pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Darolutamide (Nubeqa)

Submitted Reimbursement Request:
In combination with androgen deprivation therapy, for the treatment of patients with non-metastatic castration resistant prostate cancer who are at high risk of developing metastases (high risk defined as prostate-specific antigen doubling time ≤ 10 months) during continuous androgen deprivation therapy and have a good Eastern Cooperative Oncology Group performance status.

Submitted By: Bayer Inc.	**Manufactured By:** Bayer Inc.
NOC Date: February 20, 2020	**Submission Date:** August 27, 2019
Initial Recommendation: April 2, 2020	**Final Recommendation:** April 22, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	At the recommended dose of two 300 mg tablets twice daily, darolutamide costs $3,174.53 per 28-day cycle.

pERC RECOMMENDATION

☐ **Reimburse**
☒ **Reimburse with clinical criteria and/or conditions***
☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of darolutamide in combination with androgen-deprivation therapy (ADT) for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastases, if the following condition is met:

- cost-effectiveness being improved to an acceptable level

High risk is defined as a prostate-specific antigen doubling time (PSADT) of ≤ 10 months during continuous ADT and castration-resistant according to the Prostate Cancer Working Group 2 (PCWG2) criteria which was used in the ARAMIS trial. Absence of metastases was determined by a negative CT scan and negative bone scan. Patients should have good performance status. Treatment should continue until unacceptable toxicity or radiographic disease progression.

pERC made this recommendation because it was satisfied that, compared with ADT monotherapy, there is a net clinical benefit of darolutamide in combination with ADT based on statistically significant and clinically meaningful improvements in metastasis-free survival (MFS) and overall survival (OS), a manageable toxicity profile, and no detriment in quality of life (QoL).

pERC concluded that darolutamide aligns with the following patient values: delay in disease progression and symptoms, prolonged survival, maintenance of QoL, and additional treatment choice.

	In addition, the Committee considered evidence provided through indirect treatment comparison (ITCs) with apalutamide and enzalutamide, which are relevant comparators in this setting. pERC concluded that there is uncertainty about the comparative efficacy and safety data of darolutamide, apalutamide, and enzalutamide. pERC concluded that, at the submitted price, darolutamide in combination with ADT is not cost-effective compared with ADT monotherapy. The Committee noted that there was considerable uncertainty in the cost-effectiveness estimates compared with relevant comparators (apalutamide and enzalutamide) because of a lack of robust direct or indirect comparative clinical effectiveness data to inform the submitted economic evaluation.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Price Arrangement to Improve Cost-Effectiveness and Affordability of Darolutamide** Given that pERC was satisfied that there is a net clinical benefit of darolutamide in combination with ADT, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of darolutamide in combination with ADT to an acceptable level. pERC noted that a reduction in the price of darolutamide would be required to improve the cost-effectiveness to an acceptable level. **Generalizability of Results to Patients with Other High-Risk Factors** pERC discussed that there is currently insufficient evidence to make an informed recommendation on the use of darolutamide in combination with ADT in patients with high-risk features, other than those defined in the ARAMIS trial. Therefore, the Committee noted that a separate submission to pCODR would be required for darolutamide in patients with high-risk features other than those defined in the ARAMIS trial. **Sequencing of Treatments for Metastatic Castration-Resistant Prostate Cancer** pERC was unable to make an informed recommendation on the optimal sequencing of treatments for metastatic castration-resistant prostate cancer (CRPC) after treatment with darolutamide in the non-metastatic setting, noting that there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of darolutamide in combination with ADT and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value. **Please note:** The Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers). The number of new prostate cancer cases in 2019 has been estimated at approximately 22,900 with 4,100 expected deaths; 28% of patients progress to metastatic castration-resistant prostate cancer (mCRPC). This represents a significant patient group with a high risk for progression to metastatic disease. CRPC is defined as disease progression in the setting of castrate testosterone levels, the PCWG2 criteria for defining castration-resistant has been consistently used in prostate cancer trials. Biochemical progression, as manifested by a rise in prostate-specific antigen (PSA) alone, is often the initial sign of disease progression before the development of metastatic disease to bone or visceral organs. Current treatment options include observation or androgen-deprivation therapy (ADT) for patients with biochemical-only progression and no evidence of metastases. pERC noted that it recently conditionally recommended apalutamide in combination with ADT as well as enzalutamide in combination with ADT in a similar patient population; however, these combinations are currently not funded in the majority of Canadian jurisdictions. pERC agreed with the pCODR Clinical Guidance Panel (CGP) and registered clinicians that there is a need for new treatment options that delay the development of metastases and disease symptoms.

