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: Enzalutamide (Xtandi) **Submitted Reimbursement Request:** In combination with androgen deprivation therapy (ADT) for the treatment of patients with high-risk, non-metastatic castration-resistant prostate cancer (nmCRPC)	
Submitted By: Astellas Pharma Canada, Inc.	**Manufactured By:** Astellas Pharma Canada, Inc.
NOC Date: December 20, 2018	**Submission Date:** September 24, 2018
Initial Recommendation: March 7, 2019	**Final Recommendation:** March 26, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Enzalutamide costs $29.19 per 40 mg capsule. At the recommended dose of 4 capsules per day taken orally, enzalutamide costs $116.78 per day and $3,269.88 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 reimbursement of enzalutamide (Xtandi) 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 only if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- feasibility of adoption (budget impact) being addressed.

High risk is defined as a prostate-specific antigen doubling time (PSADT) of ≤ 10 months during continuous ADT. Patients should have good performance status and no risk factors for seizures. 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 enzalutamide plus ADT based on statistically significant and clinically meaningful improvements in metastasis-free survival (MFS), a manageable toxicity profile, no significant detriment in quality of life (QoL), and a need for treatment options in this population of patients who are at increased risk for developing metastases.

	pERC concluded that enzalutamide aligns with the following patient values: delay in disease progression and symptoms, additional treatment choice, and maintenance of QoL. In addition, the Committee considered evidence provided through indirect treatment comparisons with apalutamide, a relevant comparator in this setting. pERC concluded that enzalutamide and apalutamide may have similar efficacy and safety; however, in the absence of more robust direct evidence from a randomized trial, there is uncertainty about the comparative efficacy and safety data of these two regimens. pERC concluded that, at the submitted price and with a lack of a statistically significant overall survival (OS) benefit, enzalutamide plus ADT is not cost-effective compared with ADT monotherapy. pERC also highlighted that the submitted potential budget impact of enzalutamide plus ADT was underestimated and would be substantial. pERC therefore had concerns about the capacity of jurisdictions to implement reimbursement of enzalutamide.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of enzalutamide plus ADT, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of enzalutamide plus ADT to an acceptable level. pERC noted that a substantial reduction in the price of enzalutamide would be required in order to improve the cost-effectiveness to an acceptable level and to decrease the predicted substantial budget impact. **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 enzalutamide plus ADT in patients with high risk features, other than those defined in the PROSPER trial. Therefore, the Committee noted that a separate submission to pCODR would be required for enzalutamide in patients with high risk features other than those defined in the PROSPER 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 CRPC after treatment with enzalutamide 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 enzalutamide plus ADT and noted that a national approach to developing evidence-based clinical practice guidelines addressing sequencing of treatments would be of value. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in the summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers). The number of new prostate cancer cases in 2017 has been estimated at approximately 22,000, with a 34% annual progression to metastatic castration-resistant prostate cancer (mCRPC) and an overall mortality rate of 16%. 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. 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. No accepted standard treatment options have been defined for patients with non-metastatic castration-resistant prostate cancer (nmCRPC). In the absence of proven treatment options, observation or ADT is often recommended for patients with biochemical-only progression and no evidence of metastases. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that there is a need for new treatment options that delay the development of metastases and disease symptoms.

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

pERC deliberated on the results of one randomized, placebo-controlled, phase III trial (PROSPER) that evaluated the efficacy and safety of enzalutamide (Xtandi) 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 enzalutamide plus ADT. Key secondary outcomes — time to PSA progression and time to first use of new antineoplastic therapy — were also statistically significant in favour of enzalutamide. pERC noted that the results for OS (a secondary outcome) are immature at present. In the absence of OS data, pERC discussed the clinical meaningfulness of MFS in the nmCRPC setting. 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 PROSPER 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 is currently no standard treatments. 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 enzalutamide over placebo is a meaningful outcome in this setting.

