CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Enzalutamide (Xtandi) for non-Metastatic Castration-Resistant Prostate Cancer

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LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
APA	Apalutamide
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BIC	Bicalutamide
BICR	Blinded independent central review
BTA	Bone-targeting agents
CGP	Clinical Guidance Panel
CI	Confidence interval
CrI	Credible interval
CT	Computed tomography
CNS	Central nervous system
CRPC	Castration Resistant Prostate Cancer
ECOG	Eastern Cooperative Oncology Group
ENZ	Enzalutamide
EQ-5D	European Quality of Life-5 Dimensions health questionnaire
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels health questionnaire
ESMO	European Society for Medical Oncology
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FDA	Food and Drug Administration of the United States
FE	Fixed-effects
GnRH	Gonadotropin-releasing hormone
HR	Hazard ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes
ITT	Intent-to-treat population
IV	Intravenous
IXRS	Interactive Voice/web response system
mCRPC	Metastatic castration-resistant prostate cancer
MFS	Metastasis-free survival
MRI	Magnetic resonance imaging
n	Number of patients with event
N	Number of patients included in the analysis
N/A	Not applicable
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
nmCRPC	Non-metastatic castration-resistant prostate cancer
NR	Not reported
NYR	Not yet reached
OR	Odds ratio
OS	Overall survival
PBAC	Pharmaceutical Benefits Advisory Committee
PAG	Provincial Advisory Group
pCODR	CADTH pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
PFS	Progression-free survival
PLA	Placebo
PO	Orally
PSA	Prostate-specific antigen
PSA DT	Prostate-specific antigen doubling time
QLQ-PR25	Quality of Life Questionnaire-Prostate 25 Module

RCT	Randomized controlled trial
RE	Random-effects
RECIST	Response Evaluation Criteria in Solid Tumors
QLQ-PR25	Quality of Life Questionnaire-Prostate 25 module
HRQoL	Health-related quality of life
SAE	Serious adverse event
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
TURP	Transurethral resection of the prostate
ULN	Upper limit of normal
UK	United Kingdom
US	United States of America
WDAE	Withdrawal due to adverse event

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1 GUIDANCE IN BRIEF

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

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

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

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of enzalutamide (Xtandi) in combination with androgen deprivation therapy (ADT) compared with ADT alone in men with high-risk non-metastatic castrate resistant prostate cancer (nmCRPC).

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

Note that the Health Canada indication differs slightly from the pCODR reimbursement criteria, in that the Health Canada PM does not specify 'high-risk' nmCRPC in its indication. According to the evidence submitted to pCODR, high-risk is defined as prostate-specific antigen doubling time PSA DT≤ 10 months, during continuous ADT.

The recommended dose of enzalutamide (Xtandi) is 160 mg (four 40 mg tablets) administered orally once daily (with or without food). If a patient experiences ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted.

The PM states that enzalutamide (Xtandi) is for use in patients who are maintaining treatment with a gonadotropin-releasing hormone (GnRH) analogue or who have had previously undergone surgical castration. Patients started on enzalutamide who are receiving a GnRH analogue should continue to receive a GnRH analogue.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized controlled trial (RCT) met the selection criteria of this review. The PROSPER study was a phase 3, multinational, double-blind, placebo-controlled, RCT conducted to assess the efficacy and safety of enzalutamide in combination with ADT for the treatment of patients with nmCRPC (N = 1401). Eligible patients were randomized 2:1 to enzalutamide (160 mg per day) or matching placebo. Randomization was conducted using an interactive voice/web response service (IXRS) and was stratified by the following factors: prostate-specific antigen (PSA) doubling-time (<6 months versus ≥6 months) and baseline use of a bone-targeting agent (yes versus no).

To be eligible for enrollment 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 PSA rises at least one week apart with the last PSA more than 2 ng/mL; 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 (CT) or magnetic resonance imaging (MRI) 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 0 or 1. Key exclusion criteria included: any prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate for the treatment of prostate cancer; clinically significant cardiovascular disease; or a history of seizure or any condition that may have predisposed the patient to seizure. Patients were enrolled at 254 sites in 32 countries across North America, South America, Europe, Asia, and Australia and 7.1% of the participants were enrolled at 15 Canadian sites.[1]

Metastasis-free survival (MFS) was the primary endpoint of the PROSPER study and 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).[2] There were three key secondary endpoints: time to PSA progression; overall survival; and time to first use of new antineoplastic therapy. Additional exploratory secondary endpoints 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); Functional Assessment of Cancer Therapy-Prostate (FACT-P) global score; European Quality of Life-5 Dimensions-5 Levels health questionnaire (EQ-5D-5L); and Quality of Life Questionnaire-Prostate 25 Module (QLQ-PR25).[3]

Efficacy

The key efficacy outcomes of the PROSPER trial are presented in Table 1.

- The proportion of patients who experienced metastases or died during the study was lower in the enzalutamide group compared with the placebo group (23.5% versus 48.7%). Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for metastases or death during the study compared with placebo (hazard ratio [HR] = 0.292 [95% confidence interval [CI], 0.241 to 0.352]; p < 0.0001). The median time to event was 36.6 months (95% CI, 33.1 to not reached) in the enzalutamide group and 14.7 months (95% CI, 14.2 to 15.0) in the placebo group.[4] Results of the sensitivity analyses and subgroup analyses were similar to those reported for the primary analysis.[4]
- There was no statistically significant difference between enzalutamide and placebo for overall survival in the first and secondary interim analyses (HR = 0.795 [95% CI, 0.580 to 1.089] and 0.832 [95% CI, 0.654 to 1.059], respectively). The median time to death had not been reached in either analysis.[4,5]

- Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for PSA progression during the study (HR = 0.066 [95% CI, 0.054 to 0.081]; p < 0.0001).[2] The median time to PSA progression was 37.2 months (95% CI, 33.1 and not reached) in the enzalutamide group and 3.9 months (95% CI, 3.8 to 4.0) in the placebo group.[2]
- Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for initiating a new antineoplastic therapy during the study (HR = 0.208 [95% CI, 0.168 to 0.258)]; p < 0.0001).[2] The median time to first use of a new antineoplastic therapy was 39.6 months in the enzalutamide group and 17.7 months in the placebo group.[2]
- Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for initiating use of cytotoxic chemotherapy during the study (HR = 0.38 [95% CI, 0.28 to 0.51]; p < 0.0001).[2] The median time to initiating cytotoxic chemotherapy was 39.7 months (95% CI, 38.9 to 41.3) in the placebo group and was not reached in the enzalutamide group.[2]
- There was no statistically significant difference between the enzalutamide and placebo groups for time to pain progression (0.959 [95% CI, 0.801 to 1.149]; p = 0.6534).[2] The median time to pain progression was 18.5 months (95% CI, 17.0 to 22.1) in the enzalutamide group and 18.4 months (95% CI, 14.8 to 22.1) in the placebo group.[2] The proportions of patients with pain progression were 42.8% and 37.4% with enzalutamide and placebo, respectively.
- Treatment with enzalutamide was associated with statistically significant reductions in the hazard for initiating chemotherapy or dying (HR: 0.50 [95% CI, 0.40 to 0.64]; p < 0.0001) and initiating chemotherapy or dying due to prostate cancer (HR: 0.398 [95% CI, 0.307 0.515]; p < 0.0001).[1]
- A statistically significantly greater proportion of enzalutamide-treated patients had reductions in PSA from baseline of at least 50% (Difference 73.96% [95% CI, 70.91 to 77.02]), 90% (55.52% [95% CI, 52.28 to 58.76]), or to an undetectable level (RD: 9.65% [95% CI, 7.75 to 11.54]).[2] The proportion of patients with missing PSA baseline values (0% with enzalutamide and 0.2% with placebo) and missing post-baseline values (4.9% with enzalutamide and 6.0% with placebo) was similar between the groups.[1]

Quality of Life

Quality of life endpoints in PROSPER were exploratory secondary endpoints and included FACT-P, EQ-5D-5L, and QLQ PR25 questionnaires. There was no statistically significant difference between enzalutamide and placebo for median time to FACT-P degradation (HR: 0.92 [95% CI, 0.79 to 1.08]; p = 0.3128).[3,4] For the EQ-5D-5L and QLQ PR25 questionnaires, the proportions of patients providing a response in each domain were descriptively summarized. However, mean changes over time or difference between treatment groups were not statistically analyzed for the EQ-5D-5L and QLQ-PR25 instruments.

Table 1: Highlights of Key Efficacy Outcomes from the PROSPER trial

Efficacy outcomes	ITT population	
	Enzalutamide (N = 933)	Placebo (N = 468)
Primary Outcome		
MFS		
Number of events (%)	219 (23.5)	228 (48.7)
Median time to event, months (95% CI)	36.6 (33.1, NYR)	14.7 (14.2, 15.0)
HR (95% CI)	0.29 (0.24, 0.35)	
p-value	< 0.0001	
Key Secondary Outcomes		
Time to PSA progression		
Number of events (%)	208 (22.3)	324 (69.2)
Median time to event, months (95% CI)	37.2 (33.1, NYR)	3.9 (3.8, 4.0)

Efficacy outcomes	ITT population	
	Enzalutamide (N = 933)	Placebo (N = 468)
HR (95% CI)	0.07 (0.05, 0.08)	
p-value	< 0.0001	
Time to first use of new antineoplastic therapy		
Number of events (%)	142 (15.2)	226 (48.3)
Median time to event, months (95% CI)	39.6 (37.7, NR)	17.7 (16.2, 19.7)
HR (95% CI)	0.21 (0.17, 0.26)	
p-value	< 0.0001	
Overall Survival (first interim)		
Number of events (%)	103 (11.0%)	62 (13.2%)
Median, months (95% CI)	NYR (NYR, NYR)	NYR (NYR, NYR)
HR (95% CI)	0.795 (0.580, 1.089)	
p-value	0.1519	
Overall Survival (second interim)		
Number of events (%)	184 (19.7)	104 (22.2)
Median, months (95% CI)	NYR (49.9, NYR)	NYR (49.4, NYR)
HR (95% CI)	0.832 (0.654, 1.059)	
p-value	0.134	
Secondary Outcomes		
Time to first use of cytotoxic chemotherapy		
Number of events (%)	85 (9.1)	96 (20.5)
Median, months (95% CI)	NR (38.1, NR)	39.7 (38.9, 41.3)
HR (95% CI)	0.38 (0.28, 0.51)	
p-value	< 0.0001	
Chemotherapy-free survival		
Number of events (%)	157 (16.8)	132 (28.2)
Median time to event, months (95% CI)	38.1 (37.7, NR)	34.0 (30.3, 39.7)
HR (95% CI)	0.50 (0.40, 0.64)	
p-value	< 0.0001	
Chemotherapy-free disease-specific survival		
Number of events (%)	112 (12.0)	119 (25.4)
Median time to event, months (95% CI)	39.6 (37.7 to NYR)	38.9 (30.9 to 41.3)
HR (95% CI)	0.398 (0.307, to 0.515)	
p-value	<0.0001	
Time to pain progression		
Number of events (%)	399 (42.8)	175 (37.4)
Median time to event, months (95% CI)	18.5 (17.0, 22.1)	18.4 (14.8, 22.1)
HR (95% CI)	0.959 (0.801, 1.149)	
p-value	0.6534	
FACT-P Degradation		
Number of events (%)	506 (54.2)	239 (51.1)
Median to time event (95% CI)	11.1 (11.0 to 14.7)	11.1 (11.0 to 12.5)
HR (95% CI)	0.922 (0.787 to 1.080)	
p-value	0.3128	

AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life; ITT = intent-to treat; MFS = metastasis-free survival; NE = not estimable; NR = not reported, NYR = not yet reached; SD = standard deviation, WDAE = withdrawal due to adverse event

HR < 1 favours enzalutamide group

- **Sources:** Hussain et al., 2018;[4] clinicaltrials.gov;[2] Clinical Study Report Synopsis[3]; Clinical Summary[5]

Harms

Table 2 provides a summary of key safety outcomes.

- A greater proportion of enzalutamide-treated patients experienced at least one adverse event compared with those who received placebo (84.95% versus 75.91%). Fatigue was the most commonly reported event in both groups, occurring at a greater frequency in the enzalutamide group (32.47% versus 13.55%).[2]

- The proportion of patients who experienced at least one SAE was 24.3% in the enzalutamide group and 18.3% in the placebo group. Haematuria was the most commonly reported SAE in both the enzalutamide and placebo groups (2.2% versus 2.4%).[1,2]
- The proportion of patients who withdrew from the study treatment as a result of adverse events was 10.3% in the enzalutamide group and 7.5% in the placebo group.[1] Fatigue was the most commonly cited reason in the enzalutamide group (2.2%); with no placebo-treated patients withdrawing as a result of fatigue (0%).[1]
- Seizures were specified as an adverse event of special interest by the CGP. Seizures were reported in three enzalutamide-treated patients (0.3%) and no placebo-treated patients.[1] All three events in the enzalutamide group were considered serious and drug-related. One patient discontinued treatment as a result of a seizure.

Table 2: Highlights of Key Safety Outcomes from the PROSPER trial

Harms Outcome n (%)	Safety Population	
	Enzalutamide (N = 930)	Placebo (N = 465)
Any TEAEs	808 (86.9)	360 (77.4)
Drug-related TEAEs	581 (62.5)	211 (45.4)
Grade 3-4 TEAEs	292 (31.4)	109 (23.4)
SAEs	226 (24.3)	85 (18.3)
TEAE leading to study drug discontinuation	96 (10.3)	35 (7.5)
TEAE leading to study drug dose reduction	94 (10.1)	13 (2.8)
TEAE leading to study drug interruption	143 (15.4)	40 (8.6)
Death due to AEs	32 (3.4)	3 (0.6)

TEAE = treatment-emergent adverse event
Sources: Clinical Study Report Synopsis[3]

Limitations

The key limitations of the PROSPER trial are as follows:

- Overall survival was a pre-specified key secondary endpoint of the PROSPER study. The OS data are immature with only the first and second interim analyses having been completed at the time this review.[2,4,5]
- Fatigue is a known adverse event associated with enzalutamide treatment and a greater proportion of those who received the active treatment reported fatigue compared with placebo (32.5% versus 13.6%).[2] Hence, it is possible that some patients/investigators may have been able to make inferences regarding the allocated treatment. The CGP indicated that the adverse event profile of enzalutamide could compromise blinding for some patients and study personnel; however, the difference was not considered to have substantially affected the internal validity of the PROSPER study.
- Statistical tests for all endpoints, with the exception of the primary and key secondary endpoints, were conducted without adjustment multiple comparisons;[4] therefore, the findings should be considered hypothesis generating because of the risk of type I error.
- The methodology for several of the analyses that were conducted for the FACT-P and BPI endpoints were not documented in the statistical analysis plan for PROSPER and were only reported in conference abstracts. It is unclear if these analyses were pre-planned or conducted in a post-hoc manner by the submitter.

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

One patient input was provided to pCODR through a joint patient advocacy group submission from the Canadian Cancer Survivor Network (CCSN) and Prostate Cancer Canada (PCC) for enzalutamide for non-metastatic castrate resistant prostate cancer (nmCRPC).

From a patient's perspective, 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 quality of life (86% and 68%, respectively). Other reported symptoms resulting from prostate cancer included mental stress related to living with uncertainty, pain, and restlessness at night.

At the time of completing the survey, respondents reported receiving the following treatments: second-line hormone therapy, drugs accessed through participation in a clinical trial, chemotherapy, and palliative therapies for pain and/or bone metastases. Fatigue was listed as the most commonly experienced side effect related to the therapies that were being used by the respondents. It is unclear, based on the input, whether the fatigue mentioned is due to prostate cancer, treatments, or both. Fatigue was also experienced by two of the three respondents who reported experience with enzalutamide. These respondents expressed uncertainty about whether the fatigue experienced was due to treatment with enzalutamide or concurrent ADT.

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

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Appropriate treatments for metastatic, castration resistant disease after enzalutamide.

Economic factors:

- Add-on therapy to androgen deprivation therapy.

Registered Clinician Input

Two clinician inputs were provided for enzalutamide for patients with non-metastatic castrate resistant prostate cancer (nm-CRPC). Input was provided as one joint submission from two clinicians and one individual clinician submission. A summary of the input is

provided below.

While treatment options and available clinical evidence are both limited for patients with nm-CRPC, 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. Registered clinicians noted that there will be both high 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 appreciated option for patients and clinicians to consider, however, it may be a 'nice to have' therapy and not a necessity.