pERC deliberated on the results of one randomized, placebo-controlled, phase III trial (ARAMIS) that evaluated the efficacy and safety of darolutamide (Nubeqa) in combination with ADT compared with ADT alone in men with nmCRPC. pERC considered that metastasis-free survival (MFS), the primary outcome of the trial, was statistically significant and clinically meaningful in favour of darolutamide plus ADT. pERC discussed that the transition from nmCRPC to detectable metastatic disease is a clinically relevant event that often heralds the onset of pain and a potential for rapid decline in overall QoL. pERC agreed with the CGP and the registered clinicians providing input that the improvement in MFS of the magnitude observed in the ARAMIS trial (i.e., approximately a two-year delay in occurrence of metastasis or death) is of clinical importance in a patient population for which there are currently no standard of care treatments. pERC also noted at the time of the final OS analysis, median OS was not reached in either treatment group but was statistically significant in favour of darolutamide. Overall, pERC concluded that, given that patients with nmCRPC are at risk of progressing to metastatic disease within one to two years, a two-year increase in median MFS for darolutamide over placebo is a meaningful outcome in this setting.

pERC deliberated on the toxicity profile of darolutamide in combination with ADT and noted that the incidence and severity of adverse reactions were broadly similar between the two groups. The most frequently reported treatment-emergent adverse event (TEAE) was fatigue, which occurred more frequently in the darolutamide group. Other common TEAEs included back pain, arthralgia, diarrhea, constipation, nausea, and hypertension. pERC noted that, while a very small number of patients suffered a seizure during treatment, none of the patients with a history of seizure experienced seizures while receiving darolutamide. Overall, pERC agreed with the CGP and the registered clinicians providing input that darolutamide has a manageable safety profile.

pERC discussed the available patient-reported outcomes data from the ARAMIS trial and noted that overall quality of life (QoL) was similar between the two study groups and did not show a negative effect of darolutamide plus ADT on QoL compared with ADT plus placebo. pERC considered this to be reasonable in the nmCRPC setting, where patients' QoL is expected to be relatively high and stable.

In the absence of a direct comparison of darolutamide plus ADT with apalutamide plus ADT or enzalutamide plus ADT, pERC considered the results of a submitted network meta-analysis (NMA). pERC acknowledged the limitations noted by the CADTH Methods Team as well as the sponsor and agreed with their concerns regarding the heterogeneity across the study designs and populations. pERC agreed with the CGP and the CADTH Methods Team and cautioned against drawing conclusions from the ITCs on the

magnitude of effect of darolutamide compared with either apalutamide or enzalutamide in the absence of more robust direct evidence from a randomized trial.
pERC concluded that there is a net clinical benefit to darolutamide plus ADT compared with ADT plus placebo in the treatment of men with nmCRPC who are at high risk of developing metastases. In coming to this conclusion, pERC considered the clinically meaningful results of MFS and OS, a manageable toxicity profile, no significant detriment in QoL, and a need for treatment options that delay the onset of disease symptoms and metastases.

pERC deliberated upon a submission from one patient group. pERC noted that, according to patients, key symptoms of concern with nmCRPC are erectile dysfunction, fatigue, and urinary incontinence. Erectile dysfunction was also a reported side effect of treatments patients were currently taking. Patients valued treatment options that help to maintain or improve QoL, have reduced side effects, and lead to longer life. Few patients had direct experience with using darolutamide; those that did, reported that there had no side effects while on treatment with darolutamide. Overall, patients reported positive experiences with darolutamide. Patients were able to engage in daily activities while taking darolutamide and maintain a good QoL. pERC concluded that the use of darolutamide aligned with the following patient values: delay in disease progression and symptoms, prolonged survival, maintenance of QoL, and additional treatment choice.