pERC deliberated on the toxicity profile of enzalutamide in combination with ADT and noted that the incidence and severity of adverse reactions were broadly similar between the two groups and were consistent with the safety profile of enzalutamide in the metastatic setting. The most frequently reported treatment-emergent adverse event (TEAE) was fatigue, which occurred more frequently in the enzalutamide group. Other common TEAEs included hot flushes, hypertension, nausea, and falls. pERC noted that a very small number of patients suffered a seizure during treatment with enzalutamide and felt that enzalutamide was contraindicated in patients with risk factors for seizures. pERC discussed that a small increased fracture risk was observed with the use of enzalutamide and agreed with the CGP that increased osteopenia can potentially be mitigated with the use of bone-conserving therapies. Overall, pERC agreed with the CGP and the registered clinicians providing input that enzalutamide has a manageable safety profile.

pERC discussed the available patient-reported outcomes data from the PROSPER trial and noted that overall quality of life (QoL) was similar between the two study arms and did not show a negative effect of enzalutamide 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.

pERC concluded that there is a net clinical benefit to enzalutamide plus ADT compared with ADT plus placebo in the treatment of men with nmCRPC. In coming to this conclusion, pERC considered the clinically meaningful results in MFS, 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 joint submission from two patient advocacy groups. pERC noted that, according to patients, key symptoms of concern with nmCRPC are fatigue and sexual dysfunction. A few patients had direct experience using enzalutamide; those that did indicated that fatigue was a side effect. pERC noted that patients expressed uncertainty about whether the fatigue was due to treatment with enzalutamide or concurrent ADT. Patients reported a willingness to tolerate side effects (such as fatigue, loss of appetite, rash, and dizziness) if it would delay metastases. pERC agreed with the registered clinicians that the benefits of enzalutamide outweighed the potential risk of side effects. pERC concluded that the use of enzalutamide aligned with the following patient values: delay in disease progression and symptoms, additional treatment choice, and maintenance of QoL.

pERC deliberated upon the cost-effectiveness of enzalutamide plus ADT compared with ADT monotherapy for patients with nmCRPC. The Committee noted that while most of the inputs and assumptions selected seemed reasonable, one key limitation that had a large impact on the incremental effects was the survival extrapolation method. pERC noted that the pCODR Economic Guidance Panel (EGP) made the following changes to the model: reducing the long-term incremental MFS and OS benefits of enzalutamide plus ADT versus ADT monotherapy. pERC noted that the magnitude of long-term benefit associated with enzalutamide is unknown, given the lack of long-term data. pERC agreed with the EGP's changes 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 submitter's base-case ICER. pERC concluded that enzalutamide plus ADT could not be considered cost-effective compared with ADT monotherapy at the submitted price.

In the absence of a direct comparison of enzalutamide plus ADT with apalutamide plus ADT, pERC considered the results of a submitted network meta-analysis (NMA). pERC noted that, while the methods used to analyze the efficacy end points assumed proportional hazards, this assumption was not valid for MFS, time to cytotoxic chemotherapy, and time to PSA progression. pERC concluded that given the potential risk of bias with this limitation, the immaturity of the OS data, and the differences in the post-progression therapies that were used in the SPARTAN (apalutamide) and PROSPER trials, the cost-effectiveness of enzalutamide plus ADT compared with apalutamide plus ADT is uncertain.

pERC discussed the feasibility of implementing a reimbursement recommendation for enzalutamide plus ADT for patients with nmCRPC. pERC noted that the key factor influencing the incremental budget impact was the assumed market share (i.e., enzalutamide versus the recently approved apalutamide). Other factors included the size of the eligible patient population (i.e., high-risk nmCRPC), the drug cost, and the duration of enzalutamide therapy. Overall, the Committee concluded that the submitted Canada-wide budget impact was likely underestimated and would be substantial.

pERC discussed the Provincial Advisory Group's (PAG's) request for guidance on a number of clinical scenarios to assist with implementation:

- pERC agreed with the CGP that enzalutamide should be discontinued upon radiographic progression.
- pERC agreed with the CGP that patients who are progressing on ADT and first-generation antiandrogen, such as bicalutamide, should be evaluated for antiandrogen withdrawal syndrome by monitoring the PSA for six weeks before starting enzalutamide.
- pERC agreed that there is insufficient evidence at this point to recommend either enzalutamide or apalutamide over the other. pERC noted that the choice between enzalutamide and apalutamide will likely depend upon the relative overall cost, treatment availability, patient values and preferences, and clinical factors such as tolerability to adverse events.
- pERC agreed with the CGP that the PROSPER trial results were not generalizable to patients with a PSADT greater than 10 months.
- pERC discussed the optimal sequencing of treatments for metastatic CRPC after treatment with enzalutamide in the non-metastatic setting. pERC agreed with the CGP and with the registered clinicians providing input for this submission that adding enzalutamide to the available drug options may affect which treatment a patient will receive if they progress to metastatic disease. However, pERC was unable to make an informed recommendation on the optimal sequencing of treatments for metastatic CRPC, noting that there is insufficient evidence to inform this clinical situation.

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 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
- A joint input from two patient advocacy groups: the Canadian Cancer Survivor Network (CCSN) and Prostate Cancer Canada (PCC)
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Registered clinicians
- pCODR's Provincial Advisory Group (PAG)
- The submitter, Astellas Pharma Canada, Inc.

The pERC Initial Recommendation was to conditionally recommend reimbursement of enzalutamide (Xtandi) 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 only if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- feasibility of adoption (budget impact) being addressed.

If the aforementioned conditions cannot not be met, pERC does not recommend reimbursement of enzalutamide plus ADT.

Feedback on the pERC Initial Recommendation indicated that PAG, the submitter and registered clinicians agreed with the Initial Recommendation. All three stakeholders supported early conversion of the Initial Recommendation to a Final Recommendation. No feedback was received from patient groups.

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 enzalutamide (Xtandi) in combination with androgen deprivation therapy (ADT) compared with ADT monotherapy in men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC).

Studies included: One randomized, placebo-controlled, phase III trial

The pCODR systematic review included one randomized, placebo-controlled, phase III trial: PROSPER. The PROSPER trial evaluated the efficacy and safety of enzalutamide (Xtandi) in combination with ADT compared with ADT monotherapy in men with high-risk nmCRPC.

A total of 1,401 patients were randomized (2:1) in PROSPER, with 933 assigned to enzalutamide plus ADT and 468 to placebo plus ADT. Patients in the experimental group were treated with oral enzalutamide (160 mg once daily as four 40 mg tablets) and continuous ADT with gonadotropin-releasing hormone (GnRH) analogue or surgical castration (bilateral orchiectomy) to maintain castrate concentrations of testosterone (< 50 ng/dL). Patients in the placebo group received continuous ADT and matched placebo tablets. All patients received treatment until documented radiographic progression, withdrawal of

consent, or the development of unacceptable toxicity. Dose reduction or interruption was permitted. Any patients who experienced a grade 3-4 adverse event, attributed to study drug, could have had treatment interrupted for one week or until the toxicity grade of the adverse event improved to grade 2 or less. The study treatment would be restarted at 160 mg/day or at reduced dosage (of 120 or 80 mg per day) in consultation with the medical monitor.

The median duration of treatment was 18.4 months and 11.1 months in the enzalutamide and placebo groups, respectively. At the time of the data cut-off (June 28, 2017) the numbers of patients who were receiving the study treatments were 634 and 176 in the enzalutamide and placebo groups, respectively.