Summary of Supplemental Questions

Given the absence of head-to-head studies that have compared enzalutamide against other treatments approved for use in the treatment of nmCRPC, the pCODR Methods Team reviewed published and unpublished indirect comparisons that investigated the comparative efficacy and safety of these treatments. Three indirect comparisons were identified:

- an unpublished systematic review and network meta-analysis (NMA) included in the submitter's submission[6]
- a published indirect comparison identified by the pCODR Methods Team (Wallis et al, 2018)[7]
- a matching-adjusted indirect comparison (MAIC) published only as a conference abstract was identified by the pCODR Methods Team (Chowdhury et al, 2018)[8]

All three of the indirect comparisons were focussed on the PROSPER and SPARTAN studies (placebo-controlled RCTs involving enzalutamide and apalutamide in combination with ADT, respectively).[6-8] The submitter-provided NMA only included efficacy endpoints and reported no statistically significant difference between two treatments for the following endpoints (enzalutamide versus apalutamide): MFS (HR: 1.04 [95% CrI, 0.76 to 1.43]), overall survival (HR: 1.14 [95% CrI, 0.68 to 1.89]), time to cytotoxic chemotherapy (HR: 0.86 [95% CrI, 0.52 to 1.42]), and time to PSA progression (HR: 1.10 [95% CrI, 0.81 to 1.50]).[6] The Bucher indirect comparison reported no differences between the treatments (enzalutamide versus apalutamide) for: MFS (HR: 1.04 [95% CI, 0.78 to 1.37]), time to prostate-specific antigen progression (HR: 1.17 [95% CI, 0.84 to 1.63]), and overall survival (HR: 1.14 [95% CI, 0.69 to1.90]).[7] The MAIC published as a conference abstract also demonstrated no significant difference (apalutamide versus enzalutamide) for MFS (0.77 [95% CrI, 0.46 to 1.30]) and overall survival (0.92 [95% CrI, 0.69 to 1.24]).[8]

The submitter-provided NMA and the MAIC did not evaluate any safety endpoints; however, the published Bucher indirect comparison reported no difference between enzalutamide and apalutamide for total adverse events (odds ratio [OR]: 0.96 [95% CI, 0.53 to1.73]), grade 3–4 adverse events (OR: 0.83 [95% CI, 0.60 to 1.15]), withdrawals due to adverse events (OR: 1.03 [95% CI, 0.55 to 1.93]), or adverse events leading to death (OR: 1.09 [95% CI, 0.10 to 11.81]).[7] The pCODR Methods Team noted that adverse events and serious adverse events were more commonly reported in the placebo group of the SPARTAN trial

compared with the PROSPER study; raising questions about the comparability of the safety data from those two trials. Indirect comparisons on aggregate measure of adverse events can provide useful information regarding comparative safety, but do not provide insight into the unique adverse event profiles of enzalutamide and apalutamide (e.g., risk of seizures). There were no indirect comparisons that investigated potential differences between enzalutamide and apalutamide in the risk of seizures, falls, or fractures; adverse events of special interest for this pCODR review.

The pCODR Methods Team was unable to critically appraise the MAIC due to the absence of a publication and identified several important limitations with the submitted-provided NMA and the Bucher indirect comparison of enzalutamide and apalutamide. Most notably, the analyses for the efficacy endpoints 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 and/or reported. The potential risk of bias with this limitation is unclear and the results should be interpreted with caution. The data for overall survival data 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 overall survival.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 3 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 3: Assessment of generalizability of evidence for enzalutamide for nmCRPC

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Performance status	The included trial limited eligibility to patients with an ECOG performance status of 0 or 1.	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The benefit for patients with ECOG 2 cannot be formally concluded from the study, however it would be reasonable to expand enzalutamide to patients with a good performance status, based on clinical experience and the manageable side-effect profile of

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				similar drugs in the metastatic CRPC setting.
	Risk of metastasis	PROSPER required study participants to be at high risk for development of metastases, defined as PSADT≤ 10 months, during continuous ADT.	Are the results of the trial generalizable to patients with PSADT >10 months?	Interpretation of the trial results applies to patients at high risk for progression as defined in the PROSPER trial (PSADT≤ 10 months). There are no data to support use of enzalutamide in patients with PSADT > 10 months. Patients without the high risk features as defined in the PROSPER trial can have a prolonged, indolent course of disease and it is unclear how much benefit they would derive from enzalutamide.
	Definition of castration resistant prostate cancer	PROSPER required that patients have three PSA rises at least one week apart with the last PSA more than 2 ng/ml.	If different criteria are used to define castration resistance in the Canadian practice, are the results of the trial applicable in the Canadian setting?	The CGP feels that the definition of castration resistant prostate cancer used in the PROSPER trial is clinical reasonable, based on available evidence, and applies to the Canadian practice setting. The prostate cancer working group (PCWG) is the generally accepted definition and PROSPER used that definition and then selected the high risk group. Hence, the results of the PROSPER trial can be generalized to the PCWG definition.
Intervention	Prior treatments	PROSPER excluded patients who received prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide.	Are the results of the trial generalizable to patients who received prior chemotherapy?	The CGP feels that these are reasonable exclusion criteria, based on available evidence. Prior chemotherapy (except in the adjuvant/neoadjuvant setting) was not permitted in the PROSPER trial and these patients should be excluded from

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
				enzalutamide treatment. However, the CGP felt that enzalutamide would be a reasonable treatment option for patients who received chemotherapy in the adjuvant/neoadjuvant setting.
		The trial also excluded patients with a history of treatment with second generation anti-androgens.	Are the results of the trial generalizable to patients who received prior treatment with second generation anti-androgens?	History of treatment with second generation anti-androgens was not permitted in PROSPER and these patients should be excluded from enzalutamide treatment. CGP notes that there are no sufficient data to suggest the sequencing of enzalutamide with other second generation anti-androgens. Since apalutamide is in the same class of drugs as enzalutamide sequential treatment with both drugs does not seem promising.
		The majority of patients in PROSPER had received treatment with at least one first-generation anti-androgen (e.g., 55.6% had received bicalutamide).	Are the results of the trial generalizable to patients who had already started ADT plus an anti-androgen?	All of these patients had to have been on androgen deprivation therapy either with a LHRH antagonist alone or a LHRH plus an antiandrogen. If they had been on both the antiandrogen was to be stopped and PSA observed. That reflects a clinical standard. Hence it is fully generalizable.
		The majority of patients in the PROSPER trial (in both treatment arms) had received two or more prior hormonal therapies.	Are the results of the trial generalizable to patients who are undergoing secondary hormonal manipulation (e.g., changing bicalutamide to megestrol acetate, or	The results are fully generalizable to patients undergoing secondary hormonal manipulation. These secondary hormone maneuvers are part of standard therapy for hormone sensitive disease and can be tried. They are usually not very effective and

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
			antiandrogen withdrawal)?	the CGP assumes that the introduction of enzalutamide will decrease the use of these secondary maneuvers.
Comparator	**Standard of care**	In the PROSPER trial, placebo was used as a comparator. In 2018 pERC conditionally recommended apalutamide plus ADT for high-risk nmCRPC. It is not yet reimbursed in Canada. In order to assess the comparative efficacy and safety of enzalutamide and ADT to apalutamide and ADT in patients with nmCRPC, the pCODR Methods Team reviewed one submitter-provided NMA and one published ITC. Refer to section 7 for more details.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting? Are the findings of the PROSPER trial generalizable to patients who may receive apalutamide and ADT instead of enzalutamide and ADT?	There is currently no standard of care. Placebo is the appropriate comparator. Apalutamide has received a conditional final pERC recommendation in 2018. Once apalutamide plus ADT is reimbursed in Canada, it will be the most relevant comparator to enzalutamide plus ADT in this setting (i.e. same use of ADT, and similar mechanism of action between enzalutamide and apalutamide). Please refer to the CGP interpretation in section 1.2.4 for more information on the CGP's assessment of the NMA and ITC.
Outcomes	**Appropriateness of primary and Secondary Outcomes**	The PROSPER trial measured the following clinical outcomes: • Metastasis-free survival • Time to PSA progression • Time to first use of new antineoplastic therapy • Overall survival • Time to pain progression • Time to first use of cytotoxic chemotherapy • Chemotherapy-free disease-specific survival • Chemotherapy-free survival	Were the primary and secondary outcomes appropriate for the trial design?	For non-metastatic castration resistant prostate cancer, MFS is a meaningful endpoint for patients because it delays the onset of metastatic disease which is associated with more fatigue, pain, less wellbeing and potential bone complications such as fractures and need for radiation. The primary endpoint is supported by secondary outcomes in favour of enzalutamide. The trial also showed that enzalutamide plus ADT does not

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		• PSA response rates • FACT-P • EQ-5D-5L • QLQ-PR25		worsen/shorten the time to pain progression compared to ADT alone.
Setting	Trial centres	PROSPER was conducted at 254 sites in 32 countries: Argentina (5), Australia (23), Austria (2), Belgium (5), Brazil (13), Canada (15), Chile (3), China (20), Denmark (5), Finland (5), France (20), Germany (6), Greece (5), Hong Kong (3), Italy (9), Korea (7), Malaysia (3), Netherlands (4), New Zealand (4), Poland (5), Russia (4), Serbia (4), Singapore (2), Slovakia (7), Spain (10), Sweden (6), Taiwan (11), Thailand (4), Turkey (4), Ukraine (5), UK (10), and US (25).	Do the trial results apply to patients from Canadian centres? Are there any known differences in practice patterns between the countries listed and Canada?	Overall, most patients were from Canada or the US, where practice patterns are similar to Canada.
ADT = androgen deprivation therapy; **BICR** = blinded independent central review; **ECOG** = Eastern Cooperative Oncology Group; **MFS** = metastasis-free survival; **OS** = overall survival; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSADT**= prostate-specific antigen doubling time				

1.2.4 Interpretation

Burden of Illness and Need

Non-metastatic castrate-resistant prostate cancer (CRPC) is defined as serum testosterone at castrate level (less than 1.73 nmol/L) in a setting of rising PSA with no evidence of metastatic disease by conventional imaging such as CT or MRI or bone scan.

As per the Canadian Cancer statistics 2017, prostate cancer is the fourth most commonly diagnosed cancer with a projected incidence of 21,300 cases and the third leading causing of death in men with an expected mortality of 4100 cases.[9]

Despite the early stage diagnosis and high cure rates with surgery or radiotherapy, 28% of patients develop recurrent disease as evidenced by a biochemical recurrence (elevation in PSA) with or without metastases.[10] These patients will relapse and receive salvage therapy (androgen deprivation therapy, antiandrogens) for rising PSA in the absence of metastatic

disease and most often it takes two years from rising PSA to development of metastasis. However, patients with high-risk features (higher baseline PSA, higher PSA velocity (nanograms/ml/months), PSA doubling time (<8–10 months) have a shorter metastasis-free survival and overall survival.[11]

The optimal management of non-metastatic castrate cancer was controversial as previous trials with bisphosphonates and secondary hormone therapies failed their primary end-point.[12]

The transition of non-metastatic CRPC to metastatic CRPC has been identified as a clinically relevant event and often heralds the development of symptoms (pain, fatigue, and a decline in quality of life) and additional intervention.[13,14] For metastasis-free survival to be a reasonable endpoint, a significant clinical benefit will need to be realized with a favorable benefit–risk ratio for toxicity and cost evaluation. For example, the phase III trial of denosumab showed modest improvement in bone metastatic-free survival at risk of osteonecrosis of the jaw with no increase in overall survival.[15] Given the introduction of newer generation anti-androgens for the treatment of prostate cancer, clinical trials have investigated these agents in patients with non-metastatic CRPC at high risk of developing metastasis. Results of the SPARTAN (apalutamide or placebo) and PROSPER (enzalutamide or placebo) trials have been published.

The present pCODR review addresses patients with non-metastatic castration-resistant prostate cancer at high-risk of progression to metastatic disease. The evidence for this review is based on the PROSPER trial.

Effectiveness

The PROSPER trial is a double-blind, randomized, placebo-controlled trial evaluating enzalutamide in patients who are at high risk of developing metastatic disease with non-metastatic CRPC. The key inclusion criteria were men with histologically confirmed prostate adenocarcinoma, rising PSA despite castration level serum testosterone, PSA doubling time of ≤ 10 months while on continuous androgen deprivation therapy (ADT) and absence of metastatic disease by conventional imaging (bone scan and CT chest, abdomen and pelvis for soft tissue or MRI if indicated). Patients were stratified based on the PSA doubling time (<6 months or >6 months) and use of bone-targeted agents at baseline (yes or no) and randomized in 2:1 ratio to receive either enzalutamide or placebo. The primary endpoint of this study was metastasis-free survival and overall survival was a secondary endpoint.

Patient characteristics were balanced between the two groups and consistent with the characteristics of patients commonly seen in Canadian clinical practice. The median age was 74 years, median serum PSA level was 11 ng/mL, median PSA doubling time was 3.7 months (77% of the trial population) and 11% of patients were treated with bone resorption inhibitors.

The trial was positive in meeting its primary endpoint; the median metastatic-free survival was 36.6 months with enzalutamide versus 14.7 months in the placebo group. There was a statistically significant reduction in the hazard for metastases or death when compared

with placebo (hazard ratio, 0.29; 95% CI, 0.24 to 0.35; P<0.001) and can be considered to be clinically meaningful.

Regarding secondary endpoints, the time to PSA progression was significantly longer for enzalutamide compared to placebo (HR 0.06 (95% CI 0.05–0.08)p< 0.001.). There is also delay in first use of new antineoplastic therapy [HR 0.21, 95% CI 0.17-0.26, p<0.001), use of cytotoxic chemotherapy (HR = 0.38 [95% CI, 0.28 to 0.51]; p < 0.0001), chemotherapy free survival (HR: 0.50 [95% CI, 0.40 to 0.64]; p < 0.0001) and chemotherapy-free disease-specific survival (HR: 0.398 [95% CI, 0.307 0.515[; p < 0.0001).

There was no statistically significant difference in time to pain progression (HR: 0.959 [95% CI, 0.801 to 1.149]; p = 0.6534) and FACT-P degradation (HR: 0.92 [95% CI, 0.79 to 1.08]; p = 0.3128) while the other secondary endpoint, overall survival was immature due to the low number of events.

While an overall survival improvement could not be ascertained in this trial, the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) study and an exploratory analysis from SPARTAN trial suggests a metastasis-free survival can be a surrogate marker for overall survival.[14,16]

In order to assess the comparative efficacy and safety of enzalutamide and ADT to apalutamide and ADT in patients with nm-CRPC, the pCODR Methods Team reviewed two indirect treatment comparisons in detail:

- an unpublished systematic review and Bayesian network meta-analysis (NMA) included in the submitter's submission.[6]
- a published indirect comparison using the Bucher method that was identified by pCODR (Wallis et al, 2018)[7]

The CGP noted that in 2018 apalutamide plus ADT was approved by Health Canada, and pERC conditionally recommended reimbursement provided cost-effectiveness be improved to an acceptable level for patients with high-risk nm-CRPC. Once apalutamide plus ADT will be reimbursed in Canada, it will be the most relevant comparator to enzalutamide plus ADT in this setting (i.e. same use of ADT, and similar mechanism of action between enzalutamide and apalutamide). The CGP acknowledged that the submitter-provided NMA and the published indirect treatment comparison found no statistically significant differences between the two treatments for efficacy or safety endpoints. The quality assessments performed by the pCODR Methods Team identified several limitations with the submitted-provided NMA and the published Bucher indirect comparison of enzalutamide and apalutamide. Most notably, the analyses for the efficacy endpoints 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 and/or reported. The potential risk of bias with this limitation is unclear and the results should be interpreted with caution. The data for overall survival data 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 overall survival.

The CGP agreed with the pCODR Methods Team and concluded that given the limitations identified in the submitted NMA and the published ITC, there is no reliable estimate of the comparative efficacy or safety of enzalutamide and ADT compared with apalutamide and ADT. The CGP further noted the absence of more robust direct evidence from a randomized trial and lack of long term outcomes such as OS and QOL. The CGP acknowledges that there is insufficient evidence to demonstrate superiority of either enzalutamide or apalutamide in this patient population and the CGP cannot recommend one therapy over the other. The CGP suggested that, drug price, patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection in clinical practice. Refer to section 7 for the complete critical appraisals of the submitter-provided NMA and the published ITC.

Safety

Overall enzalutamide was well tolerated and no new toxicities were encountered in the trial; the incidence and severity of adverse events were similar in both the enzalutamide and placebo group, the median reporting period for adverse events was 18 months and 11.1 months respectively. The rate of discontinuation of the enzalutamide or placebo due to adverse events was 10.3% and 7.5% respectively while serious adverse events occurred in 24.3% and 18.3% of patients respectively, grade 3-4 adverse events occurred in 31.4% and 23.4% of patients, respectively, and death due to adverse events was observed in 3.4% and 0.6% of patients, respectively. The common toxicities were fatigue, hypertension, hot flush, nausea, diarrhea, falls, dizziness and decreased appetite. There were 17% of patients in enzalutamide group who developed fall and non-pathological fracture[4], which is likely due to osteopenia/osteoporosis from androgen deprivation therapy. Increased osteopenia is a known side effect of antiandrogen therapy and has similarly been observed with all second generation hormonal agents. This can potentially be ameliorated with the use of bone conserving therapies such as calcium, vitamin D, bisphosphonates, and/or denosumab. Also, the risks of CNS toxicities were low, 0.3% of patients suffered a seizure and 5% of patients developed mental impairment while on enzalutamide. Enzalutamide should therefore be cautioned in patients with a history of seizures and/or in patients who are on drugs which can lower the seizure threshold. A recent update also suggests that the PROSPER trial did not show a negative effect of enzalutamide plus ADT on quality of life compared with ADT plus placebo with overall similar quality of life scores between arms.[17] This seems reasonable in the nmCRPC setting, where patients' quality of life is expected to be relatively high and stable.

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

Several questions have been raised regarding the applicability of these results to certain patient populations:

1) For patients who receive ADT (e.g., GnRH agonist plus first generation anti-androgen such as bicalutamide), PAG is seeking guidance on whether there is an appropriate time period between discontinuation of bicalutamide and initiation of enzalutamide (e.g., after four week wash out period provided there is progressive disease).

a. Patients who are progressing on ADT and first-generation antiandrogen such as bicalutamide, the CGP suggest evaluating for antiandrogen withdrawal syndrome by monitoring the PSA over six weeks before starting enzalutamide.

2) PAG noted that enzalutamide is an oral treatment that can be administered at the patient's home and chemotherapy chair time is not required. PAG is seeking clarity if there may be more frequent clinic visits for monitoring of blood work and side effects (e.g., fatigue, risk of fractures) and treatment time with enzalutamide plus ADT compared with ADT alone.
    a. In the PROSPER trial patients were seen in at week 1 and week 5 and then every 16 weeks. In clinical practice we are expecting the number of visits will be more with enzalutamide initially (at least once a month for the first 3 months) and then as per the current practice every 3-4 months.