pERC deliberated upon the cost-effectiveness of darolutamide plus ADT compared with ADT monotherapy for patients with nmCRPC. pERC noted that the pCODR Economic Guidance Panel (EGP) made the following changes to the economic model: assuming similar risk of mortality between groups at trial end; selecting more optimistic parametric distribution for OS for ADT; selecting the Weibull distribution for time on treatment for darolutamide; using Canadian tariffs for utilities; and using a lifetime horizon. pERC noted that the magnitude of long-term benefit associated with darolutamide is unknown, given the lack of long-term data used in the economic model. pERC agreed with the EGP's reanalysis to assume smaller gains in survival benefit, which were overestimated in the submitted base-case incremental cost-effectiveness ratio (ICER). pERC noted that the EGP's best-estimate ICER was higher than the sponsor's base-case ICER. pERC concluded that, at the submitted price, darolutamide in combination with ADT is not cost-effective compared with ADT monotherapy. The Committee noted that there was considerable uncertainty in the cost-effectiveness estimates compared with relevant comparators (apalutamide and enzalutamide) because of a lack of robust direct or indirect comparative clinical effectiveness data to inform the submitted economic evaluation.

The Committee deliberated on the input from PAG, regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report (CGP) that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group: Canadian Cancer Survivor Network (CCSN)
- input from registered clinicians: 10 individual clinicians and two joint clinician inputs on behalf of Prostate Cancer Canada (representing four clinicians) and Cancer Care Ontario (representing three clinicians)
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group: Canadian Cancer Survivor Network (CCSN)
- one joint registered clinician input on behalf of Cancer Care Ontario
- the submitter, Bayer Inc.
- pCODR's Provincial Advisory Group (PAG)

The pERC Initial Recommendation was to recommend reimbursement of darolutamide in combination with androgen-deprivation therapy (ADT) for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastases, if the following condition is met:

- cost-effectiveness being improved to an acceptable level

Feedback on the pERC Initial Recommendation indicated that PAG, the submitter, registered clinicians, and the patient group agreed with the Initial Recommendation. All stakeholders supported early conversion of the Initial Recommendation to a Final Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial Recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation. Clarifications related to the feedback provided by stakeholders that reflected the initial deliberation by pERC were added to the Final Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the efficacy and safety of darolutamide (Nubeqa) in combination with ADT for patients with non-metastatic nmCRPC who are at high risk of developing metastases (high risk is defined as prostate-specific antigen [PSA] doubling time ≤ 10 months) during continuous ADT and who have a good Eastern Cooperative Oncology Group Performance Status (ECOG PS).

Studies included: One randomized, double-blind, placebo-controlled, phase III RCT

The pCODR systematic review included one randomized, double-blind, placebo-controlled, phase III trial: ARAMIS. A total of 1,509 men were randomized (2:1) in ARAMIS, with 955 randomized to receive darolutamide twice daily (two 300 mg tablets) and 554 to receive placebo. Patients in both treatment groups continued to receive androgen-deprivation therapy throughout the trial. The ARAMIS trial assessed the safety and efficacy of darolutamide compared to placebo in men with nmCRPC and a PSA doubling time of 10 months or less. Absence of metastases was determined by a negative CT scan and negative bone scan. 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.

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 mL; a PSA doubling time of 10 months or less; and an ECOG PS of 0 to 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.

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.