To be eligible for enrolment in PROSPER, patients had to be at least 18 years of age with histologically or cytologically confirmed adenocarcinoma of the prostate that was castration-resistant, defined as three prostate-specific antigen (PSA) rises at least one week apart with the last PSA more than 2 ng/mL; they also had to have a PSA doubling time less than or equal to 10 months during continuous ADT. Patients could have no prior or present evidence of metastatic disease as assessed by computed tomography or magnetic resonance imaging for soft tissue disease and whole-body radionuclide bone scan for bone disease. They were required to have a testosterone level of less than 50 ng/dL and an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. Patients using bone-targeting drugs were required to have been receiving a stable dose for at least four weeks prior to randomization.

Patient populations: Median age 74 years; median PSA doubling time at baseline 3.8 months

Overall, the baseline characteristics were well balanced between the enzalutamide and placebo groups. The median age in the intention-to-treat population was 74 years and 73 years in the enzalutamide and placebo groups, respectively. The median PSA doubling time at baseline was 3.8 months in the enzalutamide group and 3.6 months in the placebo group. The proportion of patients with a PSA doubling time of less than six months was 77% in both treatment groups. Bone-targeting agents were being used by 11% of patients in the enzalutamide group and 10% of those in the placebo group. The prior treatments were well balanced between the enzalutamide and placebo groups. The proportion of patients with prior radiotherapy was 46.5% in the enzalutamide group and 48.3% in the placebo group. History of prostate cancer surgery was reported for 52.8% and 56.2% in the enzalutamide and placebo groups, respectively. Prostatectomy was the common surgical procedure in both groups (25.1% in the enzalutamide and 29.7% in the placebo group).

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

The primary outcome of the study was metastasis-free survival (MFS) assessed by blinded independent central review; MFS was defined as the time from randomization to the time of radiographic progression, or death within 112 days of treatment discontinuation without evidence of radiographic progression (whichever occurred first). There were three key secondary end points: time to PSA progression, overall survival (OS), and time to first use of new antineoplastic therapy. Additional exploratory secondary end points included time to pain progression, chemotherapy-free survival, chemotherapy-free disease-specific survival, PSA response rates (reductions of 50%, 90% or to an undetectable level), and quality-of-life (QoL) outcomes.

The trial met its primary outcome and demonstrated a statistically significant improvement in MFS in the enzalutamide plus ADT group after a median follow-up time of 18.5 months; median MFS was 36.6 months in the enzalutamide plus ADT group and 14.7 months in the placebo plus ADT group (hazard ratio [HR] 0.292; 95% confidence interval [CI], 0.241 to 0.352; $P < 0.0001$). Results of the sensitivity analyses and subgroup analyses were similar to those reported for the primary analysis. Subgroup analyses were conducted for MFS based on the following characteristics: PSA doubling time (< 6 months versus ≥ 6 months), baseline use of a bone-targeting drug (yes versus no), baseline age (≤ or > the median age of 74 years), baseline ECOG Performance Status (0 or 1), geographic region (North America, Europe, or the rest of the world), total Gleason Score at diagnosis (≤ 7 or ≥ 8), and baseline PSA value (≤ or > the median value of 10.73 ug/L).

Overall survival was a pre-specified key secondary end point of the PROSPER study. The results of the first and secondary interim analyses have not shown a statistically significant difference between enzalutamide and placebo (HR 0.795; 95% CI, 0.580 to 1.089; and HR 0.832; 95% CI, 0.654 to 1.059, respectively). In the first interim analysis, 103 patients (11%) in the enzalutamide group had died compared with 62 (13.2%) of those in the placebo group. At the second interim analysis, 184 patients

(19.7%) and 104 patients (22.2%) had died in the enzalutamide and placebo groups, respectively. Overall survival data were immature at the first and second interim analyses and the median time to death had not been reached in either analysis.

Patient-reported outcomes: No difference between treatment groups

QoL was an exploratory outcome in the PROSPER trial. Health-related QoL was assessed using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) (for physical well-being, social/family well-being, emotional well-being, pain, and prostate cancer–specific symptoms), the EuroQol 5-Dimensions questionnaire (EQ-5D) (for health status, mobility, self-care, usual activity, pain or discomfort, and anxiety and depression), and the Quality of Life Questionnaire–Prostate 25 Module (QLQ-PR25).