3) PAG noted that treatment with enzalutamide in the PROSPER trial was continued until radiographic progression. Discontinuation solely because of an increase in the PSA level was discouraged, however, discontinuation on basis of clinical progression or toxic effects was allowed. If enzalutamide is recommended for reimbursement, PAG is seeking guidance on the appropriate criteria for discontinuation of enzalutamide (i.e., definition of progression).
    a. The CGP suggests to define disease progression according to radiological progression as per Prostate Cancer Working Group (PCWG) 3 for bone lesions and RECIST criteria 1.1 for soft tissue lesions.

       Definition of radiological progression and discontinuation of enzalutamide:

       The PROSPER trial patients were seen at week 1 and week 5 and then every 16 weeks. Radiological imaging with bone scan and CT scan were obtained every 16 weeks. The trial defined the radiological progression of the disease as the appearance of one or more bone lesions on bone scan (if one bone lesion, confirm with either an X-ray or CT or MRI) or soft metastatic disease as per RECIST 1.1 by CT or MRI.

       The prostate cancer clinical trials are following PCWG 3 recommendations on trial design and objectives were published in 2015 while the PROSPER trial enrolled the first patient in November 2013. For the first time, PCWG 3 described the imaging modalities method and frequency to measure outcomes for "progression nonmetastatic castrate-resistant prostate cancer to metastatic castrate-resistant prostate cancer."

       The following statement is based on GCP consensus:
       GCP suggest reviewing the patient for toxicity every four weeks for the first one to three months, at week 12-16 and then every 12-16 weeks for clinical tolerability and PSA response or disease progression.

       If the patient is asymptomatic with an ongoing PSA response, we suggest monitoring the patient every 12 to 16 weeks and at the time of symptoms or rising PSA, assess for radiological progression of the disease with a follow-up bone scan and CT scan.

If there is no PSA response after 12-16 weeks of enzalutamide or at any time patient develops clinical symptoms suggesting disease, assess for radiological progression of the disease with a follow-up bone scan and CT scan.

GCP suggest following the PCWG3/RECIST 1.1 guideline on bone scan and CT scan to document the radiological progression of the disease and discontinue the treatment. If applicable GCP also recommend to account for flare on the bone scan.

As the patient needs to be assessed for PSA response and timing of follow-up imaging, there is a slightly increased number of visits in the first few months.

4) PAG noted that apalutamide for non-metastatic castration-resistant prostate cancer was recently reviewed at pCODR. PAG is seeking guidance on whether there are specific clinical situations where apalutamide or enzalutamide would be the preferred treatment for patients with nm-CRPC (e.g., apalutamide has less toxic CNS effects and may be safer in patients with a history of seizures)?
    a. The CGP noted that there is insufficient evidence at this point (no head-to-head comparison) to demonstrate superiority of either enzalutamide or apalutamide in this patient population. Therefore, the CGP cannot recommend one therapy over the other. Further, giving 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 from these results. Overall, the CGP agreed that, the choice between apalutamide and enzalutamide in clinical practice should be guided by drug price, patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement).

5) PAG is seeking guidance on which treatment options would be available to patients in the metastatic setting following enzalutamide treatment in the non-metastatic castration-resistant prostate cancer setting? In additional PAG is particularly seeking guidance on the following treatment options (i.e., abiraterone or chemotherapy) in the metastatic setting following enzalutamide in the non-metastatic setting.
    a. CGP notes that there is not sufficient data to make an evidence-based recommendation and therefore the following statements are based on expert opinion only.

    CGP considers nonmetastatic castrate-resistant prostate cancer as micrometastatic disease that could not be detected by conventional imaging. The use of apalutamide or enzalutamide in these patients should be considered as first-line therapy in non-metastatic castrate-resistant disease.

    Treatment options after failure of apalutamide or enzalutamide:

    Similar to the setting of mCRPC patients who progressed on enzalutamide, the next line of therapy could be abiraterone/prednisone, docetaxel, radium-223 or cabazitaxel. Since apalutamide is in the same class of drugs as enzalutamide, there is no clinical evidence to suggest efficacy or safety on switching to another next generation antiandrogen (apalutamide to enzalutamide or enzalutamide to apalutamide) upon radiological disease progression; CGP does not recommend this practice. Whether re-challenging with enzalutamide is potentially reasonable after interim treatment with other options is currently unknown. The data available to date for the sequence of

enzalutamide followed by abiraterone/prednisone demonstrate a very modest benefit for this sequence.

Further, there is currently insufficient evidence to recommend either arbiraterone/prednisone or chemotherapy over the other. The CGP suggests that patient values and preferences, co-morbidities, expected dug toxicities, and treatment availability (provincial reimbursement) should guide treatment selection in clinical practice.

1.3 Conclusions

The Clinical Guidance Panel concluded that there **is** a net overall clinical benefit to enzalutamide plus ADT compared with ADT alone for high-risk non-metastatic castration-resistant prostate cancer patients based on one high-quality randomized controlled trial that demonstrated clinically meaningful and statistically significant benefit in metastasis-free survival and most secondary endpoints including time to PSA progression, first use of new antineoplastic therapy, use of cytotoxic chemotherapy, chemotherapy free survival and chemotherapy-free disease-specific survival for enzalutamide compared with placebo. The overall survival is currently immature. The grade 3 and 4 adverse events were low and clinically acceptable without worsening health related quality of life. Currently, there are no accepted standard treatment options for patients with non-metastatic castration-resistant prostate cancer. The optimal management of nmCRPC remains an unmet need for a large number of patients.

This recommendation was based on the PROSPER trial which evaluated the use of enzalutamide in high-risk non-metastatic castration resistant prostate cancer.

In making this recommendation, the Clinical Guidance Panel considered:

- The transition from non-metastatic CRPC to detectable metastatic CRPC is a clinically relevant event and often associated with the onset of pain, fatigue, weakness, a decline in overall quality of life, psychological burden and additional interventions.
- While significant advances have been achieved in recent years in the treatment of castration resistant prostate cancer, it remains an incurable disease. A significant portion of patients with prostate cancer will eventually relapse and progress to overt metastatic disease which is associated with a high burden of symptoms, decrease in quality of life and death.
- No data exist for low risk patients with a PSA doubling time of > 10 months and it is uncertain whether the benefit observed in PROSPER extends to this patient population.
- The identification of non-metastatic patients in PROSPER was based principally on PSA and conventional imaging modalities of bone scan and CT. Advanced imaging techniques currently in development (e.g. PET scans) may have an ability to detect metastases earlier than current imaging techniques. As a result more patients may be identified with evidence of early metastatic disease. The impact of treatments in this future cohort of patients has yet to be determined.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Prostate cancer is the second most common cancer and the sixth leading cause of cancer death among men worldwide, with an estimate of 1.1 million cases and 307,000 deaths in 2012.[18,19] This translates to 15% of all new cases of cancer in men.[20] In Canada, an estimated 21,300 men were diagnosed with prostate cancer in 2017, representing 21% of all new cancers in men with 4,100 deaths from prostate cancer representing 10% of all cancer deaths in men. Hence there were 11 deaths weekly.[21]

2.2 Accepted Clinical Practice

Treatment options for localized prostate cancer include active surveillance if very low risk, and radical prostatectomy or radiation therapy (intensity modulated radiation therapy or brachytherapy). There is no definitive evidence that one treatment modality is superior in efficacy. However, despite local ablative treatment, 28% of patients develop recurrent disease as evidenced by a biochemical recurrence (elevation in PSA) with or without metastases.[10] Aside from salvage local therapies, such as salvage radiation therapy after previous prostatectomy or salvage prostatectomy after previous radiation therapy, standard first-line therapy for recurrence remains androgen deprivation therapy (ADT). The majority of patients initially respond to androgen deprivation therapy but almost all eventually progress to castration resistant prostate cancer (CRPC). Evidence of disease progression with prostate cancer include an increase in PSA, new metastases, or progression of existing metastases while on androgen deprivation therapy (ADT); all of which are considered castration-resistant disease.

Non-metastatic Castration-Resistant Prostate Cancer (nmCRPC) is commonly defined as two consecutive rising PSA values >0.2 ng/mL following radical prostatectomy[20] or any PSA increase of 2 ng/mL higher than the PSA nadir value regardless of the serum concentration of the nadir after primary radiation therapy.[22,23] High risk features are generally defined by a shorter PSA doubling time (<8–10 months) and higher baseline PSA.

Patients with non-metastatic castration resistant prostate cancer (nmCRPC) are at risk of progressing to metastatic disease imminently within 1 to 2 years.[24,25] The onset of metastases is usually accompanied by a decreased quality of life, increased symptoms such as pain, weight loss, loss of appetite etc., and a limited life expectancy.[26-28] Overall survival of patients with metastatic disease is approximately 2.5 years.[29]

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

Treatment of non-metastatic CRPC

There are no accepted standard treatment options for patients with non-metastatic castration-resistant prostate cancer as all previous phase 3 trials of denosumab, zolendronic acid,

atrasentan, zibotentan, and clodronic acid failed to show an overall survival (OS) benefit in this population.[15,30-33] Patients with nmCRPC were specifically excluded from both the COU-AA-302 study (abiraterone/prednisone for chemotherapy-naïve metastatic CRPC) and the PREVAIL study (enzalutamide for chemotherapy-naïve metastatic CRPC).[34,35] Consequently, the optimal management of nmCRPC remains an unmet need for a large number of patients.

In the absence of proven treatment options, observation is often recommended for patients with biochemical-only progression and no evidence of metastases. Alternatively, initial therapy with the addition of an anti-androgen such as bicalutamide or an androgen synthesis inhibitor such as ketoconazole can be used although no secondary hormonal therapy has been found to extend survival for patients with CRPC. If patients are treated with combined androgen blockade, anti-androgen withdrawal as well as low dose prednisone are considered further options. In general, early chemotherapy with docetaxel is not recommended for those patients without metastatic disease outside the context of a clinical trial.

Recently, apalutamide, an oral, next-generation androgen receptor inhibitor has received Health Canada approval for the treatment of patients with non-metastatic castration-resistant prostate cancer. Since then, it has further received a positive conditional pCODR recommendation for high-risk patients with nm-CRPC. Apalutamide binds directly to the ligand-binding domain of the androgen receptor and prevents androgen-receptor translocation, DNA binding, and androgen-receptor–mediated transcription. In combination with ADT has been shown to have significantly improved metastasis-free survival compared with those receiving ADT plus placebo in non-metastatic CRPC.[36] It is likely that apalutamide will become a treatment option in this patient population.

Enzalutamide has been tested in this space within the randomized, double-blind, placebo-controlled phase III PROSPER trial comparing enzalutamide + ADT with placebo + ADT in patients with nm-CRPC. Enzalutamide, an androgen receptor inhibitor, blocks the Androgen Receptor (AR) pathway at three stages. It blocks the binding of androgens to AR, inhibits nuclear translocation of activated AR and also impairs binding of activated AR with DNA.[24] The PROSPER study demonstrated substantial clinical benefit for treatment with enzalutamide + ADT through statistically significant and clinically meaningful improvements in metastatic-free survival (MFS), time to the first use of a subsequent antineoplastic therapy, and potential improvement in overall survival based on positive survival trend.

2.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of Enzalutamide for patients with non-metastatic castration-resistant prostate cancer.

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

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

2.4 Other Patient Populations in Whom the Drug May Be Used

Enzalutamide has Health Canada approval in the setting of medical or surgical castration for the treatment of metastatic castration-resistant prostate cancer (CRPC) in patients who:
• are chemotherapy-naïve with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy.
• have received docetaxel therapy.

No evidence exists for the use of enzalutamide in:

- Low risk nm-CRPC

With regard to Castration-Sensitive Metastatic Prostate Cancer (mCPSPC), there are two phase III trials evaluating enzalutamide, namely the ENZAMET and ARCHES trials.

The ANZUP ENZAMET Trial (NCT02446405) is an open label randomized phase III trial with 1,100 patients with mCSPC receiving ADT with or without docetaxel plus enzalutamide or ADT with or without docetaxel plus a nonsteroidal androgen antagonist. ENZA-MET. Preliminary data should be available in 2020 and may provide insight as to whether ADT plus enzalutamide is more efficacious than standard ADT and also whether ADT plus enzalutamide has a synergistic effect with docetaxel.

The ARCHES trial (NCT02677896) investigated enzalutamide in the maintenance setting for patients with metastatic castration-sensitive disease as measured by radiographic progression-free survival. It also evaluates the safety of enzalutamide plus ADT in metastatic hormone sensitive prostate cancer. At the time of the first analysis (median follow-up of 14.4 months) enzalutamide plus ADT significantly improved radiographic progression-free survival versus placebo plus ADT while overall survival data remained immature. Completion date for the study is December 2023.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient input was provided to pCODR through a joint patient advocacy group submission from the Canadian Cancer Survivor Network (CCSN) and Prostate Cancer Canada (PCC) for enzalutamide for non-metastatic castrate resistant prostate cancer (nmCRPC). Information was obtained via a survey on SurveyMonkey publicized on CCSN's website, Facebook and Twitter accounts, and sent to individuals on their mailing list. Approximately 125 prostate cancer support groups and CCSN's Prostate Cancer Advisory Council were also emailed the survey. It was noted that CCSN collected the information from patients and caregivers, while PCC coordinated the clinician information. Overall, 15 patients with prostate cancer and five caregivers completed the survey, with three respondents reporting experience with enzalutamide.

From a patient's perspective, 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 quality of life (86% and 68%, respectively). Other reported symptoms resulting from prostate cancer included mental stress related to living with uncertainty, pain, and restlessness at night.

At the time of completing the survey, respondents reported receiving the following treatments: second-line hormone therapy, drugs accessed through participation in a clinical trial, chemotherapy, and palliative therapies for pain and/or bone metastases. Fatigue was listed as the most commonly experienced side effect related to the therapies that were being used by the respondents. It is unclear, based on the input, whether the fatigue mentioned is due to prostate cancer, treatments, or both. Fatigue was also experienced by two of the three respondents who reported experience with enzalutamide. These respondents expressed uncertainty about whether the fatigue experienced was due to treatment with enzalutamide or concurrent ADT.

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

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Prostate Cancer

When asked about symptoms or problems that affected daily living and quality of life, symptoms reported by over half of respondents were fatigue (84%) and sexual dysfunction (69%). Other reported symptoms are included in table 1. Of these symptoms, respondents were asked to rank the top three symptoms they felt were most important to control. Respondents reported the symptoms they felt were most important to control in the

following descending order: fatigue (79%), pain (36%), anxiety and panic attacks (32%), urinary incontinence (26%), sexual dysfunction (26%), living with uncertainty (26%), not sleeping at night – restlessness (26%), and feeling isolated or lonely (16%). None of the respondents indicated weight loss or a loss of appetite as being a symptom they felt important to control.

Table 3.1: Symptoms Affecting Day-to-Day Living and Quality of Life, n=20

Symptom	Proportion of Respondents, %	Rank, %
Fatigue	84	79
Sexual dysfunction	68	26
Living with uncertainty	47	26
Pain	37	36
Not sleeping at night – restlessness	36	26
Urinary incontinence	32	26
Anxiety, panic attacks	26	32
Feeling isolated or lonely	21	16
Weight loss, lack of appetite	11	0

Respondents were asked to rate their top three symptoms most important to control. The percentage recorded in this column refers to the percentage of respondents who reported the symptom as most important to control.

Fatigue was highlighted by CCSN as a symptom that had a substantial impact for the respondents. Fatigue was reported by 84% of respondents, with 79% of patients reporting it negatively affecting their daily living and quality of life.

3.1.2 Patients' Experiences with Current Therapy for Prostate Cancer

Respondents indicated using the following treatments: second-line hormone therapy (85%), a drug provided via a clinical trial (46%), chemotherapy (31%), and pain palliation for bone metastasis (8%). When asked to report which treatments respondents thought were most effective at controlling common aspects of prostate cancer, 50% indicated second-line hormone therapy and palliation for bone metastasis, and 40% reported therapies obtained via clinical trials. Half of respondents indicated that chemotherapy was not effective at controlling aspects of prostate cancer; CCSN suggested that this information emphasizes the need for treatments that delay the need to prescribe chemotherapy to patients.

Fatigue (82%) was listed as the most common side effect related to therapies currently being used by respondents. Other side effects of treatments included anxiety or depression

(29%), pain (23%), anemia (23%), irregular heartbeat (n=1), sinus congestion (n=1), swollen hands (n=1), weakness (n=1), hot flashes (n=1), and weight gain (n=1).

While just over half of the 20 respondents did not experience issues with accessing treatment (53%), 21% of respondents did. Limited availability of treatment communities and travel costs associated with receiving treatment were listed as reasons for issues with access experienced by respondents. CCSN noted that some respondents indicated multiple issues related to access of treatment, and that some did not answer the question.

3.1.3 Impact of Prostate Cancer and Current Therapy on Caregivers

The five caregivers who responded to CCSN's survey commented on challenges they experienced related to caring for someone with prostate cancer, and how their lives have been impacted. Caregivers mentioned impacts on the sexual intimacy, reduced social engagement, difficulty with managing their loved one's side effects, such as fatigue, anxiety and depression, and mental stress regarding the future.

- *"Managing side effects; helping spouse when he is anxious and depressed."*
- *"We are unable to travel, discontinued our sexual intimacy, must accommodate fatigue into daily activities, reduced social & recreational activities."*
- *"Worry of the unknown."*
- *"Lots of time required to tend to a patient."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Enzalutamide

Three respondents reported receiving enzalutamide for nm-CRPC as part of a clinical trial. Of the three respondents, two experienced fatigue as the primary side effect related to enzalutamide. However, the respondents were uncertain whether the fatigue was a result of treatment with enzalutamide, or the concurrent ADT that was continued throughout the trial.