Patient populations: Median age 74 years; median PSA doubling time at baseline 4.4 months

Overall, the baseline characteristics of patients in the ARAMIS trial were well balanced between the darolutamide and placebo groups. The median age in both treatment groups was 74 years. The median PSA doubling time at baseline was 4.4 months in the darolutamide group and 4.7 months in the placebo group. The proportion of patients with a PSA doubling time of less than six months was 70% in the darolutamide group and 67% in the placebo group. 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. As compared to the darolutamide group, slightly more patients in the placebo group had a history of treatment with a bone sparing drug (6% versus 3%), presence of lymph nodes on central imaging review (< 2 cm) (10.5% versus 11.9%) and an ECOG PS of 0 (71% versus 68%); however, patients in both groups had a similar proportion to those who have received two or more previous hormonal therapies (76% for both).

Key efficacy results: Clinically meaningful improvement in metastasis-free survival in favour of darolutamide

The primary efficacy outcome in the ARAMIS trial was MFS, defined as time from randomization to confirmed evidence of distant metastasis on imaging or death from any cause, whichever occurred first. Secondary outcomes included: OS, time to pain progression, time to cytotoxic chemotherapy and time to first symptomatic skeletal event. Exploratory outcomes included progression-free survival (PFS), time to PSA progression, PSA response rate, health-related QoL (HRQoL) and safety.

The trial met its primary outcome and demonstrated a statistically significant improvement in MFS in the darolutamide plus ADT group after a median follow-up of 18.4 and 16.8 months in the darolutamide and placebo groups, respectively. Median MFS was 40.4 months in the darolutamide group compared to 18.4 months in the placebo group.

OS was a secondary outcome in the trial. At the primary analysis, there were 78 deaths (8.2%) in the darolutamide group compared to 58 (10.5%) in the placebo group. Median OS was not reached in either treatment group and there was no statistically significant difference between the darolutamide and placebo groups on the effect of OS (HR = 0.71; 95% CI, 0.50 to 0.99; P = 0.045). At the final analysis for OS, darolutamide was associated with statistically significant prolonged OS compared to placebo.

Patient-reported outcomes: No difference between groups

HRQoL was an exploratory outcome 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 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. 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. 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. Similar results were observed for the FACT-P PCS score. 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. 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. Similar results were observed for the EQ-5D-3L visual analogue scale.

Safety: Manageable toxicity profile, similar between groups

Slightly more TEAEs of any grade occurred in the darolutamide group (83.2%) compared to the placebo group (76.9%). Grade 3 or 4 TEAEs were similarly reported across both treatment groups (darolutamide: 24.7% versus placebo: 19.5%). Hypertension was the most common grade 3 or 4 TEAE to occur among patients within the trial.

Serious AEs (SAEs) occurred more frequently among patients in the darolutamide group compared to the placebo group (24.8% versus 20%). Treatment related SAEs occurred at a similar frequency between both treatment groups (1.0% versus 1.1%, respectively). TEAEs of special interest occurred more commonly among patients in the darolutamide group (43%) compared to the placebo group (33%). Grade 3 or 4 TEAEs of special interest were similarly observed across both groups (darolutamide: 10% and placebo: 6%). Fatigue was the most common TEAE of special interest, occurring in 15.8% of patients in the darolutamide group and 11.4% of patients in the placebo group.

A very small proportion of patients (0.2%) in both treatment groups suffered a seizure during treatment; none of the 12 patients enrolled with a history of seizure (all of whom were enrolled in the darolutamide group) experienced seizures while receiving darolutamide. Death occurred in 3.9% of patients in the darolutamide group compared to 3.2% of patients in the placebo group. One death in the darolutamide group and two in the placebo group were reported to be drug related.

Limitations: No direct comparative data to recently recommended apalutamide and enzalutamide

The CADTH Methods Team summarized and critically appraised a sponsor-provided indirect treatment comparison (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 PS. The CADTH Methods Team concluded that due to high heterogeneity between the three clinical trials (differences in the number of patients who initiated new anti-cancer therapy prior to metastasis, who had metastasis at baseline, who received bone targeting agents, and who had a history of seizures; as well as differences in ECOG PS and median MFS estimates across control groups, and PSA being unblinded in ARAMIS), the comparative effectiveness estimates from the ITC and NMA are likely biased, and the magnitude or the direction of the bias cannot be established. 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 CADTH Methods Team identified four additional abstracts that reported on indirect treatment comparisons of darolutamide versus apalutamide and enzalutamide. 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, but the safety results appear to be 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.