The EQ-5D and the QLQ-PR25 outcomes were only reported descriptively, and no formal statistical testing was conducted. Baseline FACT-P scores were reported to be comparable between the study groups, although no formal statistical testing was conducted to test potential differences between the study groups at baseline. The FACT-P questionnaire was assessed at baseline and every 16 weeks during the study and after treatment discontinuation (for patients who attended long-term study visits) until about 41 months. Completion rates were high for patients remaining on study (> 85% for all visits). Unadjusted completion rates declined more in the placebo group due to attrition and continuous recruitment of patients up to the database lock (at week 97, 20% and 39% of patients in the placebo and enzalutamide groups, respectively, reported QoL data). Time to degradation in FACT-P global score was an exploratory secondary end point of the PROSPER study and was defined as the time from randomization to the first assessment with a decrease from baseline of at least 10 points. The proportions of patients who met the criteria for FACT-P degradation were similar in the enzalutamide group (54%) and the placebo group (51%). There was no statistically significant difference between the groups for time to FACT-P degradation (HR 0.92; 95% CI, 0.79 to 1.08; $P = 0.3128$). No statistically significant differences were reported between the enzalutamide and placebo groups in change from baseline in FACT-P scores during the treatment and follow-up phases.

Safety: Manageable toxicity profile, similar between groups

The incidence and severity of adverse reactions with enzalutamide plus ADT were broadly similar to those in the ADT plus placebo group. Treatment-emergent adverse events (TEAEs) (any grade) were reported in 86.9% of patients in the enzalutamide group and in 77.4% of patients in the placebo group. Fatigue was the most commonly reported event in both groups, occurring at a greater frequency in the enzalutamide group (32.47% versus 13.55%). Other common TEAEs included hot flushes (13.01% with enzalutamide versus 7.74% with placebo), hypertension (11.83% with enzalutamide versus 5.16% with placebo), nausea (11.18% with enzalutamide versus 8.60% with placebo), and falls (11.4% with enzalutamide versus 4.1% with placebo). The proportion of patients with grade three or grade 4 TEAEs was 31.4% in the enzalutamide group and 23.4% in the placebo group. Mortality due to AEs was reported in 3.4% of patients in the enzalutamide group and in 0.6% of those in the placebo group; serious TEAEs occurred in 24.3% and 18.3% of patients in the enzalutamide and placebo groups, respectively. Hematuria was the most commonly reported serious adverse event (SAE) in both the enzalutamide and placebo groups (2.2% versus 2.4%). The proportion of patients who withdrew from the treatment as a result of adverse events was 10.3% in the enzalutamide group and 7.5% in the placebo group. Fatigue was the most commonly cited reason for withdrawing from the enzalutamide group (2.2%), with no placebo-treated patients withdrawing as a result of fatigue (0%).

Fractures were more commonly reported in the enzalutamide group (11.2%) compared with the placebo group (5.6%). The most common types of fracture in the enzalutamide group of the PROSPER study were rib fractures (4.2%), spinal compression fractures (1.8%), femur fractures (0.5%), and upper limb fractures (0.5%). The proportions of patients who experienced a fracture that was classified as an SAE or grade 3 or greater event or that led to discontinuation were 2.8%, 2.4%, and 0.2%, respectively. According to the European Medicines Agency's (EMA's) public assessment report the study protocol did not include classification of fractures as being nonpathological or pathological; therefore the distinction between these events could not be reliably elucidated from the trial data.

A very small number of patients (0.3%) suffered a seizure during treatment with enzalutamide. No patient suffered a seizure in the placebo group. All three events in the enzalutamide group were considered serious and drug-related. One patient discontinued treatment as a result of a seizure.