A longer life and delayed or halted progression of tumours were reported as expectations of treatment with enzalutamide by the respondents.

3.3 Additional Information

CCSN provided quotes from respondents that highlight the unmet needs with their current therapies. The quotes indicate a need for more treatment and treatments that aid in improving quality of life. Overall, 40% of respondents indicated that their current therapies were not addressing their needs.

- *"I would like to treat the disease whilst it still is in the prostate but my urologist likes the watch and wait approach because he says the quality of life more important."*
- *"Lack of sexual therapy to regain proper function."*
- *"Soon I will run out of options for treatment."*

The sentiments expressed in the above quotes are mirrored in the responses provided by 16 respondents to CCSN in regards to expectations patients have of new drugs, including improvement in quality of life (75%), a delayed need for chemotherapy or palliative care (38%), and a delayed onset of symptoms (38%). A large percentage of respondents also indicated expectations for access to a new treatment option (69%). CCSN stated that patients reported a willingness to tolerate the following side effects for treatment if it could delay metastasis of their prostate cancer: fatigue (86%), loss of appetite (57%), rash (29%), and dizziness (14%). CCSN highlighted the challenges patients experience when deciding to undergo treatments, as they must balance the side effects in return for a treatment that may slow disease progression.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Appropriate treatments for metastatic, castration resistant disease after enzalutamide

Economic factors:

- Add-on therapy to androgen deprivation therapy

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that the current treatment for non-metastatic castration-resistant prostate cancer is androgen deprivation therapy (ADT).

4.2 Eligible Patient Population

PAG is seeking clarity on whether or not patients with PSA doubling time greater than 10 months or patients with ECOG performance status of 2 or greater would be eligible for treatment with enzalutamide.

For patients who receive ADT (e.g., GnRH agonist plus anti-androgen such as bicalutamide), PAG is seeking guidance on whether there is an appropriate time period between discontinuation of bicalutamide and initiation of enzalutamide (e.g., after four week wash out period provided there is progressive disease).

4.3 Implementation Factors

PAG noted that enzalutamide is an oral treatment that can be administered at the patient's home and chemotherapy chair time is not required. However, PAG identified that there may be more frequent clinic visits for monitoring of blood work and side effects (e.g., fatigue, risk of fractures) and treatment time compared to ADT alone.

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

PAG noted that treatment with enzalutamide in the PROSPER trial was continued until radiographic progression. Discontinuation solely because of an increase in the PSA level was discouraged, however, discontinuation on basis of clinical progression or toxic effects was allowed. If enzalutamide is recommended for reimbursement, PAG is seeking guidance on the appropriate criteria for discontinuation of enzalutamide (i.e., definition of progression).

4.4 Sequencing and Priority of Treatments

PAG noted that apalutamide for non-metastatic castration-resistant prostate cancer was recently reviewed at pCODR. PAG is seeking guidance on what clinical scenarios apalutamide or enzalutamide would be the preferred treatment for patients with non-metastatic castration-resistant prostate cancer in this setting. PAG is also seeking guidance on whether there are specific clinical situations where apalutamide or enzalutamide would be the preferred treatment.

PAG is also seeking guidance on treatment options (e.g., abiraterone or chemotherapy) in the metastatic setting following enzalutamide in the non-metastatic setting.

4.5 Companion Diagnostic Testing

None required.

4.6 Additional Information

None provided.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided for enzalutamide for patients with non-metastatic castrate resistant prostate cancer (nm-CRPC). Input was provided as one joint submission from two clinicians and one individual clinician submission. A summary of the input is provided below.

While treatment options and available clinical evidence are both limited for patients with nm-CRPC, 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. Registered clinicians noted that there will be both high incident and prevalent cases due to prostate cancer being a very common form of cancer, and extrapolations made using clinical trial data. 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 appreciated option for patients and clinicians to consider, however, it may be a 'nice to have' therapy and not a necessity.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for non-Metastatic Castration Resistant Prostate Cancer

One of the clinicians identified three possible treatment options for patients:

1. Watchful waiting and delaying systemic treatment for when metastases become radiographically apparent and/or symptomatic
2. Further endocrine manipulations such as bicalutamide/bicalutamide withdrawal. Although, the clinician input indicated that long term benefit with bicalutamide/bicalutamide withdrawal is unproven.
3. Apalutamide obtained through Janssen's compassionate/special access program.

The other clinicians indicated that patients with non-metastatic castration resistant prostate cancer are a new population without funded options. There are currently no standard treatment options for this patient population and clinical trial data are also limited.

5.2 Eligible Patient Population

One of the clinician inputs suggested that only patients at high risk of developing metastases should be eligible for enzalutamide. The other clinician input expressed an expectant high incident and prevalent population that would be eligible for enzalutamide, as prostate cancer is a common cancer with most patients developing metastatic disease following the non-metastatic setting. The availability of new treatments, including apalutamide and potentially enzalutamide, in addition to enhanced monitoring techniques to identify eligible patients, were stated by the clinician input to result in an estimated moderately large eligible (both incident and prevalent) patient population. A high prevalence of patients to be eligible for enzalutamide from the clinician input was based on median duration of treatment observed in the PROSPER and SPARTAN trials.

5.3 Relevance to Clinical Practice

One of the clinician inputs highlighted the risk of toxicity associated with enzalutamide treatment, including significant fatigue and potentially significant drug-drug interactions. While seizures have not been observed in the trial population, it was noted that patients at-risk of seizures were excluded from the PROSPER trial. In addition, overall survival has not yet been demonstrated through the trial and data is currently immature. However, the clinician input mentioned a dramatic improvement in radiographic progression-free survival (rPFS), consistent with benefits observed from apalutamide and from the phase 2 TERRAIN study analyzing the efficacy of enzalutamide in patients with metastatic castration-resistant prostate cancer. One of the clinician inputs noted that enzalutamide aligns with patient values and supported the use of enzalutamide based on the magnitude of PFS benefit, the severity of symptoms that ensue when radiographic progression is observed, and biological plausibility. While not all patients in this setting will want active treatment, the majority of patients will.

Currently, patients may be given a number of downstream metastatic treatment options, including docetaxel chemotherapy, cabazitaxel chemotherapy, abiraterone acetate, radium 223, and rapidly evolving agents in trials such as PARP inhibitors. Given the delay to radiographically apparent metastases, symptoms, and downstream treatment options including chemotherapy, the input suggested it may be reasonable to offer enzalutamide in the non-metastatic setting for patients to maintain their quality of life and delay cancer related morbidity. Therefore, for most patients the benefits of receiving enzalutamide were thought to outweigh the risks of toxicity.

Prescription of enzalutamide to patients with good ECOG performance status, good life expectancy, without contraindications to enzalutamide, and with whom there was discussion of benefits and harms related to enzalutamide were suggested to help mitigate costs. The clinician input stated that prescription of enzalutamide should be made by clinicians and pharmacists with expertise in prostate cancer. One of the clinician inputs suggested that both patients and clinicians would be highly accepting of enzalutamide, and that clinicians would already be familiar with enzalutamide; unlike considerations needed for novel toxicities with apalutamide treatment, including rash and gastrointestinal issues. The other clinician input mentioned that while enzalutamide would be “nice to have” as an available therapy, it is not necessary.

5.4 Sequencing and Priority of Treatments with Enzalutamide

One of the clinician inputs indicated that patients who progress with enzalutamide are provided with either chemotherapy or enroll into a clinical trial. Patients may be ineligible for abiraterone or enzalutamide as a subsequent therapy if they have M1 CRPC; these patients may be restricted to the use of chemotherapy, for example cabazitaxel. The use of enzalutamide was stated to remove the option of second generation hormonal therapies as first-line therapy for patients with M1 prostate cancer, similar to apalutamide.

The other clinician input submission suggested that enzalutamide would result in a downstream shift of all currently available treatments, where patients would receive

enzalutamide followed by docetaxel/radium 223, abiraterone acetate, cabazitaxel. This is in agreement with the other clinician input that suggested enzalutamide take the place of hormonal therapy as first-line treatment.

Abiraterone acetate is not indicated for use in this specific patient population in Canada. One of the clinicians indicated that abiraterone acetate would not likely have a significant role as a therapy in this patient population as it has not yet been formally evaluated. Upon progression with enzalutamide, some patients may be only eligible for chemotherapy or clinical trials.

The other clinician input submission suggested that almost all patients would be provided either enzalutamide or abiraterone over the next couple of years; they also highlighted that the costs of enzalutamide and abiraterone would be similar monthly, but that abiraterone will become generic soon.

5.5 Companion Diagnostic Testing

Companion diagnostic testing is not required. One of the clinician input submissions indicated the ArV7 biomarker is a factor that does not commonly mediate resistance at this early stage in a patient's treatment journey.

5.6 Additional Information

None.

5.7 Implementation Questions

- In clinical practice, what treatment options would be available to patients in the metastatic setting following enzalutamide treatment in the non-metastatic castration-resistant prostate cancer setting? Which sequence of treatments would be preferred?
- Apalutamide for the treatment of non-metastatic castrate resistant prostate cancer is currently under review at pCODR, and may become an available treatment option in the future. In what clinical scenarios would apalutamide or enzalutamide be the preferred treatment for non-metastatic castration-resistant prostate cancer? Please comment on the preference considering patient preference, efficacy, safety, and administration.

None of the clinicians provided input that directly addressed the above implementation questions. Apalutamide was recently reviewed at pCODR and received a positive recommendation conditional on cost-effectiveness being improved to an acceptable level.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the beneficial and harmful effects of enzalutamide for the treatment of patients with high-risk nm-CRPC.

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

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were selected for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team will be provided in Appendix A in the Clinical Guidance Report.

Table 4: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of enzalutamide for nm-CRPC will be included	Adult men with high-risk non-metastatic castration-resistant prostate cancer who have no previous or current evidence of metastatic disease as assessed by CT or MRI for soft-tissue disease and by whole-body radionuclide bone scanning. <u>Subgroups:</u> • Age (<65 years vs. 65 to <75 years vs. ≥75 years) • Baseline ECOG performance status (0-1 vs. ≥2) • Baseline serum PSA level (≤median vs. >median) • Baseline PSA doubling time (>6 months vs. ≤6 months) • Use of bone sparing agents (yes vs. no) • Local or regional nodal disease at baseline (N0 vs N1) • Previous prostate cancer treatments (type of treatment) • Race (White vs. Black vs. Asian vs. other)	Enzalutamide (160 mg PO once daily) + ADT	• Apalutamide (240 mg PO once daily) + ADT • Placebo + ADT	**Efficacy** **Primary:** • Metastasis-free survival **Secondary:** • Time to PSA progression • Time to first use of new antineoplastic therapy • Overall survival • Time to pain progression • Time to first use of cytotoxic chemotherapy • Chemotherapy-free disease-specific survival • Chemotherapy-free survival • PSA response rates **Safety** • AEs • SAEs • Grade 3/4 AEs • WDAE

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
	• Geographical region (e.g., North America, Europe, Asia-Pacific)			**Patient-reported outcomes** • FACT-P • EQ-5D-5L • QLQ-PR25

ADT = androgen deprivation therapy; **AE** = adverse events; **CT** = computed tomography; **ECOG** = Eastern Cooperative Oncology Group; **EQ-5D-5L** = European Quality of Life-5 Dimensions-5 Levels health questionnaire; **FACT-P** = Functional Assessment of Cancer Therapy-Prostate questionnaire; **HRQoL** = health-related quality of life; **MRI** = Magnetic resonance imaging; **OS** = overall survival; **PO** = oral; **PSA** = prostate specific antigen; **QLQ-PR25** = Quality of Life Questionnaire-Prostate 25 module; **RCT** = randomized controlled trial; **SAE** = serious adverse events; **WDAE** = withdrawal due to adverse events

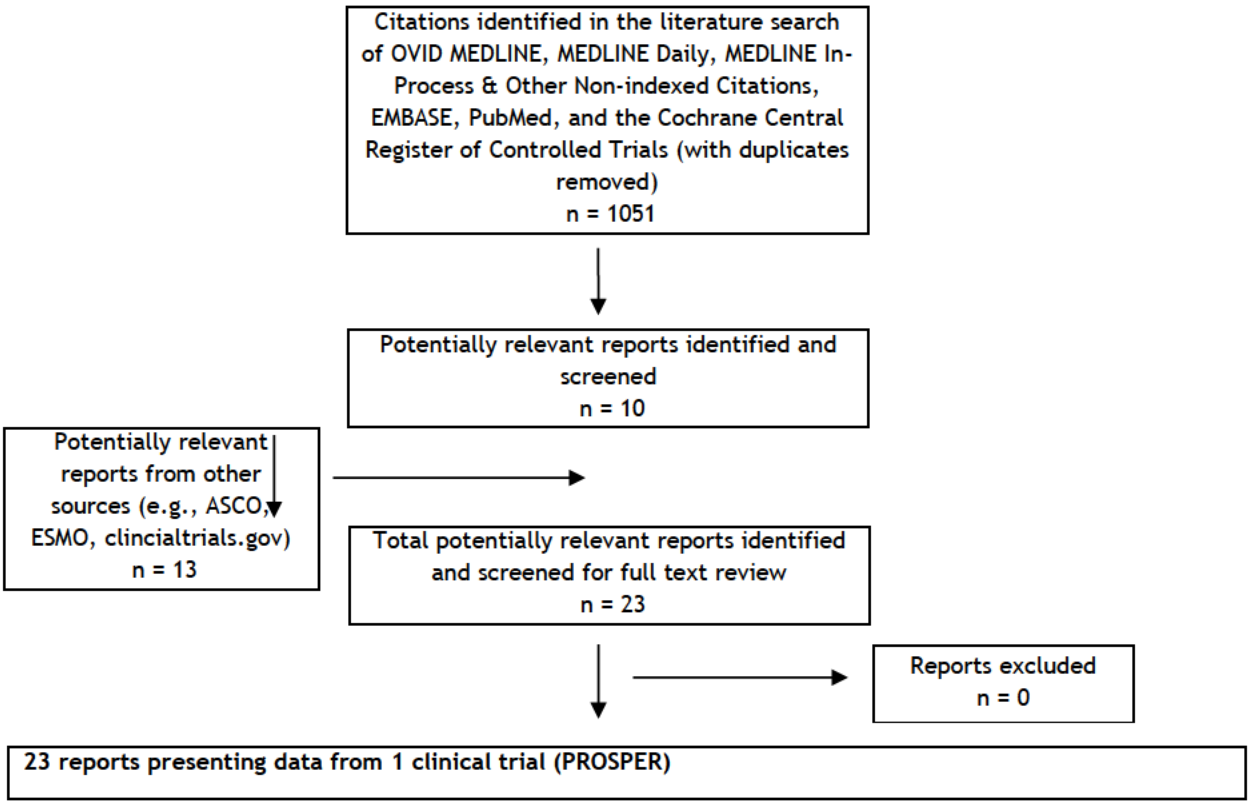
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Eighteen reports from one clinical trial (PROSPER) were included in the pCODR systematic review. There were no excluded studies. Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

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



- Gurney et al., 2018[37]
- Hussain et al., 2018[4]
- Saad et al., 2018[38]
- Saad et al., 2018[39]
- Shore et al., 2018[40]
- Sternberg et al., 2018[41]
- Stockler et al., 2018[42]
- Tombal et al., 2018[43]
- Heidenreich et al., 2014[44]
- Hussain et al., 2014[45]
- Attard et al., 2018[46]
- Attard et al., 2018[17]
- Sternberg et al., 2014[47]
- Hussain et al., 2018[48]
- Clinical Study Report[1]
- Clinical Study Report Synopsis[3]
- Common Technical Document 2.7.3[49]
- Common Technical Document 2.7.4[50]
- Product Monograph[51]
- ClinicalTrials.gov[2]
- Clinical Summary[5]
- EMA Assessment Report[52]
- NICE Committee Papers[53]

6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

One randomized trial met the selection criteria of this review. PROSPER (n = 1401) was a multinational, multicentre, phase 3 randomized (2:1 ratio), double-blind trial comparing enzalutamide with placebo in patients with nmCRPC. Relevant information on trial characteristics is summarized below.