Need and burden of illness: Need for treatment that delays development of metastases

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. Despite early-stage diagnosis and high cure rates with surgery or radiotherapy, most patients will develop recurrent disease with or without metastases. Salvage therapies include observation or salvage radiation therapy after previous prostatectomy or salvage prostatectomy after prior radiation therapy or ADT. Most patients initially respond to ADT; however, almost all the patients will progress to develop CRPC. No accepted standard treatment options have been implemented for patients with nmCRPC in Canada. In 2018 and 2019, pERC conditionally recommended apalutamide plus ADT and enzalutamide plus ADT for high-risk nmCRPC, respectively. However, apalutamide and enzalutamide are not yet reimbursed in the majority of Canadian jurisdictions. In the absence of treatment options, there is an urgent need for new treatment options that delay the development of metastases and disease symptoms.

Registered clinician input: Darolutamide may have more favourable toxicity profile

Clinician input was provided from a total of 17 clinicians: 10 individual inputs and two joint inputs on behalf of Prostate Cancer Canada (four clinicians) and Cancer Care Ontario (three clinicians). Clinicians highlighted an unmet need, as nmCRPC patients are a relatively new group of patients with few treatment options available. Apalutamide and enzalutamide were considered the most relevant comparators to darolutamide, but only ADT is currently funded in Canada for nmCRPC patients. Clinicians agreed to generalize treatment with darolutamide to patients who received prior chemotherapy but expressed different opinions regarding generalization to patients with prior immunotherapy. ECOG PS of 0 or 1 were considered acceptable eligibility criteria for darolutamide, but one clinician stated that androgen receptor inhibitors are generally benign and may be beneficial for patients with poorer ECOG PS. Use of another anti-androgen therapy as a subsequent treatment was not supported by registered clinicians. Chemotherapy was acknowledged as the most appropriate treatment for patients following progression on darolutamide. In addition to apalutamide and enzalutamide, darolutamide was considered as a "nice to have" therapy. Although, the side-effect profile of darolutamide was considered favourable and may require less monitoring, especially for patients with seizure history and comorbidities.

PATIENT-BASED VALUES

Values of patients with prostate cancer: Maintaining QoL; improved survival; and less side effects

One patient group, CCSN, provided input on darolutamide for nmCRPC. The symptom most affecting patient's QoL due to prostate cancer was reported to be erectile dysfunction. Erectile dysfunction was also a reported side effect of treatments that patients were currently taking. Patients expressed a desire for treatment options with improved side effects. Patients also commented on requiring better communication about treatments they are being prescribed with more information about side effects (e.g., erectile dysfunction). Maintenance of QoL was highlighted as an important factor to consider for new treatment options. Patients also reported hopes for delaying the need for hormone therapy and improved survival. Feelings of depression, nausea and vomiting, bowel incontinence, diarrhea, dizziness, feelings of anxiety, loss of bone mass and development of breasts or having breast tenderness were symptoms patients reported as being unacceptable for new treatments for prostate cancer. Patients valued treatment options that help to maintain or improve QoL, have reduced side effects (e.g., erectile dysfunction), and lead to longer life.

Patient values on treatment: Few patients (n = 5) with direct experience using darolutamide

Five patient respondents reported being treated with darolutamide. None of these patients reported experiencing side effects while they were treated with darolutamide. Patient respondents commented on being able to engage in daily activities while taking darolutamide and maintain a good QoL. 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 an issue with their cardiovascular health, but the patient stated the benefits of darolutamide still outweighed the side effects.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analyses

The EGP assessed one cost-utility analysis (cost per quality-adjusted life-years [QALYs] gained) of darolutamide plus ADT compared with ADT alone in patients with nmCRPC who are at high risk of developing metastasis.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were MFS, OS, time on treatment (ToT), and utilities.

Costs considered in the analysis included those related to drug acquisition and administration, monitoring care, health care resource utilization, subsequent treatment, and terminal care.

