**No.** There were no closed loops in the NMA.	**Unclear**. The study authors did not report any details on formation of the network.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**No.** The studies included in the Sponsor-Provided ITC and NMA and the Altavilla et al (2019) NMA were multinational trials that were well-conducted and well-reported but neither the Sponsor-Provided ITC and NMA and the Altavilla et al (2019) NMA performed a critical appraisal of the studies.	
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**Unlikely.** All studies were published at the time the ITC and NMAs were completed. All studies included appear to report their planned outcomes.	
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** There were systematic differences in the baseline patient or study characteristics that impact the treatment effects.	**Unclear.** This was not reported by the study authors.

ISPOR Questions	Sponsor-Provided ITC and NMA	Altavilla et al (2019) NMA[15]
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Yes.** The Sponsor assessed the effect of switching to a new anti-cancer therapy prior to metastases as event and baseline metastasis. Sensitivity analyses were performed to examine censoring rules across the three studies. In addition, there may be other sources of heterogeneity that could not be examined or adjusted for, such as: the proportion of patients who initiated new anti-cancer therapy prior to metastasis; PSA performance unblinded in ARAMIS; Patients with baseline metastasis; MFS not measured the same way across the three trials; differences in (proportions of) treatment effect modifiers; and patients with history of seizure not excluded in ARAMIS.	**Unclear.** This was not reported by the study authors.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes**. The Sponsor-Provided ITC and NMA used a Bayesian NMA (standard approach) to analyze data on outcomes of interest from the included RCTs.	**Unclear.** This was not reported by the study authors.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable.** There were no closed loops.	**Unclear.** The study authors did not report any details on the formation of their network.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the NMA?	**Not applicable.** There were no closed loops in the networks.	**Unclear.** This was not reported by the study authors.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**No.** There were no subgroup analyses or meta-regressions performed based on patient characteristics. Sensitivity analyses were performed to examine censoring rules across the three studies.	**Unclear.** This was not reported by the study authors.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** A fixed effects model was used because there were only a few studies included in the NMA.	**No.** The study authors did not report the type of model that was used.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable.** The authors only performed fixed-effects analyses for all outcomes.	**No.** The study authors did not report their assumptions about how they explored heterogeneity.

ISPOR Questions	Sponsor-Provided ITC and NMA	Altavilla et al (2019) NMA[15]
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Yes.** It is unclear if the sensitivity analysis was pre-specified by the authors.	**Unclear.** The authors did not report any subgroup analysis to explore heterogeneity.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** Evidence network diagrams were provided for all of the endpoints.	**Unclear.** Evidence network diagrams were not reported for all of the endpoints.
19. Are the individual study results reported?	**Yes.** Individual study results were reported for the endpoints of interest.	**Unclear.** The individual study results were not reported.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or NMA?	**Yes.** The Sponsor-Provided ITC and NMA provided direct and indirect estimates of effect (when available).	**Unclear.** The direct and indirect estimates of effect were not reported.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** Measures of uncertainty were reported for the direct estimates of effect (95% CI) and for the indirect estimates (95% credible intervals) reported in the submitter-provided NMA.	**Unclear.** Measures of uncertainty were not reported.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**Not applicable.** Ranks were not reported for the Sponsor-Provided ITC and NMA and the Altavilla et al (2019) NMA.	
23. Is the impact of important patient characteristics on treatment effects reported?	**Not reported**	**Not reported**
24. Are the conclusions fair and balanced?	**Yes, in part.** The conclusions of the Sponsor-Provided ITC and NMA accurately reflect the results, which suggest that darolutamide increases the risk of MFS as compared to apalutamide and enzalutamide. In addition, there was no statistical differences between darloutamide, apalutamide and enzalutamide for OS. However, the study author stated the estimates from the Sponsor-Provided ITC and NMA should be considered unreliable due to the high degree of heterogeneity among the included studies.	**Yes, in part.** The study authors accurately reflect the results, which suggest that apalutamide, enzalutamide and daroluatmide are associated with an increased risk of AEs but it depends on the type of agent that is used. In addition, the authors state that these results should be interpreted with caution due to the limitations of NMAs.
25. Were there any potential conflicts of interest?	**Unclear**. The Sponsor-Provided ITC and NMA was unpublished and was prepared by a consultant for the Sponsor of darolutamide.	**Unclear**. These details were not reported.
26. If yes, were steps taken to address these?	**Unclear**. These details were not reported.	

ISPOR Questions	Sponsor-Provided ITC and NMA	Altavilla et al (2019) NMA[15]
CI = confidence interval; **CrI** = credible interval; **NMA** = network-meta-analysis; **nmCRPC** = non-metastatic castration-resistant prostate cancer; **RCT** = randomized controlled trial † Adapted from Jansen et al., 2014[49]		

7.1.6 Conclusion

Sponsor-Provided ITC and NMA

The Sponsor-Provided ITC and NMA compared darolutamide to apalutamide and enzalutamide in patients with nmCRPC who are at high risk of developing metastases during continuous ADT and who have a good ECOG performance status. The results of the ITC and NMA suggest that darolutamide increases the risk of MFS as compared to apalutamide and enzalutamide. In addition, there was no statistical differences between darolutamide, apalutamide and enzalutamide for OS.