Table 5: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
PROSPER (MDV3100-14) NCT02003924 **Characteristics:** multinational, multicentre, phase 3 randomized (2:1 ratio), double-blind, placebo-controlled trial **N randomized:** 933 enzalutamide 468 placebo **Number treated:** 930 (99.7%) enzalutamide 465 (99.4%) placebo **Number of locations:** 254 sites in 32 countries **Patient Enrolment Dates:** November 26, 2013 to June 28, 2017 **Data cut-offs:** • June 28 2017 (primary analysis and first interim analysis of OS) **Funding:**	**Key Inclusion Criteria:** • Men ≥18 years of age • Histologically or cytologically confirmed adenocarcinoma of the prostate. • Ongoing ADT or prior bilateral orchiectomy. • Testosterone ≤50 ng/dL • Progressive disease defined as a ≥3 rising PSA values with most recent PSA ≥2 ng/mL • PSA DT ≤10 months • No evidence of metastases (assessed by CT/MRI and whole-body radionuclide bone scan). • ECOG performance score 0 or 1 **Key Exclusion Criteria:** • Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, for the treatment of prostate cancer • Clinically significant cardiovascular disease • History of seizure or any condition that may have predisposed the patient to seizure	**Intervention:** • Enzalutamide (160 mg PO once daily) + ADT **Comparator:** • Matching placebo + ADT **Duration:** Continuous daily dosing until disease progression, incidence of AEs, or withdrawal of consent	**Primary:** • Metastasis-free survival **Key Secondary:** • Time to PSA progression • Time to first use of new antineoplastic therapy • Overall survival **Secondary:** • Time to pain progression • Time to first use of cytotoxic chemotherapy • Chemotherapy-free disease-specific survival • Chemotherapy-free survival • PSA response rates • FACT-P • EQ-5D-5L • QLQ-PR25 **Safety** • AEs • SAEs

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Pfizer (Medivation Inc) and Astellas Pharma			• Grade 3/4 AEs • WDAE • AESI

ADT = androgen deprivation therapy; **AE** = adverse event; **BICR** = blinded independent central review; **CT/MRI** = computed tomography/magnetic resonance imaging; **ECOG** = Eastern Cooperative Oncology Group; **EQ-5D-5L** = European Quality of Life-5 Dimensions-5 Levels health questionnaire; **FACT-P** = Functional Assessment of Cancer Therapy-Prostate; **MFS** = metastasis-free survival; **nmCRPC** = non-metastatic castration resistant prostate cancer; survival; **PO** = orally; **PSA** = prostate-specific antigen; **PSADT** = Prostate-specific antigen doubling time; **SAE** = serious adverse event; **WDAE** = withdrawal due to adverse event
Sources: Hussain et al., 2018[4] and Clinical Study Report Synopsis[3]

Table 6: Select quality characteristics of PROSPER

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
PROSPER	ENZ + ADT vs. Placebo + ADT	MFS	1440 (960 ENZ and 480 placebo)	1401 (933 ENZ and 468 placebo)	Central (IXRS) stratified by: • PSA DT (<6 months versus ≥6 months) • Baseline use of a BTA (yes versus no)	Yes			MFS final OS data not final	No	Yes

ADT = androgen deprivation therapy; BTA = bone targeting therapy; ENZ = enzalutamide; ITT = intention to treat; IXRS = Interactive voice/web response system; MFS = metastasis-free survival; PSA DT = prostate-specific antigen doubling time

a) Trials

PROSPER

The PROSPER study was a phase 3, multinational, double-blind, placebo-controlled, RCT conducted to assess the efficacy and safety of enzalutamide in combination with ADT for the treatment of patients with nmCRPC. To be eligible for enrollment 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 PSA rises at least one week apart with the last PSA more than 2 ng/mL; 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 CT/MRI 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 ECOG Performance Status 0 or 1. Those using bone targeting agents were required to have been receiving a stable dose for at least four weeks prior to randomization.[4]

Key exclusion criteria included: any prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate for the treatment of prostate cancer; clinically significant cardiovascular disease; or a history of seizure or any condition that may have predisposed the patient to seizure. Patients were also excluded if they had any of the following laboratory values: absolute neutrophil count <1000/μL; platelet count <100,000/μL; hemoglobin <10 g/dL; total bilirubin ≥1.5 times the upper limit of normal (ULN); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times ULN; creatinine >2 mg/dL; or albumin <3.0 g/dL.[4]

Eligible patients were randomized 2:1 to enzalutamide (160 mg per day) or matching placebo. Randomization was conducted using an IXRS and was stratified by the following factors:[4]

- PSA doubling time (<6 months versus ≥6 months)
- Baseline use of a bone-targeting agent (yes versus no).

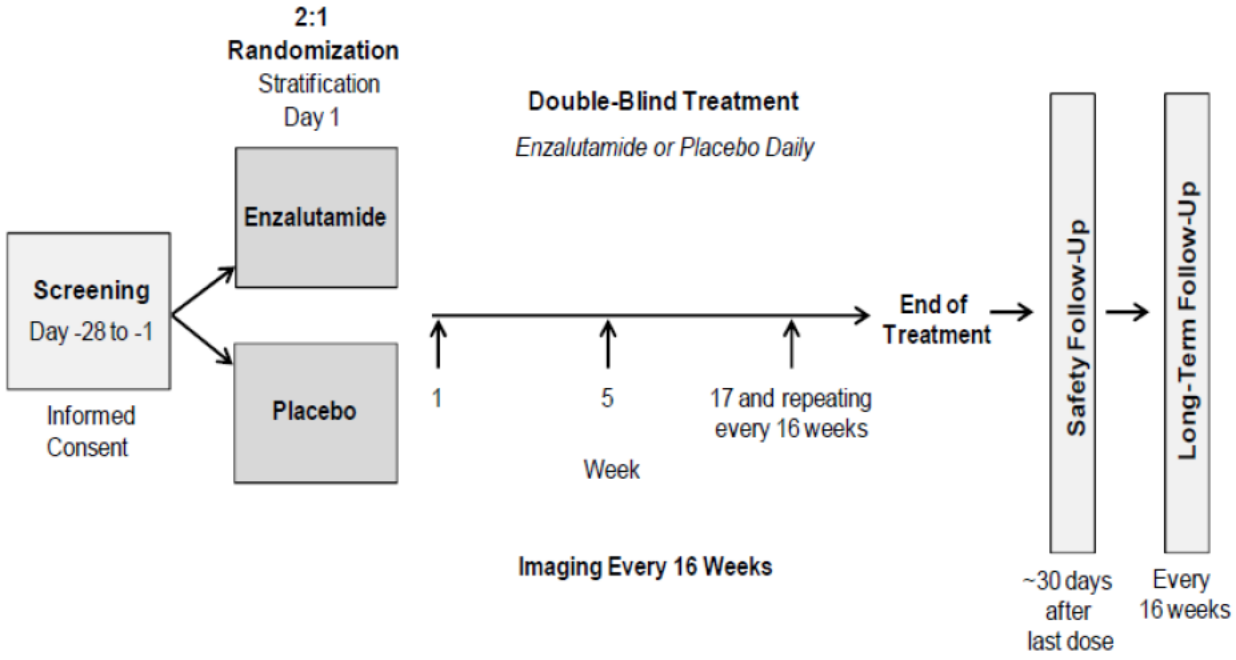
The study design is illustrated in Figure 6.2. As shown, the study consisted of four phases:[4]

- a screening phase of up to 28 days before randomization to establish eligibility and document baseline measurements;

- a double-blind treatment phase where patients were administered enzalutamide or matching placebo;
- a safety follow-up phase of approximately 30 days
- a long-term follow-up phase to monitor survival status.

The study was conducted at 254 sites in 32 countries in North America (United States [25] and Canada [15]), Europe (Austria [2], Belgium [5] Denmark [5], Finland [5], France [20], Germany [6], Greece [5]Italy [9], Netherlands [4], Poland [5], Russia [4], Serbia [4], Slovakia [7], Spain [10], Sweden [6], Ukraine [5], UK [10]), Asia (China [20], Hong Kong [3], Korea [7], Malaysia [3], Singapore [2], Taiwan [11], Thailand [4], Turkey [4]), South America (Argentina [5], Brazil [13], Chile [3]) and Oceania (Australia [23] and New Zealand [4]).[3]

Figure 6.2: PROSPER Trial Study Design



Source: EMA Assessment Report[52]

Table 7: Protocol Amendments in the PROSPER

Protocol version (date)	Amendment Description
Amendment 1	Clarification of requirements for continuing the use of BTAs during the study; provide the rationale for why disease progression did not mandate discontinuing the study treatment; provide information on the method for calculating PSA DT; provide the rationale for allowing the use of concomitant medications that lowered the seizure threshold, and to clarify the determination of radiographic events for the analysis of MFS.

Protocol version (date)	Amendment Description
Amendment 2	Revise timing and plan for the analyses of the primary endpoint (i.e., MFS) and secondary endpoints, based on results from three studies (STRIVE, PREVAIL, and TERRAIN).The statistical analysis plan was updated to decouple the MFS analysis and the final OS analysis, resulting in reduced target sample size and target hazard ratio for MFS required fewer events.
Amendment 3	Revised testing methodology for the key secondary endpoints (OS and time to PSA progression). The analysis of OS was revised to have a secured type I error rate and would be tested regardless of the outcome from the remaining key secondary endpoints and time to PSA progression would be tested at a lower type I error rate (0.02).

BTA = bone targeting agent; MFS = metastasis-free survival; OS = overall survival; PSA = prostate-specific antigen; PSA DT = prostate-specific antigen doubling time

Source: Clinical Study Report Synopsis[3]

b) Populations

There were 1401 patients randomized to receive enzalutamide (933) or placebo (468) in the PROSPER study. Patients enrolled at 254 sites in 32 countries across North America, South America, Europe, Asia, and Australia.[3] There were 99 patients enrolled at the 15 Canadian sites (7.1%).[1]

Baseline and demographic characteristics for patients enrolled in the PROSPER study are summarized in Table 8. Overall, the baseline characteristics were well balanced between the enzalutamide and placebo groups. The median age in the ITT population was 74 and 73 years in the enzalutamide and placebo groups, respectively.[4] The median PSA doubling time at baseline was 3.8 months in the enzalutamide group and 3.6 months in the placebo group.[4] The proportion of patients with a PSA doubling time of less than six months was 77% in both treatment groups.[4] Bone-targeting agents were being used by 11% of patients in the enzalutamide group and 10% of those in the placebo group.[4]

Table 8: Baseline Characteristics from the PROSPER Study

Characteristic		Enzalutamide (N = 933)	Placebo (N = 468)
Age (years)	Mean	73.8 (7.83)	72.9 (7.63)
	Median (range)	74 (50 to 95)	73 (53 to 92)
Race/Ethnicity	Asian	142 (15.2)	88 (18.8)
	African American	21 (2.3)	10 (2.1)
	Native Hawaiian/ Pacific Islander	3 (0.3)	2 (0.4)
	White	671 (71.9)	320 (68.4)
	Multiple	4 (0.4)	4 (0.9)
	Other	15 (1.6)	5 (1.1)
	Missing	77 (8.3)	39 (8.3)
ECOG performance-status score	0	747 (80.1)	382 (81.6)
	1	185 (19.8)	85 (18.2)
	Missing data	1 (0.1)	1 (0.2)
Serum PSA (ng/ml)	Median (range)	11.1 (0.8 to 1071.1)	10.2 (0.2 to 467.5)
	Median (range)	3.8 (0.4 to 37.4)	3.6 (0.5 to 71.8)

Characteristic		Enzalutamide (N = 933)	Placebo (N = 468)
PSA doubling time (months)	<6 months	715 (76.6)	361 (77.1)
	≥6 months	217 (23.3)	107 (22.9)
	Missing data	1 (<0.1)	0
Months from diagnosis to randomization	Mean (SD)	99.1 (57.27)	94.1 (56.73)
	Median (range)	90.4 (2.2 to 381.8)	86.8 (2.2 to 275.7)
Use of bone-targeting agent, n (%)	No	828 (88.7)	420 (89.7)
	Yes	105 (11.3)	48 (10.3)
Total Gleason score group, n (%)	Low (2 to 4)	21 (2.3)	12 (2.6)
	Medium (5 to 7)	491 (52.6)	230 (49.1)
	High (8 to 10)	381 (40.8)	207 (44.2)
	Unknown	40 (4.3)	19 (4.1)

ECOG = Eastern Cooperative Oncology Group; n = number of patients with results; N = total number of patients; PSA = prostate specific antigen; SD = standard deviation
Sources: clinicaltrials.gov;[2] EMA Assessment Report[52]

Prior Exposure to Prostate Cancer Therapies

Table 9 provides a summary of the prior prostate cancer treatments used by patients enrolled in the PROSPER study. 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 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). No previous prostate cancer treatments were reported for 3.4% in the enzalutamide group and 5.1% in the placebo group.[1]

Table 9: Overall Summary of Prior Prostate Cancer Therapy; Intent-to-treat Population

Prior therapies, n (%)		Enzalutamide (N = 933)	Placebo (N = 468)
Number of unique prior prostate cancer therapies	0	32 (3.4)	24 (5.1)
	1	296 (31.7)	135 (28.8)
	2	329 (35.3)	146 (31.2)
	3	179 (19.2)	94 (20.1)
	≥4	97 (10.4)	69 (14.7)
Number of unique prior hormonal therapies	0	34 (3.6)	24 (5.1)
	1	320 (34.3)	142 (30.3)
	2	339 (36.3)	151 (32.3)
	3	164 (17.6)	101 (21.6)
	≥4	76 (8.1)	50 (10.7)
Prior non-hormonal therapy use	Yes	93 (10.0)	42 (9.0)
	No	840 (90.0)	426 (91.0)
Use of bone-targeting agents at baseline	Yes	20 (2.1)	6 (1.3)
	No	913 (97.9)	462 (98.7)
History of radiotherapy	Yes	434 (46.5)	226 (48.3)
	No	499 (53.5)	242 (51.7)
Prior radiotherapy	External beam	378 (40.5)	204 (43.6)
	Brachytherapy	40 (4.3)	25 (5.3)
	Systemic	27 (2.9)	7 (1.5)
Type of prior radiotherapy	Primary	304 (32.6)	158 (33.8)
	Palliative	26 (2.8)	20 (4.3)
	Salvage	114 (12.2)	52 (11.1)

Prior therapies, n (%)		Enzalutamide (N = 933)	Placebo (N = 468)
History of prostate cancer surgery	Yes	493 (52.8)	263 (56.2)
	No	440 (47.2)	205 (43.8)
Type of prior of prostate cancer surgery	Prostatectomy	234 (25.1)	139 (29.7)
	Orchiectomy	119 (12.8)	62 (13.2)
	TURP	83 (8.9)	35 (7.5)
	Cryoablation	3 (0.3)	1 (0.2)
	Nephrostomy tube replacement	4 (0.4)	1 (0.2)
	Other	150 (16.1)	72 (15.4)

n = number of patients with results; N = total number of patients; TURP = Transurethral resection of the prostate
Source: EMA Assessment Report[52]

c) Interventions

Study Treatments

Study participants received four 40 mg capsules (160 mg) of enzalutamide or matching placebo orally once per day (up to a maximum of 42.8 months) until radiographic progression. All patients were required to maintain ongoing androgen deprivation therapy with a GnRH agonist/antagonist or have undergone a prior bilateral orchiectomy. Any patients who experienced a grade 3-4 adverse event that was attributed to study drug and could not be addressed using adequate medical intervention could have had treatment with the study 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 dosage was also reduced to 80 mg per day if the patient was receiving concomitant treatment with a strong cytochrome P450 2C8 inhibitor.

Compliance with the study treatments was evaluated by counting the number of capsules at each study visit and overall compliance was reported to be 96.0% in the enzalutamide group and 98.3% in the placebo group. The proportion of enzalutamide-treated patients who required dose modification in PROSPER was 17.4% compared with 10.8% in the placebo group. The proportion of patients who required a dose reduction due to adverse events was greater in the enzalutamide group compared with the placebo group (10.1% versus 2.8%, respectively). Similarly, the proportion of patients dose interruptions was greater in the enzalutamide group compared with the placebo group (15.4% versus 8.6%, respectively).[52]

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

Table 10 provides a summary of the post-baseline systematic therapies for prostate cancer that were initiated by patients in the PROSPER study. A greater proportion of placebo-treated patients initiated treatment with at least one post-baseline antineoplastic treatment for prostate cancer compared with enzalutamide-treated patients (55.5% versus 26.2%).[1]

Table 10: Post-baseline systemic therapies for prostate cancer in the PROSPER trial

Subsequent systemic therapies, n (%)	Enzalutamide (N = 930)	Placebo (N = 465)
≥1 post-baseline antineoplastic treatment	244 (26.2)	258 (55.5)
Antineoplastic agents	89 (9.6)	98 (21.1)
Docetaxel	72 (7.7)	94 (20.2)

Subsequent systemic therapies, n (%)	Enzalutamide (N = 930)	Placebo (N = 465)
Corticosteroids for systemic use	36 (3.9)	65 (14.0)
Prednisone	21 (2.3)	38 (8.2)
Drugs for treatment of bone diseases	44 (4.7)	64 (13.8)
Denosumab	25 (2.7)	38 (8.2)
Zoledronic acid	21 (2.3)	26 (5.6)
Endocrine therapy	167 (18.0)	185 (39.8)
Abiraterone	65 (7.0)	129 (27.7)
Leuprorelin	49 (5.3)	21 (4.5)
Bicalutamide	15 (1.6)	29 (6.2)
Sex hormones and modulators of the genital system	23 (2.5)	56 (12.0)
Antiandrogens	20 (2.2)	51 (11.0)
n = number of patients with results; N = total number of patients **Source:** Clinical Study Report[1]		

d) Outcomes

Primary Endpoint

MFS was the primary endpoint of the PROSPER study and was defined as the time from randomization to the time radiographic progression or death within 112 days of treatment discontinuation without evidence of radiographic progression (whichever occurred first).[2] Assessments were scheduled for every 16 weeks and included whole-body radionuclide scans for bone and soft tissue disease by CT scan or MRI.[4]

Radiographic progression was defined as:

- Bone disease - the appearance of at least one metastatic lesion on bone scan. When bone lesions were found in a single region, confirmation was required using a second imaging modality (e.g., plain film, CT, or MRI). Appearance of metastatic lesions in 2 or more of the 5 regions on a bone scan did not require the additional confirmation step.
- Soft tissue disease - as defined by RECIST 1.1.