Drug costs: Treatment cost of darolutamide and comparators

Darolutamide costs $28.34 per 300 mg tablet. At the recommended dose of two 300 mg tablets twice daily (total of 1,200 mg day) darolutamide costs $113.38 per day and $3,174.53 per 28-day cycle.

Apalutamide costs $28.34 per 60 mg tablet. At the recommended dose of 240 mg (four 60 mg tablets) administered orally once daily, apalutamide costs $113.36 per day and $3,174.08 per 28-day cycle.

Enzalutamide costs $29.20 per 40 mg tablet. At the recommended dose of 160 mg (four 40 mg tablets) administered orally once daily, enzalutamide costs $116.78 per day and $3,269.88 per 28-day cycle.

ADT therapy: Weighted average of ADT treatments (i.e., degarelix, leuprorelin (leuprolide), goserelin, triptorelin, and buserelin) based on market share assumptions plus steroid treatment of prednisone/ prednisolone:

Per pack/dose per pack:
- Degarelix costs $345.00/120 mL or $255.00/80 mg
- Leuprorelin (leuprolide) costs $359.33/3.75 mg
- Goserelin costs $390.50/3.6 mg
- Triptorelin costs $346.31/3.75 mg
- Buserelin costs $84.10/10 mL
- Prednisone costs $13.11/5 mg
- Prednisolone costs $0.17/10 mg

Per 28-day cycle drug costs are:
- Degarelix costs $255.00
- Leuprorelin (leuprolide) costs $359.33
- Goserelin costs $390.50
- Triptorelin costs $346.31
- Buserelin costs $84.10
- Prednisone costs $13.11
- Prednisolone costs $0.17

Cost-effectiveness estimates: Not cost-effective at the submitted price; uncertainty in comparative effect estimates derived from ITC

The sponsor-provided economic analysis assessed the cost-effectiveness of darolutamide in combination with ADT compared with ADT alone. The submitted base-case ICERs were lower than the EGP's reanalyzed ICER estimate (submitted probabilistic ICER versus EGP's reanalyzed probabilistic ICER: $141,069 versus $177.087). The EGP made the following changes to the model to address some of the limitations:

- Assuming similar risk of mortality between groups at trial end of 3.8 years (instead of assuming OS benefit observed during the trial continues for another six months after the end of trial) to address the uncertainty from the immaturity of OS data, the large drop in the available population at risk starting from approximately 28 months, and the uncertainty in OS extrapolation.
- Selecting the more optimistic generalized gamma parametric distribution for OS for the ADT group (instead of the Weibull distribution) considering the uncertainty with long-term extrapolation with immature data.
- Selecting the Weibull distribution for ToT for darolutamide (instead of Gompertz distribution) based on model fit statistics.
- Using Canadian tariffs for utilities (instead of UK tariffs) to better reflect the preferences of the Canadian population.
- Increasing the submitted 10-year time horizon to a lifetime horizon (corresponding to 25 years) to fully capture all downstream consequences (i.e., costs and benefit) of the different treatment options, as recommended by CADTH guidelines.

The EGP noted several limitations in the submitted analysis, particularly the uncertainty in the clinical comparative efficacy data. The sponsor provided an ITC and NMA to present relative treatment effect estimates between comparators (apalutamide, enzalutamide) in the absence of head-to-head data. The EGP agreed with the CADTH Methods Team and the CGP that, given the limitations in the submitted ITC

and NMA the comparative effectiveness of darolutamide in combination with ADT versus apalutamide and enzalutamide remains uncertain (see the Limitations section in the Evidence in Brief earlier in this document for more details on the ITC and NMA).