Limitations: No direct comparative data to recently approved apalutamide

The pCODR Methods Team summarized and critically appraised a submitter-provided network meta-analysis (NMA) and a published indirect treatment comparison (ITC). The submitter-provided NMA provided comparative efficacy between enzalutamide plus ADT and apalutamide plus ADT. The published ITC was conducted to compare the relative efficacy and toxicity of enzalutamide plus ADT and apalutamide plus ADT. The pCODR Methods Team identified several important limitations with the submitter-provided NMA and the published Bucher indirect comparison of enzalutamide and apalutamide. Most notably, the analyses for the efficacy end points were conducted using methods that assumed proportional hazards for the included studies. This assumption was not valid for MFS, time to cytotoxic chemotherapy, and time to PSA progression. Alternative modelling approaches that do not rely on proportional hazards were not explored or reported. The potential risk of bias with this limitation is unclear, and the results should be interpreted with caution. The data for OS were immature for both the PROSPER and SPARTAN trials, and there were differences in the post-progression therapies that were used in the two studies. Given these limitations, conclusions cannot be drawn from the indirect comparisons regarding the comparative efficacy of enzalutamide and apalutamide for OS. pERC agreed with the Methods Team that, given the above limitations, the comparative effectiveness of enzalutamide plus ADT versus apalutamide plus ADT remained uncertain.

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

Prostate cancer is the most common cancer diagnosed in Canadian men (excluding non-melanoma skin cancers). The number of new prostate cancer cases in 2017 has been estimated at approximately 22,000 men, with a 34% annual progression to metastatic CRPC and an overall mortality rate of 16%. Therefore, a significant patient group is at high risk for progression to metastatic disease. CRPC is defined as disease progression in the setting of castrate testosterone levels. Biochemical progression as manifested by a rising PSA alone is often the initial sign of disease progression before the development of metastatic disease in bone or visceral organs. No accepted standard treatment options have been implemented for patients with nmCRPC in Canada. In 2018, pERC conditionally recommended apalutamide plus ADT for high-risk nmCRPC. Apalutamide, however, is not yet reimbursed in Canada. In the absence of treatment options, observation or ADT is often recommended for patients with biochemical-only progression and no evidence of metastases. There is an urgent need for new treatment options that delay the development of metastases and disease symptoms.

Registered clinician input: Enzalutamide may affect which treatment patients receive if they progress to metastatic disease; benefits expected to outweigh potential toxicity risks

Clinician input was provided as one joint submission from two clinicians and one individual clinician submission. The clinicians providing input noted that treatment options and available clinical evidence were limited for patients with nmCRPC. Available treatment options include watchful waiting, chemotherapy, bicalutamide, and apalutamide. Use of enzalutamide was suggested to be restricted to patients at high risk of developing metastases. It was suggested that the use of enzalutamide, as well as the use of apalutamide, in the non-metastatic setting takes away the use of second-generation hormonal therapy as first-line therapy for the metastatic setting. It was also noted that there will be high numbers of both incident and prevalent cases due to prostate cancer being a very common form of cancer and the relatively long median duration of treatment observed in the PROSPER and SPARTAN trials. Enzalutamide may cause potentially serious side effects in patients, including severe fatigue and drug-drug interactions; however, the benefits were expected to outweigh the potential toxicity risks to patients. Clinician input suggested that enzalutamide would be an appropriate option for patients and clinicians to consider, however, it may be a “nice to have” therapy and not a necessity.

PATIENT-BASED VALUES

Values of patients with prostate cancer: Maintaining quality of life; access to a new treatment option; delaying the need for chemotherapy or palliative care; delaying onset of symptoms

One patient input was provided to pCODR through a joint submission from two patient advocacy groups. Patients expressed a number of negative sentiments about their experiences with prostate cancer. Fatigue and sexual dysfunction were the most commonly reported symptoms related to prostate cancer that have an impact on patients’ day-to-day living and QoL (86% and 68%, respectively). Other reported symptoms resulting from prostate cancer included mental stress related to living with uncertainty, pain, and restlessness at night. With regard to patients’ experience with current therapy for prostate cancer,

fatigue was listed as the most commonly experienced side effect related to the therapies that were currently being used by the respondents. However, based on the input, it was not clear whether the fatigue mentioned was due to prostate cancer, treatment, or both. Patients reported a willingness to tolerate side effects (such as fatigue, loss of appetite, rash, and dizziness) if the treatment would delay metastases. Half of respondents indicated that chemotherapy was not effective at controlling aspects of prostate cancer.