The primary analysis also included any events that were detected in unscheduled scans.[4] The radiographic data were evaluated by a BICR.[2] MFS data were censored for patients without known radiographic or death at the time of the data cut-off (June 28, 2017).[2] The analyses of MFS and all secondary endpoints were conducted when approximately 440 MFS events had been reported.[4]

Key secondary endpoints

The following were pre-specified key secondary endpoints of the PROSPER study:[4]

- Time to PSA progression was defined as the time from randomization to the time of first PSA value demonstrating progression, which was subsequently confirmed. PSA progression was defined according to Prostate Cancer Working Group 2 (PCWG2) guidelines (time to a ≥25% increase and an absolute increase of 2 ng/mL).[2]
- OS was defined as the time from randomization to death from any cause.[2]
- Time to first use of new antineoplastic therapy was defined as the time from randomization the time of first usage of a new antineoplastic for prostate cancer.[2]

For all of the endpoints noted above, patients who did not have an event prior to the data cut-off were censored at the time of their last assessment.[2]

Exploratory Secondary Endpoints

The following were exploratory secondary endpoints in the PROSPER study:[2]

- Pain progression was defined as an increase from baseline of at least two points in question 3 of the BPI-SF question 3 (i.e., self-rated worst pain score in the last 24 hours). Time to pain progression was defined as the time from randomization to onset of pain progression.
- Chemotherapy-free disease-specific survival was defined as the time from randomization to first use of cytotoxic chemotherapy for prostate cancer or death due to prostate cancer as assessed by the investigator.
- Chemotherapy-free survival was defined as the time from randomization to first use of cytotoxic chemotherapy for prostate cancer or death due to any cause.
- PSA responses were defined as a maximal decline from baseline in PSA of ≥50%, ≥90%, or to an undetectable level (i.e., below the lower limit of quantification of 0.02 ng/mL). PSA responses were to be confirmed by a second consecutive value at least three weeks later. Patients with missing PSA values were assumed to be non-responders.
- The Functional Assessment of Cancer Therapy – Prostate (FACT-P) is a disease-specific, 27-item, self-reported instrument used to assess the quality-of-life of patients with prostate cancer. The questionnaire has four domains (physical, social/family, emotional, and functional well-being). Each item is scored using a four-point Likert scale. Missing data were excluded from the analysis of FACT-P scores. The time to degradation in FACT-P global score was defined as the time from randomization to a decrease of ≥10-point from baseline in the FACT-P global score.
- The European Quality of Life-5 Dimensions-5 Levels health Questionnaire (EQ-5D-5L) is a standardized instrument for evaluating health-related quality of life. Patients self-reported on their current mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item was scored using a five-point scale ranging from 5 (no problem) to 0 (extreme problem).
- The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Prostate 25 module (QLQ-PR25) was also used to assess the quality of life of patients enrolled in the trial. Patients self-rated the following items: pain related to urination, ease and frequency of urination, bowel and other problems, changes in body weight, sexual interest, and sexual activity. Items are scored using a four-point scale ranging from "not at all to "very much" within each dimension. Missing data were excluded from the analysis.[4]

For all of the time to event endpoints noted above, patients who did not have an event prior to the data cut-off were censored at the time of their last assessment.[2]

e) Statistical Analyses

Table 11 provides an overview of the statistical approaches used for the primary, key secondary, and secondary endpoints in the PROSPER trial. Hazard ratios for all time to event endpoints were obtained using Cox regression model with treatment as covariate and stratified by PSA DT (<6 or ≥6 months) and prior or current use of a bone-targeting therapy (yes or no). The placebo and enzalutamide groups were compared using a log-rank test that was stratified by the above noted characteristics. Differences in PSA response rates were compared using Cochran-Mantel-Haenszel test of means, with the same stratification factors as the other endpoints (i.e., baseline PSA DT and use of bone-targeting agent). There were no statistical analyses reported for changes in EQ-5D-5L or QLQ-PR25. All efficacy analyses were conducted using the ITT population.

Table 11: Overview of Statistical Analyses in the PROSPER trial

Endpoint	Statistical Approach	Statistical test	Adjustment Factors	Sensitivity Analyses
Primary Endpoint				
• Metastases-free survival	HR from Cox regression model	Stratified log-rank test	• PSA DT (<6 vs. ≥6 months) • Prior or current BTA use (yes vs. no)	• Including progression after alternative therapy as an event • Including post treatment deaths • Impact of antineoplastic therapies • Event based on investigator assessment • Impact of clinical deterioration
Key secondary endpoints				
• Time to PSA progression • Overall survival • Time to first use of new antineoplastic therapy	HR from Cox regression model	Stratified log-rank test	• PSA DT (<6 vs. ≥6 months) • Prior or current BTA use (yes vs. no)	None conducted
Secondary endpoints				
• Time to pain progression • Chemotherapy-free disease-specific survival • Chemotherapy-free survival • Time to degradation in FACT-P • Time to first use of cytotoxic chemotherapy	HR from Cox regression model	Stratified log-rank test	• PSA DT (<6 vs. ≥6 months) • Prior or current BTA use (yes vs. no)	None conducted
• Time to confirmed degradation in FACT-P	HR from Cox regression model	Not reported	Not reported	Not reported
• Change from baseline in FACT-P	MMRM	95% CI did not include zero	Not reported	Not reported
• PSA response rates	Difference in response rate	CMH mean score test	• PSA DT (<6 vs. ≥6 months) • Prior or current BTA use (yes vs. no)	None conducted
• EQ-5D-5L	No statistical analyses			
• QLQ-PR25	No statistical analyses			

BTA = bone-targeting agents; **CMH** = Cochran-Mantel-Haenszel; **EQ-5D-5L** = European Quality of Life-5 Dimensions-5 Levels health Questionnaire; **FACT-P** = Functional Assessment of Cancer Therapy-Prostate; **HR** = hazard ratio; **PSA** = Prostate-specific antigen; **QLQ-PR25** = Quality of Life Questionnaire-Prostate 25 module
Sources: clinicaltrials.gov;[2] Hussain et al., 2018;[4] Attard et al., 2018;[17] Saad et al., 2018[39]; EMA Assessment Report[52]

Adjustment for Multiplicity

The analyses for the primary and key secondary endpoints were conducted in accordance with a pre-specified statistical testing hierarchy:[2,4]

1. The difference between enzalutamide and placebo in MFS was tested first at a 0.05 significance level.
2. If enzalutamide was superior to placebo for MFS, time to PSA progression was tested at a 0.02 significance level.
3. If enzalutamide was superior to placebo for time to PSA progression, time to first use of new antineoplastic therapy was subsequently test at a 0.02 significance level.
4. The difference between enzalutamide and placebo for overall survival was tested at a 0.05 significance level if the analyses for time to PSA progression and time to first use of new antineoplastic therapy were statistically significant. If one of both of those endpoints failed to demonstrate statistical significance, overall survival was tested at a 0.03 significance level.

The analysis plan for overall survival consists of three interim analyses (135, 285, and 440 events) and a final analysis (596 events). If any of the interim analyses demonstrate statistical significance it would be declared the final analysis and no further testing would be conducted. To maintain the overall type 1 error rate, the significance levels specified in Table 12 were used in the PROSPER study. All other endpoints were analyzed without adjustment for multiplicity, including sensitivity analyses and subgroup analyses performed for the primary endpoint.

Table 12: Analyses for Overall Survival

Analysis	Events	Error Rate	
		0.03	0.05
First interim	135	0.001	0.001
Second interim	285	0.001	0.002
Third interim	440	0.009	0.018
Final analysis	596	0.026	0.044
Source: EMA Assessment Report[52]			

f) Patient Disposition

Patient disposition for the PROSPER study is summarized in Table 13. A total of 1401 patients were randomized (2:1) to receive enzalutamide (n = 933) or placebo (n = 468). Nearly all patients received at least one dose or partial dose of the study treatments (99.7% and 99.4% in the enzalutamide and placebo groups, respectively).[2] A greater proportion of patients in the placebo group discontinued treatment compared with those in the enzalutamide group (61.8% versus 31.7%). Disease progression was the most commonly cited reason for discontinuation in both groups (14.8% in the enzalutamide group and 44.2% in the placebo group). Discontinuation due to PSA progression was reported for 0.3% of enzalutamide-treated patients compared with 2.4% of placebo-treated patients.[1]

Table 13: Patient Disposition from PROSPER

Disposition, n (%)	Enzalutamide	Placebo
Randomized	933	468
Treated	930 (99.7)	465 (99.4)
Ongoing in study	634 (68.0)	176 (37.6)
Discontinued intervention	296 (31.7)	289 (61.8)
Disease progression	138 (14.8)	207 (44.2)
Radiographic progression	135 (14.5)	196 (41.9)

Disposition, n (%)	Enzalutamide	Placebo
PSA progression	3 (0.3)	11 (2.4)
Protocol violation	1 (0.1)	2 (0.4)
Lost to follow-up	2 (0.2)	1 (0.2)
Other than specified	18 (1.9)	19 (4.1)
Withdrawal by subject	49 (5.3)	34 (7.3)
Adverse event	91 (9.8)	29 (6.2)
Ongoing long-term follow-up	174 (18.6)	211 (45.1)
Discontinued from long-term follow-up	125 (13.4)	81 (17.3)
Death	103 (11.0)	62 (13.2)
Withdrawal by subject	19 (2.0)	17 (3.6)
Lost to follow-up	2 (0.2)	0 (0.0)
Other	1 (0.1)	2 (0.4)
Study terminated by sponsor	0 (0.0)	0 (0.0)
Major protocol deviation	54 (5.8)	24 (5.1)
Eligibility criteria were not met	20 (2.1)	15 (3.2)
Received excluded concomitant medication	19 (2.0)	6 (1.3)
Received the wrong treatment	7 (0.8)	0 (0.0)
Did not receive required concomitant medication	5 (0.5)	1 (0.2)
Did not discontinue per protocol	2 (0.2)	0 (0.0)
Received incorrect dose	1 (0.1)	1 (0.2)
Procedures performed before consent	0 (0.0)	1 (0.2)

PSA = prostate-specific antigen
Sources: clinicaltrials.gov;[2] EMA Assessment Report[52]

g) Limitations/Sources of Bias

Internal Validity

Overall, PROSPER is a well-designed and well-conducted RCT. Randomization was conducted centrally using appropriate methods with adequate measures to conceal treatment allocation (i.e., interactive voice/web response system [IXRS]).[2] The number of patients randomized into the enzalutamide (933) and placebo groups (468) reflected the planned 2:1 ratio for the PROSPER study.[4] Randomization was stratified by PSA doubling-time (< 6 months or ≥ 6 months) and use of a bone-targeting agent (yes or no).[4] These are relevant prognostic factors for patients with high risk nmCRPC and were also used in the pivotal trial for apalutamide (SPARTAN).[54] The SPARTAN trial also included loco-regional disease (N0 or N1) as a stratification factor; whereas, the PROSPER trial was limited to patients with N0 disease. The CGP indicated that the stratification factors used in PROSPER were appropriate. Reviewers for the EMA noted that stratification according to region would have been appropriate, but subgroup analyses did not demonstrate any important differences according to region (see Figure 6.3).[52]

The treatment groups were generally well-balanced with respect to key baseline and demographic characteristics. Median time from diagnosis to randomization was slightly greater in the enzalutamide group compared with the placebo (90.4 versus 86.8 months).[1] The CGP indicated that this difference is not likely to be clinically relevant in context of patients with nmCRPC. The proportion of patients with a total Gleason between 8 and 10 (i.e., high) at baseline was slightly greater in the placebo group compared with the enzalutamide group (44.2% versus 40.8%).[1] As such patients are at greater risk for disease progression, the GCP indicated that this difference could have an impact on the study results of the PROSPER trial.

Study treatments were administered in a double-blind manner with both the enzalutamide and placebo groups being issued the same number of tablets.[4] The active and placebo tablets were identical in appearance.[4] Fatigue is a known adverse event associated with enzalutamide treatment and a greater proportion of those who received the active treatment reported fatigue compared with placebo (32.5% versus 13.6%).[2] Hence, it is possible that some patients/investigators may have been able to make inferences regarding the allocated treatment. Reviewers for the EMA also noted that differences in PSA progression could have an impact on blinding.[52] The CGP indicated that the adverse event profile of enzalutamide could compromise blinding for some patients and study personnel; however, the difference was not considered to have substantially affected the internal validity of the PROSPER study. In addition, the primary endpoint was evaluated by a BICR.

Reviewers for the FDA have previously stated that MFS is considered to be an appropriate primary endpoint in the setting of nmCRPC as long as it was of sufficient magnitude and was accompanied by data from supportive secondary endpoints such as overall survival.[55] In the PROSPER study the primary efficacy endpoint (i.e., MFS) was evaluated by a BICR, which is an accepted strategy to reduce potential bias in the interpretation of the radiographic data[56] and aligned with scientific advice from the EMA.[52] The CGP consulted by the pCODR Methods Team indicated that the use of a BICR is an important strength of the PROSPER study, as there can be considerable variation in routine clinical practice regarding whether or not a patient with nmCRPC has experience disease progression.

Patient disposition was thoroughly documented and well reported by the submitter. Major protocol deviations were balanced across the two treatment groups; reviewers for the EMA noted that no important biases were identified with the violations.[52] The CGP noted that similar rates of discontinuation due to adverse events would be anticipated in routine practice with enzalutamide. Compliance with the study treatments was evaluated by counting the number of capsules at each study visit and overall compliance was reported to be 96.0% in the enzalutamide group and 98.3% in the placebo group.[1] The CGP indicated that compliance rates in routine practice may be lower than those reported in the PROSPER study.

Statistical power calculations were reported for PROSPER;[4] enrolment was slightly below the target number (i.e., 1401 versus 1440), but sufficient to observe the number the events required for the primary endpoint. Statistical tests for all endpoints, with the exception of the primary and key secondary endpoints, were conducted without adjustment multiple comparisons; therefore, the findings should be considered hypothesis generating because of the risk of type I error.[4] Exploratory subgroup analyses were pre-specified in the protocol for the PROSPER study and investigated treatment effects based on relevant patient characteristics (e.g., PSA doubling-time).[4]

Fractures were adverse event of interest for CGP. The EMA noted that the study protocol did not include classification of fractures as being non-pathological or pathological; therefore the distinction between these events could not be reliably elucidated from the trial data.[52]

External Validity

The CGP noted that the eligibility criteria for PROSPER were appropriate and would not have excluded relevant patient populations. The CGP noted that the definition for high-risk patients based on PSA doubling-time of ≤10 months, that was used in the PROSPER, was reasonable. Based on the baseline demographic and disease characteristics, the CGP indicated that the patient population of the PROSPER study was a reasonable reflection of the target population in Canada. It was noted that the proportion of patients who had undergone a bilateral orchiectomy (approximately 13%)[1] would be lower in Canadian practice, but this would not be expected to compromise the generalizability of the study results to the Canadian setting.

To be eligible for enrollment in PROSPER patients could not have a history of seizure or any condition that may have predisposed them to seizures.[4] There is currently a black box warning regarding the risk of seizure in the Canadian product monograph for enzalutamide[51] and the CGP indicated that patients would be screened for a risk of seizure prior to initiating treatment with enzalutamide. Hence, the exclusion of these patients is reflective of routine practice in Canada.

The CGP also stated that MFS is a clinically relevant endpoint for patients with nmCRPC, noting that progression to metastatic disease is often associated with decreased quality of life for those living with the condition (e.g., need for cytotoxic therapies, pain, anxiety). Similar comments were made by the EMA's Scientific Advisory Group on Oncology which included patient perspectives.[52]

The GCP indicated that the protocol for dosage adjustment that was used in the PROSPER study was generally reflective of what would occur in routine clinical practice. However, it was noted that the proportion of enzalutamide-treated patients who required dose modification in PROSPER (17.4%) may be lower than what has been observed in clinical practice with enzalutamide. However, treatment is currently limited to patients with metastatic disease and, as such, clinical experience is based on patients who are less healthy than those enrolled in the PROSPER study (i.e., nmCRPC).

As noted above, the use of a BICR for evaluating disease progression can be an important strength in terms of the internal validity of a trial conducted in patients with nmCRPC. However, the use of a centralized reviewer is not reflective of routine clinical practice where individual physicians and healthcare teams would make the determination regarding whether or not a patient has experienced disease progression.

Patients were enrolled at 254 sites in 32 countries across North America, South America, Europe, Asia, and Australia and 7.1% of the participants were enrolled at 15 Canadian sites.[1,3] Results were similar across the subgroup analyses conducted for geographic regions (**Error! Reference source not found.**) and the CGP noted that clinical practice would not be expected to vary substantially across the different regions, particularly for nmCRPC where the current standard of care would simply be to continue treatment with ADT until disease progression has been observed.

The PROSPER study was designed solely to investigate the safety and efficacy of enzalutamide treatment in the non-metastatic setting and does not provide insight into the optimal sequencing of enzalutamide treatment in patients with prostate cancer (i.e., prior to or after diagnosis of metastatic disease).

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Metastasis-Free Survival (MFS)

Time to MFS was the primary endpoint of the PROSPER study and the results are summarized in Table 14. The proportion of patients who experienced metastases or died during the study was lower in the enzalutamide group compared with the placebo group (23.5% versus 48.7%). Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for metastases or death during the study compared with placebo (HR = 0.292 [95% CI, 0.241 to 0.352]; p < 0.0001). The median time to event was 36.6 months (95% CI, 33.1 to NYR) in the enzalutamide group and 14.7 months (95% CI, 14.2 to 15.0) in the placebo group.

Results of the sensitivity analyses were similar to those reported for the primary analyses of MFS. Subgroup analyses were conducted for MFS based on the following characteristics: PSA DT (<6 months versus ≥6 months); baseline use of BTA (yes versus no); baseline age (≤ or > the median age of 74 Years); baseline ECOG Performance Status (0 or 1); geographic region (North America, Europe, and the rest of the world); total Gleason Score at Diagnosis (≤7 or ≥8); baseline PSA value (≤ or < the median value of 10.73 ug/L). The results are summarized in Figure 6.3. Enzalutamide was superior to placebo across all subgroup analyses.