The Sponsor-Provided ITC and NMA was conducted using the relevant patient population (i.e., patients with high risk nmCRC). The patient populations of the ARAMIS, PROSPER and SPARTAN studies aligned with the indication under review (i.e., patients with nmCRPC). The indirect comparisons included relevant efficacy outcomes, such as MFS and OS but there were no analyses conducted for any safety endpoints or HRQoL. The Sponsor-Provided NMA was limited to the use of fixed-effects models. However, given the lack of trials included in the NMA this was deemed appropriate.

There are a few limitations of the Sponsor-Provided ITC and NMA that warrant discussion. First, there was no literature search strategy or the study selection process. Similarly, there were no methodological details reported regarding data extraction and it was not reported if a risk of bias assessment was performed by the Sponsor. Therefore, there are some concerns regarding missing studies from this analysis and the absence of formal risk of bias assessment. However, the Sponsor stated that to date there are only three phase 3, randomized, placebo controlled clinical trials that have assessed the efficacy and safety of androgen receptor-axis-targeted therapies, which include: SPARTAN, PROSPER and ARAMIS.[3] Second, there was a high degree of heterogeneity among the ARAMIS, PROSPER and SPARTAN trials. This implies that there may be systematic differences between the patient populations among the three included studies. Although the Sponsor did adjust for differences in censoring across the three trials, the other sources of known heterogeneity may potentially confound the outcomes of interest because they were not captured in the prediction models. It should be noted that the bias resulting from missing prognostic factors is very difficult to quantify, and as a result, it is unclear what impact the missing prognostic factors have on the results of the ITC and NMA. In fact, given the heterogeneity among the trials, the Sponsor has stated the estimates from the ITC and NMA should be considered unreliable. Additionally, the Sponsor-Provided ITC and NMA was completed by external consultancy groups hired by the submitter. As a result, the information provided in the reports should be viewed considering this potential conflict of interest and lack of peer-review. Due to the above limitations, the comparative efficacy estimates obtained are likely biased, and it is not possible to quantify or identify the direction of the bias. As a result, the estimates may over- or underestimate the true treatment effect associated with darolutamide.

Altavilla et al (2019) NMA[15]

Overall, the results of the NMA suggest that apalutamide, enzalutamide and daroluatmide are associated with an increased risk of AEs but it depends on the type of agent that is used.

However, the authors stated that there were limitations in the NMA, and therefore, these results should be interpreted with caution. The pCODR Methods Team was unable to fully critically appraise the NMA due to the absence of a publication.

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were identified.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Genitourinary Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on darolutamide (Nubeqa) for non-metastatic castration resistant prostate cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. Bayer Inc., as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Genitourinary Clinical Guidance Panel is comprised of darolutamide (Nubeqa) for non-metastatic castration resistant prostate cancer. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

Literature Search Methods

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** August 2019, **Embase** 1974 to 2019 September 06, **Ovid MEDLINE(R) ALL** 1946 to September 06, 2019

#	Searches	Results
1	(nubeqa* or darolutamide* or darramamide* or BAY 1841788 or BAY1841788 or ODM 201 or ODM201 or ORM 16497 or ORM16497 or ORM 16555 or ORM16555 or X05U0N2RCO).ti,ab,ot,kf,kw,hw,nm,rn.	284
2	1 use medall	52
3	1 use cctr	45
4	*darolutamide/	50
5	(nubeqa* or darolutamide* or darramamide* or BAY 1841788 or BAY1841788 or ODM 201 or ODM201 or ORM 16497 or ORM16497 or ORM 16555 or ORM16555).ti,ab,kw,dq.	234
6	or/4-5	236
7	6 use oemezd	142
8	7 not conference abstract.pt.	96
9	7 and conference abstract.pt.	46
10	limit 9 to yr=2014-current	42
11	2 or 3 or 8	193
12	remove duplicates from 11	131
13	10 or 12	173
14	limit 13 to english	153

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#5	Search **#3 AND publisher[sb]** Filters: **English**	6
#4	Search **#3 AND publisher[sb]**	7
#3	Search **(#1 OR #2)**	52
#2	Search **(nubeqa*[tiab] OR darolutamide*[tiab] OR darramamide*[tiab] OR BAY 1841788[tiab] OR BAY1841788[tiab] OR ODM 201[tiab] OR ODM201[tiab] OR ORM 16497[tiab] OR ORM16497[tiab] OR ORM 16555[tiab] OR ORM16555[tiab] OR X05U0N2RCO[rn])**	51
#1	Search **"darolutamide" [Supplementary Concept]**	19

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Nubeqa/darolutamide, nmCRPC

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Nubeqa/darolutamide, nmCRPC

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Nubeqa/darolutamide, nmCRPC — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[50]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Nubeqa and darolutamide.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of February 20, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[51] Included in this search were the websites

of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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