In terms of expectations for alternative treatment options, focus was placed on maintaining QoL, having access to a new treatment option, delaying the need for chemotherapy or palliative care, and delaying onset of symptoms.

Patient values on treatment: Few patients (n = 3) with direct experience using enzalutamide
Two out of three respondents who had experience with enzalutamide indicated that fatigue was a side effect. However, these respondents expressed uncertainty about whether the fatigue experienced was due to treatment with enzalutamide or concurrent ADT.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analyses
The pCODR Economic Guidance Panel (EGP) assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years [QALYs] gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) of enzalutamide plus ADT compared with ADT monotherapy or apalutamide for the treatment of men with nmCRPC.

Basis of the economic model: Clinical and economic inputs
The key clinical outcomes considered in the cost-utility analysis were MFS, OS, and utilities.

Costs considered in the analysis included those related to drug treatment costs, disease management, subsequent treatment costs, end of life, and AEs.

Drug costs: Treatment cost of enzalutamide and comparators
Enzalutamide costs $29.19 per 40 mg capsule. At the recommended dose of 160 mg (four 40 mg capsules) administered orally once daily, enzalutamide costs $116.78 per day and $3,269.88 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.

Bicalutamide costs $1.27 per 50 mg tablet. At the recommended dose of 50 mg once daily, bicalutamide costs $1.27 per day and $35.56 per 28-day cycle.

ADT therapy:

Leuprolide costs $39.60 per mg. At the recommended dose of one 22.5 mg subcutaneous depot injection administered once every three months, leuprolide costs $10.60 per day and $297.00 per 28-day cycle.

Clinical effectiveness estimates: Not cost-effective at the submitted price
pERC deliberated upon the cost-effectiveness of enzalutamide plus ADT in men with nmCRPC and concluded that enzalutamide is not cost-effective when compared with ADT monotherapy at the submitted price. pERC noted that the submitter's base-case incremental cost-effectiveness ratio (ICER) was lower than the EGP's reanalyzed ICER. This was primarily due to reducing the long-term incremental MFS and OS benefits of enzalutamide plus ADT versus ADT monotherapy. Specifically, the EGP made the following two changes:

- The gamma parameter for the projection of MFS for placebo was adjusted to create a less favourable divergence in MFS between enzalutamide and placebo.
- The parameters of the Weibull function for ADT monotherapy were adjusted to create a less favourable divergence in long-term OS between enzalutamide and placebo.

The EGP noted that the factor that most influences the incremental effectiveness of enzalutamide plus ADT compared with ADT monotherapy is the projection of benefit in the metastatic stage. The difference in cost is driven by the upfront cost of the drug and the cost of the drug in the metastatic stage. Overall, pERC agreed with the EGP's reanalyses and the limitations identified in the submitted economic model. pERC concluded that enzalutamide with ADT was not cost-effective compared with ADT monotherapy at the submitted price.

In the absence of a direct comparison of enzalutamide plus ADT with apalutamide plus ADT, the submitter provided a network meta-analysis (NMA). The pCODR Methods Lead noted that while the methods used to analyze the efficacy end points assumed proportional hazards, this assumption was not valid for MFS, time to cytotoxic chemotherapy, and time to PSA progression. Given the potential risk of bias with this limitation, the immaturity of the OS data, and the differences in the post-progression therapies that were used in the SPARTAN and PROSPER trials, the cost-effectiveness of enzalutamide plus ADT compared with apalutamide plus ADT is uncertain.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact underestimated and would be substantial

To assess the feasibility of implementing a reimbursement recommendation for enzalutamide plus ADT for patients with nmCRPC, the submitter provided a Canada-wide budget impact analysis spanning three years. The EGP noted that the factors that influence the budget impact include the assumed market share (i.e., enzalutamide versus apalutamide), the size of the eligible patient population (i.e., prevalence of CRPC), the drug cost, and the duration of enzalutamide therapy. Overall, the Committee concluded that the submitted Canada-wide budget impact was likely underestimated and would be substantial.