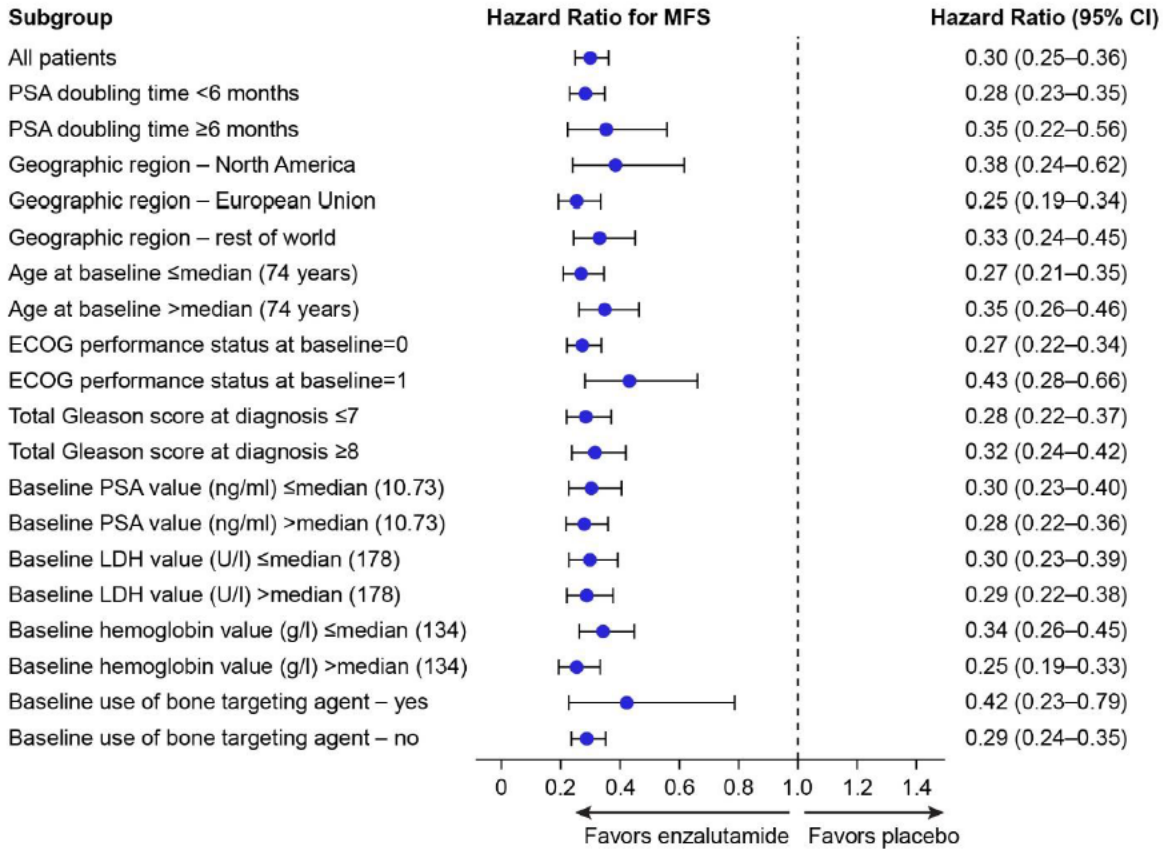
Table 14: Metastasis-Free Survival from the PROSPER Study

Analysis		Enzalutamide (N = 933)	Placebo (N = 468)
Primary analysis	Patients with events (%)	219 (23.5)	228 (48.7)
	Median time to event (95% CI)	36.6 (33.1 to NYR)	14.7 (14.2 to 15.0)
	HR (95% CI)	0.292 (0.241 to 0.352)	
	P value	<0.0001	
Sensitivity analysis 1 (Inclusion of progression after alternative therapy as an event)	Patients with events (%)	Not disclosable	Not disclosable
	Median time to event (95% CI)	Not disclosable	Not disclosable
	HR (95% CI)	0.30 (0.25 to 0.36)	
	P value	Not disclosable	
Sensitivity analysis 2 (Inclusion of any post-treatment death as an event)	Patients with events (%)	230 (25)	234 (50)
	Median time to event (95% CI)	36.0 (Not disclosable)	14.7 (Not disclosable)
	HR (95% CI)	0.296 (0.246 to 0.357)	
	P value	Not disclosable	
Sensitivity analysis 3 (Censoring patients who received any antineoplastic therapy without evidence of metastasis)	Patients with events (%)	Not disclosable	Not disclosable
	Median time to event (95% CI)	Not disclosable	Not disclosable
	HR (95% CI)	0.28 (0.23 to 0.33)	
	P value	Not disclosable	
Sensitivity analysis 4 (MFS based on Investigator assessment)	Patients with events (%)	Not disclosable	Not disclosable
	Median time to event (95% CI)	Not disclosable	Not disclosable
	HR (95% CI)	0.32 (0.26 to 0.39)	
	P value	Not disclosable	
Sensitivity analysis 5 (Impact of clinical deterioration for patients who discontinued study drug primarily due to AE defined by investigator prior to protocol-defined evidence of radiographic deterioration)	Patients with events (%)	Not disclosable	Not disclosable
	Median time to event (95% CI)	Not disclosable	Not disclosable
	HR (95% CI)	0.33 (0.28 to 0.39)	
	P value	Not disclosable	

CI = confidence interval; HR = hazard ratio; NYR = not yet reached

Analysis		Enzalutamide (N = 933)	Placebo (N = 468)
P-value calculated using a stratified log-rank test by PSA doubling time (< 6 months and ≥ 6 months) and prior/concurrent use of a bone targeting agent (yes or no). HR was calculated using a Cox regression model (with treatment as covariate) stratified by PSA doubling time (< 6 months and ≥ 6 months) and prior/concurrent use of a bone targeting agent (yes or no). **Source:** EMA Assessment Report[52]			

Figure 6.3: Subgroup Analyses for MFS from the PROSPER Study



CI denotes confidence interval, ECOG Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, MFS metastasis-free survival, PSA prostate-specific antigen.

From: N Engl J Med, Hussain M, Fizazi K, Saad F, et al., Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer, 378(26):2465-2474. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Overall Survival (OS)

Overall survival was a pre-specified key secondary endpoint of the PROSPER study. As shown in Table 15, 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 0.832 [95% CI, 0.654 to 1.059], respectively).[2,5] In first interim analysis, 103 patients (11%) in the enzalutamide group had died compared with 62 (13.2%) of those in placebo group.[4] At the second interim analysis, 184 patients (19.7%) and 104 patients (22.2%) had died in the enzalutamide and placebo groups, respectively.[5] 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.[2,4,5]

Table 15: Overall Survival from the PROSPER Study

Overall Survival	Enzalutamide (N = 933)	Placebo (N = 468)
First interim analysis		
Patients with event (%)	103 (11.0%)	62 (13.2%)
Median, months (95% CI)	NYR (NYR to NYR)	NYR (NYR to NYR)
HR (95% CI)	0.795 (0.580 to 1.089)	
p-value	0.1519	
Second interim analysis		
Patients with event (%)	184 (19.7)	104 (22.2)
Median, months (95% CI)	NYR (49.9 to NYR)	NYR (49.4 to NYR)
HR (95% CI)	0.832 (0.654 to 1.059)	
p-value	0.1344	

CI = confidence interval; HR = hazard ratio; NYR = not yet reached

Sources: EMA Assessment Report;[52] clinicaltrials.gov;[2] Clinical Summary[5]

Time to PSA progression

Time to PSA progression was a pre-specified secondary endpoint of the PROSPER study and the results are summarized in Table 16. The proportion of patients who experienced PSA progression during the study was lower in the enzalutamide group compared with the placebo group (22.3% versus 69.2%).[3] Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for PSA progression during the study (HR = 0.066 [95% CI, 0.054 to 0.081]; $p < 0.0001$).[2] The median time to PSA progression was 37.2 months (95% CI, 33.1 and not reached) in the enzalutamide group and 3.9 months (95% CI, 3.8 to 4.0) in the placebo group.[2]

Table 16: Time to PSA progression from the PROSPER Study

Time to PSA progression	Enzalutamide (N = 933)	Placebo (N = 468)
Number of events (%)	208 (22.3)	324 (69.2)
Median time to event, months (95% CI)	37.2 (33.1 to NYR)	3.9 (3.8 to 4.0)
HR (95% CI)	0.066 (0.054 to 0.081)	
p-value	< 0.0001	

CI = confidence interval; HR = hazard ratio; NYR = not yet reached; PSA = prostate specific antigen
Sources: EMA Assessment Report[52]

Time to first use of new antineoplastic therapy

Table 17 provides a summary of the results for to first use of new antineoplastic therapy and time to initiation of cytotoxic chemotherapy (both were secondary endpoints of the PROSPER study). The proportion of patients who initiated treatment with a new antineoplastic therapy during the study was lower in the enzalutamide group (15.2%) compared with the placebo group (48.3%).[1] Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for initiating a new antineoplastic therapy during the study (HR = 0.208 [95% CI, 0.168 to 0.258)]; p < 0.0001).[2] The median time to first use of a new antineoplastic therapy was 39.6 months in the enzalutamide group and 17.7 months in the placebo group.[2]

The proportion of patients who initiated treatment with cytotoxic chemotherapy during the study was lower in the enzalutamide group (9.1%) compared with the placebo group (20.5%).[1] Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for initiating use of cytotoxic chemotherapy during the study (HR = 0.38 [95% CI, 0.28 to 0.51]; p < 0.0001).[2] The median time to initiating cytotoxic chemotherapy was 39.7 months (95% CI, 38.9 to 41.3) in the placebo group and was not reached in the enzalutamide group.[2]

Table 17: Time to first use of new antineoplastic therapy or cytotoxic chemotherapy from the PROSPER Study

Endpoint	Enzalutamide (N = 933)	Placebo (N = 468)
Use of new antineoplastic therapy		
Number of events (%)	142 (15.2)	226 (48.3)
Median time to event, months (95% CI)	39.6 (37.7 to NYR)	17.7 (16.2 to 19.7)
HR (95% CI)	0.208 (0.168 to 0.258)	
p-value	<0.0001	
Use of cytotoxic chemotherapy		
Number of events (%)	85 (9.1)	96 (20.5)
Median time to event, months (95% CI)	NYR (38.1 to NYR)	39.7 (38.9 to 41.3)
HR (95% CI)	0.38 (0.28 to 0.51)	
p-value	< 0.0001	

CI = confidence interval; **HR** = hazard ratio; **n** = number of patients with results; **N** = total number of patients; **NYR** = not yet reached
Source: clinicaltrials.gov;[2] Clinical Study Report Synopsis[3]

Time to pain progression

Time to pain progression was a secondary endpoint of the PROSPER study. Pain progression was defined as increase from baseline of at least two points on the BPI-SF self-rated pain scale. As shown in **Table 18**, there was no statistically significant difference between the enzalutamide and placebo groups for time to pain progression (0.959 [95% CI, 0.801 to 1.149]; p = 0.6534).[2] The median time to pain progression was 18.5 months (95% CI, 17.0 to 22.1) in the enzalutamide group and 18.4 months (95% CI, 14.8 to 22.1) in the placebo group.[2]

Table 18: Time to pain progression from the PROSPER Study

Time to pain progression	Enzalutamide (N = 933)	Placebo (N = 468)
Number of events (%)	399 (42.8)	175 (37.4)
Median time to event, months (95% CI)	18.5 (17.0 to 22.1)	18.4 (14.8 to 22.1)

Time to pain progression	Enzalutamide (N = 933)	Placebo (N = 468)
HR (95% CI)	0.959 (0.801 to 1.149)	
p-value	0.6534	
CI = confidence interval; HR = hazard ratio; n = number of patients with results; N = total number of patients Source: clinicaltrials.gov;[2] Clinical Study Report Synopsis[3]		

Chemotherapy-free survival

Chemotherapy-free survival and chemotherapy-free disease-specific survival were secondary endpoints of the PROSPER study and the results are summarized in Table 19. Chemotherapy-free survival included events of initiating chemotherapy and all-cause mortality, which occurred in a lower proportion of enzalutamide-treated patients compared with placebo-treated patients (16.8% versus 28.2%).[1] Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for initiating chemotherapy or death (HR: 0.50 [95% CI, 0.40 to 0.64]; p < 0.0001).[3] The median time to event was 38.1 months (95% CI, 37.7 to NYR) in the enzalutamide group and 34.0 months (95% CI, 30.3 to 39.7) in the placebo group.[2]

Treatment with enzalutamide was also associated with a statistically significant reduction in the hazard for initiating chemotherapy or death due to prostate cancer (HR: 0.398 [95% CI, 0.307 0.515[; p < 0.0001).[3]

Table 19: Chemotherapy-free survival from the PROSPER Study

	Enzalutamide (N = 933)	Placebo (N = 468)
Chemotherapy-free survival		
Number of events (%)	157 (16.8)	132 (28.2)
Median time to event, months (95% CI)	38.1 (37.7 to NYR)	34.0 (30.3 to 39.7)
HR (95% CI)	0.504 (0.400 to 0.636)	
p-value	<0.0001	
Chemotherapy-free disease-specific survival		
Number of events (%)	112 (12.0)	119 (25.4)
Median time to event, months (95% CI)	39.6 (37.7 to NYR)	38.9 (30.9 to 41.3)
HR (95% CI)	0.398 (0.307, to 0.515)	
p-value	<0.0001	
CI = confidence interval; HR = hazard ratio; n = number of patients with results; N = total number of patients; NYR = not yet reached Source: clinicaltrials.gov;[2] Clinical Study Report Synopsis[3]		

Prostate Specific Antigen (PSA) response rate

As shown in Table 20, a statistically significantly greater proportion of enzalutamide-treated patients had reductions in PSA from baseline of at least 50% (RD: 73.96% [95% CI, 70.91 to 77.02]), 90% (55.52% [95% CI, 52.28 to 58.76]), or to an undetectable level (RD: 9.65% [95% CI, 7.75 to 11.54]).[2] The proportion of patients with missing PSA baseline values (0% with enzalutamide and 0.2% with placebo) and missing post-baseline values (4.9% with enzalutamide and 6.0% with placebo) was similar between the groups.[1]

Table 20: Prostate Specific Antigen Response Rates from the PROSPER Study

PSA Responder Analyses	PSA Response, n (%)		Enzalutamide versus placebo	
	Enzalutamide	Placebo	RD (95% CI)	p-value
≥ 50% decrease from baseline	712 (76.3%)	11 (2.4%)	73.96 (70.91 to 77.02)	<0.0001
≥ 90% decrease from baseline	522 (55.9%)	2 (0.4%)	55.52 (52.28 to 58.76)	<0.0001
Decrease to undetectable level	90 (9.6%)	0 (0.0%)	9.65 (7.75 to 11.54)	<0.0001

P-value was based on a Cochran-Mantel-Haenszel mean score test stratified by PSA doubling time (<6 or ≥ 6 months) and prior concurrent use of a bone targeting agent (yes or no).
CI = confidence interval; n = number of patients with event; PSA = prostate specific antigen; RD = risk difference
Source: clinicaltrials.gov[2]

Quality of Life

FACT-P Questionnaire

Baseline FACT-P total scores were reported to be comparable between the study arms, however, this was only reported descriptively.[39] Time to degradation in FACT-P global score was an exploratory secondary endpoint of the PROSPER study and was defined as the time from randomization to the first assessment with decrease from baseline of at least 10 points. 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, see Table 22 below. Median treatment duration was 18.4 months and 11.1 months for the enzalutamide and placebo groups, respectively. 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 enzalutamide and placebo groups, respectively, reported quality of life data).[39]

As shown in **Table 21**, the proportion of patients who met the criteria for FACT-P degradation was similar in the enzalutamide group (54%) and the placebo group (51%).[4] 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).[3,4] The manufacturer also reported the results based on 'confirmed' degradation in FACT-P score, which was defined as the time from randomization to the time when the patient has a decrease in FACT-P from baseline of at least 10 points for two consecutive visits. These analyses were reported as conference abstracts and appear to be post-hoc analyses (i.e., they were not listed in the manufacturers pre-planned statistical analysis plan or study protocol). Treatment with enzalutamide was associated with a statistically significant reduction in the hazard for FACT-P degradation compared with placebo (HR: 0.83 [95% CI, 0.69 to 0.99; p = 0.037).

In an exploratory analysis reported in a conference abstract, the manufacturer reported that there was no statistically significant difference between the enzalutamide and placebo groups for change from baseline in FACT-P scores (least squares mean difference 2.03 [95% CI: −0.97 to 5.04]). Unadjusted mean changes in FACT-P scores from baseline to week 177 are also summarized in **Table 21**.