The main factor that influenced the incremental cost of darolutamide in combination with ADT was the cost of darolutamide. The main factors that influenced the clinical gains associated with darolutamide in combination with ADT included the choice of time horizon, time point when equivalent mortality between darolutamide in combination with ADT and ADT alone is assumed, and parametric distribution type for OS and time on treatment for darolutamide.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact likely underestimated

The EGP noted that the key factors influencing the budget impact included the market share for ADT (more patients on ADT add darolutamide such as patients with seizures) with potential incremental budget impact rather than cost saving. With all other scenarios, darolutamide continued being a cost-saving alternative, assuming it would take more market share from enzalutamide (a more costly drug) than from apalutamide (a similar costing drug) and assuming no shift in the overall proportion of patients receiving an androgen receptor-axis-targeted therapy (ARAT). The CGP felt that market share distributions between the ARATs are difficult to predict at this point given insufficient evidence to choose one ARAT over the other. The EGP noted a limitation of the budget impact analysis was the consideration of incident nmCRPC cases while ignoring the existing prevalent nmCRPC cases at drug launch. Doubling of the number of nmCRPC cases that would receive treatment would result in greater cost savings with the introduction of darolutamide.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Avram Denburg who was not present for the meeting
- Dr. Christopher Longo who was not present for the discussion and deliberation for this review
- Dr. Maureen Trudeau who did not vote due to her role as the pERC Chair.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of darolutamide for nmCRPC, through their declarations, one member had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC base its recommendations on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations 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 clinical information; therefore, this information has been redacted in the publicly available guidance reports.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• 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.	• pERC noted that the definition of CRPC in the ARAMIS trial is as follows: *"(…) 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."* (Fizazi et al. 2019). pERC agreed with the CGP that this definition has been consistently used in previous trials (i.e., SPARTAN and PROSPER) and aligns with 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 PS of 2 or greater.
	• pERC agreed with the CGP that prior chemotherapy or immunotherapy (except in the adjuvant/neoadjuvant setting) was not permitted in the ARAMIS trial and these patients should be excluded from darolutamide treatment.
	• pERC agreed with the CGP that 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.
	• pERC agreed with the CGP that while the benefit for patients with ECOG 2 cannot be formally concluded from the ARAMIS study, 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.

• PAG noted the following groups of patients would need to be addressed on a time-limited basis:
  • Patients currently treated with ADT alone and who meet the criteria of the ARAMIS trial
  • Patients that experience intolerance to apalutamide or enzalutamide and appropriateness of switching to darolutamide.
	• pERC noted that, at the time of implementing a reimbursement recommendation for darolutamide in combination with ADT, jurisdictions may want to consider addressing the time-limited need to offer darolutamide in combination with ADT to patients who currently receive ADT monotherapy and meet the criteria of the ARAMIS trial or switch to darolutamide for patients that experience intolerance to apalutamide or enzalutamide.

• PAG noted that there is potential for indication creep to use darolutamide in high-risk patients (e.g., Gleason score 8 to 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.	• pERC noted that the interpretation of the trial results applies to patients at high risk for progression as defined in the ARAMIS trial (PSADT ≤ 10 months). As such, the ARAMIS results cannot be generalized to high-risk patients (e.g., Gleason score 8 to 10, high PSA at diagnosis, etc.) who have not had a PSA progression in the non-metastatic setting. • pERC agreed that the setting of the ARAMIS trial was limited to nmCRPC. As such, the trial results cannot be generalized to the non-metastatic hormone sensitive prostate cancer setting.
• 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.	• pERC agreed with the CGP 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, comorbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.
• 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.	• pERC agreed with the CGP that there is insufficient 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. • 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; pERC agreed with the CGP and does not recommend this practice. Registered clinicians noted that chemotherapy was the most appropriate treatment for patients following progression on darolutamide.
• 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.	• pERC was unable to make an informed recommendation on the use of darolutamide for patients who have been treated with abiraterone, enzalutamide, apalutamide, or other second-generation antiandrogens through a clinical trial or private drug insurance, as there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of darolutamide plus ADT and noted that a national approach to develop evidence-based clinical practice guidelines would be of value.

ADT = androgen-deprivation therapy; CGP = Clinical Guidance Panel; ECOG PS = Eastern Cooperative Oncology Group Performance Status; nmCRPC = non-metastatic castration-resistant prostate cancer; PCG2 = Prostate Working Group 2; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time.