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 Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
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. Christian Kollmannsberger and Dr. Henry Conter, who were excluded from voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

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 enzalutamide for the treatment of non-metastatic castration-resistant prostate cancer, through their declarations, two members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, two of these members were 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*. There was no non-disclosable information in this Recommendation document.

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 is seeking clarity on whether or not the following patients would be eligible for treatment with enzalutamide: ○ patients with PSA doubling times > 10 months ○ patients with ECOG Performance Status ≥ 2.	• PROSPER required study participants to be at high risk for development of metastases, defined as PSADT ≤ 10 months, during continuous ADT. pERC agreed with the CGP that currently there is insufficient evidence to make an informed recommendation on the use of enzalutamide plus ADT in patients with PSADT > 10 months. • PROSPER required study participants to have an ECOG performance status of 0 or 1. The benefit for patients with ECOG 2 cannot be formally concluded from the study. However, pERC agreed with the CGP that it would be reasonable to expand enzalutamide to patients with a good performance status, based on clinical experience and the manageable side-effect profile.
• PAG is seeking guidance on whether there is an appropriate time period between discontinuation of bicalutamide and initiation of enzalutamide for patients who receive ADT (e.g., gonadotropin-releasing hormone analogue agonist plus antiandrogen such as bicalutamide).	• pERC agreed with the CGP that patients who are progressing on ADT and first-generation antiandrogen, such as bicalutamide, should be evaluated for antiandrogen withdrawal syndrome by monitoring the PSA for 6 weeks before starting enzalutamide.
• PAG is seeking guidance on the appropriate criteria for discontinuation of enzalutamide (i.e., definition of progression).	• pERC agreed with the CGP that treatment should be discontinued upon radiographic disease progression.
• PAG is seeking guidance on what clinical scenario(s) would make apalutamide or enzalutamide the preferred treatment for patients with non-metastatic castration-resistant prostate cancer: ○ Are there specific clinical situations where apalutamide or enzalutamide would be the preferred treatment (e.g., apalutamide has less toxic CNS effects and may be safer in patients with a history of seizures)?	• pERC agreed that there is insufficient evidence at this point to recommend either enzalutamide or apalutamide over the other. pERC noted that the choice between enzalutamide and apalutamide will likely depend upon the relative overall cost, treatment availability, patient values and preferences, and clinical factors such as tolerability to adverse events. • pERC agreed with the CGP that given the small numbers of patients with CNS toxicity (e.g., seizure, mental impairment disorder) across both trials (PROSPER and SPARTAN), it is not possible to draw firm conclusions with respect to preferred treatment from these results.
• PAG is also seeking guidance on treatment options (e.g., abiraterone or chemotherapy) in the metastatic setting following enzalutamide in the non-metastatic setting.	• pERC agreed with the CGP and with the registered clinicians providing input for this submission that adding enzalutamide to the available drug options may affect which treatment a patient will receive if they progress to metastatic disease. However, pERC noted that there is insufficient evidence to inform this clinical situation; as a result, pERC was unable to make an informed recommendation on the optimal sequencing of treatments for metastatic CRPC after treatment with enzalutamide in the non-metastatic setting. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of enzalutamide plus ADT and

	noted that a national approach to developing evidence-based clinical practice guidelines would be of value.

ADT = androgen deprivation therapy; CGP = pCODR Clinical Guidance Panel; CNS = central nervous system; CRPC = castration-resistant prostate cancer; PAG = pCODR Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time.