Table 21: Degradation in FACT-P in the PROSPER Study

FACT-P	Enzalutamide (N = 933)	Placebo (N = 468)
FACT-P Degradation[1,3,4]		

FACT-P	Enzalutamide (N = 933)		Placebo (N = 468)	
Patients with FACT-P degradation, n (%)	506 (54.2)		239 (51.1)	
Median time to event, months (95% CI)	11.1 (11.0 to 14.7)		11.1 (11.0 to 12.5)	
HR (95% CI)	0.922 (0.787 to 1.080)			
p-value	0.3128			
Confirmed FACT-P Degradation[17]				
Number of events	376		181	
Median time to event, months (95% CI)	22.11 (18.63, 25.86)		18.43 (14.85, 9.35)	
HR (95% CI)	0.83 (0.69 to 0.99)			
p-value	0.037			
Change from baseline in FACT-P (MMRM)[b39]				
LS mean (SE) change at 97 weeks	−7.17 (0.92)		−9.20 (1.45)	
LS mean difference (95% CI)	2.03 (−0.97 to 5.04)			
Change from baseline[a] (ITT)[2]	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Baseline	887	119.5 (17.75)	439	120.8 (16.73)
Change from baseline at week 17	815	−4.0 (14.03)	403	−3.0 (13.87)
Change at week 33	718	−4.6 (14.82)	329	−3.5 (13.74)
Change at week 49	621	−3.9 (14.70)	239	−5.0 (15.71)
Change at week 65	522	−4.0 (15.84)	183	−5.7 (15.04)
Change at week 81	427	−4.1 (15.01)	139	−7.5 (16.42)
Change at week 97	354	−4.9 (15.31)	90	−5.9 (15.80)
Change at week 113	264	−5.5 (16.07)	68	−5.8 (13.16)
Change at week 129	186	−6.3 (17.33)	37	−8.1 (13.99)
Change at week 145	109	−5.5 (18.75)	17	−9.8 (15.47)
Change at week 161	38	−8.9 (19.88)	6	−7.0 (10.95)
Change at week 177	5	−4.8 (13.19)	1	−5 (NR)

CI = confidence interval; FACT-P = Functional Assessment Cancer Therapy-Prostate; HR = hazard ratio; LS = least squares; n = number of patients with results; N = total number of patients; NR = not reported; SD = standard deviation; SE = standard error

Sources: clinicaltrials.gov;[2] EMA Assessment Report;[52] Clinical Study Report Synopsis;[3] Attard et al., 2018;[17] Saad et al., 2018[39]

[a] Lower represent lower levels of functioning/worse quality of life.
[b] Adjustment factors were not reported in the conference abstract

EQ-5D-5L questionnaire

EQ-5D-5L was a secondary endpoint of the PROSPER study. The proportions of patients providing a response in each domain were descriptively summarized. However, mean changes over time or difference between treatment groups were not statistically analyzed. EQ-5D-5L declined marginally as compared with baseline scores but remained similar between groups. However, this was only reported descriptively and no formal statistical testing was conducted.[2]

Harms Outcomes

Adverse Events

Table 22 provides a summary of the adverse events that were reported in at least 5% of patients in one or both the treatment groups in the PROSPER study. A greater proportion of enzalutamide-treated patients experienced at least one adverse event compared with those who received placebo (84.95% versus 75.91%). Fatigue was the most commonly reported event in both groups, occurring at a greater frequency in the enzalutamide group (32.47% versus 13.55%).[2] Falls were more commonly reported in the enzalutamide group compared with the placebo group (11.18%

versus 3.87%), as were decreases in weight (5.91% versus 1.51%) and appetite (9.57% versus 3.87%). Hypertension was reported in 11.83% of enzalutamide-treated patients compared with 5.16% of placebo-treated patients.

Table 22: Adverse events reported in ≥5% of Patients in Either Group of the PROSPER Study

System Organ Class	Adverse Events, n (%)	Enzalutamide (N = 930)	Placebo (N = 465)
Total	At least one AE	790 (84.95)	353 (75.91)
Gastrointestinal disorders	Constipation	84 (9.03)	32 (6.88)
	Diarrhoea	90 (9.68)	44 (9.46)
	Nausea	104 (11.18)	40 (8.60)
General disorders	Asthenia	82 (8.82)	28 (6.02)
	Fatigue	302 (32.47)	63 (13.55)
Infections and infestations	Urinary tract infection	35 (3.76)	25 (5.38)
Injury, poisoning, procedural complications	Fall	104 (11.18)	18 (3.87)
Investigations	Weight decreased	55 (5.91)	7 (1.51)
Metabolism and nutrition disorders	Decreased appetite	89 (9.57)	18 (3.87)
Musculoskeletal and CT disorders	Arthralgia	78 (8.39)	32 (6.88)
	Back pain	72 (7.74)	33 (7.10)
Nervous system disorders	Dizziness	91 (9.78)	20 (4.30)
	Headache	85 (9.14)	21 (4.52)
Renal and urinary disorders	Haematuria	48 (5.16)	30 (6.45)
	Urinary retention	17 (1.83)	24 (5.16)
Vascular disorders	Hot flush	121 (13.01)	36 (7.74)
	Hypertension	110 (11.83)	24 (5.16)

AE = adverse event; CT = connective tissue; n = number of patients with event; N = number of patients in the safety population; SAE = serious adverse event
Source: Clinicaltrials.gov[2]

Serious Adverse Events

Table 23 provides a summary of the serious adverse events that were reported in the PROSPER study. The proportion of patients who experienced at least one SAE was 24.3% in the enzalutamide group and 18.3% in the placebo group. Haematuria was the most commonly reported SAE in both the enzalutamide and placebo groups (2.2% versus 2.4%).[1,2]

Table 23: Serious Adverse Events in ≥0.5% of Patients in Either Group in the PROSPER study

SAE, n (%)	Enzalutamide (N = 930)	Placebo (N = 465)
At least one SAE	226 (24.3)	85 (18.3)
Haematuria	20 (2.2)	11 (2.4)
Urinary retention	7 (0.8)	8 (1.7)
Renal failure acute	4 (0.4)	7 (1.5)
Urinary tract infection	5 (0.5)	6 (1.3)
Pneumonia	9 (1.0)	1 (0.2)
Atrial fibrillation	6 (0.6)	3 (0.6)
Fall	7 (0.8)	2 (0.4)
Acute myocardial infarction	6 (0.6)	2 (0.4)
Adenocarcinoma of colon	5 (0.5)	2 (0.4)
Anaemia	5 (0.5)	1 (0.2)
Cardiac failure	6 (0.6)	0 (0.0)

SAE, n (%)	Enzalutamide (N = 930)	Placebo (N = 465)
Chest pain	5 (0.5)	1 (0.2)
Myocardial infarction	6 (0.6)	0 (0.0)
Pulmonary embolism	3 (0.3)	3 (0.6)
Coronary artery disease	5 (0.5)	0 (0.0)
Osteoarthritis	2 (0.2)	3 (0.6)
Back pain	1 (0.1)	3 (0.6)
Hydronephrosis	1 (0.1)	3 (0.6)
Urethral stenosis	1 (0.1)	3 (0.6)
Obstructive uropathy	0 (0.0)	3 (0.6)

n = number of patients with event; N = number of patients in the safety population; SAE = serious adverse event
Source: EMA Assessment Report[52]

Withdrawals Due to Adverse Events

Table 24 provides a summary of adverse events that led to discontinuation from the study treatments in PROSPER. Overall, 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.[1] Fatigue was the most commonly cited reason in the enzalutamide group (2.2%); with no placebo-treated patients withdrawing as a result of fatigue (0%).[1]

Table 24: Withdrawals from study treatment due to adverse events

Withdrawal due to adverse events, n (%)	Enzalutamide (N = 930)	Placebo (N = 465)
Any withdrawal due to adverse events	96 (10.3)	35 (7.5)
Cardiac disorders	6 (0.6)	3 (0.6)
Cardiac failure	3 (0.3)	0 (0.0)
Gastrointestinal disorders	12 (1.3)	4 (0.9)
Nausea	5 (0.5)	1 (0.2)
Dysphagia	2 (0.2)	1 (0.2)
Abdominal pain	0 (0.0)	2 (0.4)
General disorders and admin. site conditions	28 (3.0)	6 (1.3)
Fatigue	20 (2.2)	0 (0.0)
Asthenia	6 (0.6)	2 (0.4)
General physical health deterioration	1 (0.1)	2 (0.4)
Oedema peripheral	0 (0.0)	2 (0.4)
Investigations	4 (0.4)	0 (0.0)
Weight decreased	3 (0.3)	0 (0.0)
Metabolism and nutrition disorders	5 (0.5)	0 (0.0)
Decreased appetite	4 (0.4)	0 (0.0)
Musculoskeletal and connective tissue disorders	6 (0.6)	3 (0.6)
Musculoskeletal pain	2 (0.2)	1 (0.2)
Bone pain	2 (0.2)	0 (0.0)
Neoplasms benign, malignant and unspecified	19 (2.0)	6 (1.3)
Adenocarcinoma of colon	2 (0.2)	1 (0.2)
Metastases to liver	2 (0.2)	1 (0.2)
Chronic lymphocytic leukaemia	2 (0.2)	0 (0.0)
Nervous system disorders	25 (2.7)	7 (1.5)
Cerebrovascular accident	3 (0.3)	1 (0.2)
Headache	2 (0.2)	1 (0.2)
Spinal cord compression	2 (0.2)	1 (0.2)
Cognitive disorder	2 (0.2)	0 (0.0)
Dizziness	2 (0.2)	0 (0.0)

Withdrawal due to adverse events, n (%)	Enzalutamide (N = 930)	Placebo (N = 465)
Ischaemic stroke	2 (0.2)	0 (0.0)
Lethargy	2 (0.2)	0 (0.0)
Memory impairment	2 (0.2)	0 (0.0)
Psychiatric disorders	3 (0.3)	1 (0.2)
Depression	3 (0.3)	0 (0.0)
Renal and urinary disorders	3 (0.3)	7 (1.5)
Haematuria	2 (0.2)	1 (0.2)
Obstructive uropathy	0 (0.0)	2 (0.4)
Respiratory, thoracic and mediastinal disorders	7 (0.8)	3 (0.6)
Dyspnoea	3 (0.3)	1 (0.2)
n = number of patients with event; N = number of patients in the safety population Source: Clinical Study Report[1]		

Seizures

Seizures were specified as an adverse event of special interest in the PROSPER study and these events were identified by the Clinical Guidance Panel as an event of particular interest for this pCODR review. Seizures were reported in three enzalutamide-treated patients (0.3%) and no placebo-treated patients.[1] All three events in the enzalutamide group were considered serious and drug-related. One patient discontinued treatment as a result of a seizure. The event rate was 0.2 events per 100 patient-years in the enzalutamide group.[1] The submitter reported that no seizures led directly to death, but noted that one enzalutamide-treated patient died due to pneumonia aspiration three days after experiencing a grade 3 grand mal seizure.[1]

Falls

Falls were pre-specified as an adverse event of clinical interest and identified by the CGP as an event of particular interest for this pCODR review. Falls were more commonly reported in the enzalutamide group compared with the placebo group.[52] Falls were reported for 11.4% of enzalutamide-treatment patients compared with 4.1% of placebo-treated patients.[52] When adjusted for the duration of exposure to the study treatments, the event rate for enzalutamide-treated patients was 9.5 per 100 patient-years compared with 4.1 per 100 patient-years in the placebo group.[52] Falls were not cited as the primary reason for discontinuation for any patients.[52]

Fractures

Fractures were pre-specified as an adverse event of clinical interest and identified by the CGP as an event of particular interest for this pCODR review. Fractures were more commonly reported in the enzalutamide group compared with the placebo group.[52] Fractures were reported for 11.2% of enzalutamide-treatment patients compared with 5.6% of placebo-treated patients.[52] The event rates for fracture were 9.5 per 100 patient years and 5.1 per 100 patient years in the enzalutamide and placebo groups, respectively.[52] The most common types of fracture in the enzalutamide group of the PROSPER study were rib fractures (4.2%), spinal compression fracture (1.8%), femur fractures (0.5%), and upper limb fracture (0.5%).[52] The proportions of patients who experienced a fracture that was classified as an SAE, grade ≥ 3 event, or led to discontinuation were 2.8%, 2.4%, and 0.2%, respectively.

The EMA reported the results of a post-hoc analysis that demonstrated that 48% and 52% of patients in the enzalutamide and placebo groups (respectively) experienced a fracture within two

days of a reported fall. Thus, 49% of patients that reported a fracture in the enzalutamide arm and 38.5% in the placebo arm had suffer from a previous fall.

6.4 Ongoing Trials

No ongoing trials were identified as being relevant to this review.

7 SUPPLEMENTAL QUESTIONS

Given the absence of head-to-head studies that have compared enzalutamide against other treatments approved for use in the treatment of nmCRPC, the pCODR Methods Team reviewed published and unpublished indirect comparisons that investigated the comparative efficacy and safety of these treatments. Three indirect comparisons were identified:

- an unpublished systematic review and network meta-analysis (NMA) included in the submitter's submission[6]
- a published
- indirect comparison identified by the pCODR Methods Team (Wallis et al, 2018)[7]
- a matching-adjusted indirect comparison (MAIC) published only as a conference abstract was identified by the pCODR Methods Team (Chowdhury et al, 2018)[8]

7.1 Summary of Submitter's Indirect Comparison

7.1.1 Objectives of the Indirect Comparisons

The objectives of the indirect comparisons were reported as follows:

- The submitter-provided NMA was conducted to investigate the clinical efficacy of enzalutamide compared to current standard of care and current and emerging therapies for the management of adult patients with nmCRPC.[6]
- The published Bucher indirect comparison was conducted to compare the relative efficacy and toxicity of enzalutamide and apalutamide.[7]
- The MAIC was conducted to indirectly compare enzalutamide and apalutamide on MFS and overall survival.

7.1.2 Study Selection

Eligibility criteria for the indirect comparisons are summarized in Table 25. Eligibility criteria were not reported in the MAIC abstract.

Table 25: Eligibility Criteria for the Indirect Comparisons

Criteria	Submitter-provided	Wallis
Study designs	• NMA limited to RCTs (other studies appear to have been eligible for the systematic review)	• Placebo-controlled phase 3 RCTs
Populations	• Adults with nmCRPC. • Studies that included mixed populations if they reported outcomes separately for nmCRPC patients or were comprised of ≥80% of nmCRPC patients	• Patients with nmCRPC
Intervention/ Comparators	• Enzalutamide (any dosage) • Androgen deprivation therapy • Anti-androgens (first- and second-generation) including bicalutamide, flutamide, abiraterone, apalutamide, and ODM-201 • Docetaxel • Sipuleucel-T • Active surveillance (including placebo) • Denosumab	• Novel androgen axis inhibitors
Outcomes	• Overall survival • PFS (time to radiographic progression or death) • MFS • PSA response	**Primary outcomes:** • Investigator-adjudicated MFS **Secondary outcomes:** • PSA progression

Criteria	Submitter-provided	Wallis
	• Time to PSA progression • Time to first use of cytotoxic chemotherapy • Chemotherapy-free survival • Chemotherapy-free disease specific survival • Time to pain progression • Time to opiate use for prostate cancer pain • Time to treatment discontinuation • Adverse events	• Overall survival • Any adverse events • Grade 3 or 4 adverse events • Withdrawals due adverse events • Mortality due to adverse events

MFS = metastases-free survival; **NMA** = network meta-analysis; **nmCRPC** = non-metastatic castration-resistant prostate cancer; **RCT** = randomized controlled trial; **PSA** = prostate specific antigen; **PFS** = progression-free survival
Sources: Submitter-provided NMA and SLR[6,57] and Wallis et al, 2018[7]

Submitter-Provided NMA

A systematic review was conducted by the study authors to identify relevant studies. The literature search for the systematic review was comprehensive, involving multiple databases (e.g., PubMed, MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Database of Abstracts of Reviews of Effects [DARE]). In addition to the database search, the authors conducted separate literature searches for conference abstracts (e.g., ASCO and ESMO) and clinical trial registries. The search was conducted without restrictions for publication date or language; however, the selection criteria were limited to publications with an English language abstract. The methods for the literature search were well reported and the complete search strategies were included in the NMA and systematic review reports.[6,57]

Study selection, data extraction, and quality assessment were performed by a single-reviewer with a second review performing a quality check (methods for the check were not reported). Any discrepancies were resolved through consensus or by consulting a third-reviewer. Risk of bias assessment was performed using the criteria recommended by NICE 2015.[58] Key aspects of the appraisal included: methodology for randomization and allocation concealment; similarity of the treatment groups; blinding; rates of withdrawal; selective reporting of outcomes; use of an ITT analysis; handling of missing data.[58]

The systematic review methodology states that outcomes of interest were extracted from systematic reviews and meta-analyses, RCTs, non-randomised studies, observational comparative studies, case-cohort studies and registries. However, inclusion in the NMA was limited to RCTs by the authors, on the basis that this would minimize the risk of confounding.[57]

The submitter's list of interventions and comparators was based on drugs that have been studies in patients with nmCRPC or are expected to be approved by regulators for the nmCRPC indication. Hence, the list of comparators is considerably larger than the comparators of interest in this pCODR review (i.e., apalutamide). The inclusion criteria for the submitter's NMA does not specify that enzalutamide was to be used in combination with ADT (i.e., the indication approved for Health Canada) nor is it limited to studies that used the dosage regimen recommended in the Canadian product monograph (i.e., 160 mg once per day with reduced dosages as required).

Efficacy outcomes included overall survival, PFS, MFS, PSA response, time to PSA progression, time to first use of cytotoxic chemotherapy, chemotherapy-free survival, chemotherapy-free disease

specific survival, time to pain progression, time to opiate use for prostate cancer pain, and time to treatment discontinuation.[6] This outcomes generally align with the outcomes of interest for this pCODR review (Table 4), as well as those studied in the PROSPER trial.[1]

Wallis et al (2018) Indirect Comparison
It does not appear that Wallis et al (2018)[7] conducted a systematic literature review to identify studies, as there are few details reported regarding the literature search strategy and methods for study selection, data extraction, and risk of bias assessment (if applicable) were not reported. The authors stated that they conducted a search PubMed and multiple databases of conference proceedings (specific details were not reported). There were no details reported regarding search limitations and key terms. A copy of the literature search strategy was not reported and there were no details regarding excluded studies.

The authors reported that eligible studies included placebo-controlled phase 3 RCTs that investigated the use of novel androgen axis inhibitors in combination with ADT for patients with nmCRPC. The primary efficacy outcome of interest was investigator-adjudicated MFS. Secondary outcomes included overall survival and time to PSA progression. The following four safety endpoints were also evaluated: total adverse events; grade 3 or 4 adverse events; withdrawals due adverse events; and fatal adverse events. These outcomes generally align with the outcomes of interest for this pCODR review, as well as those studied in the PROSPER trial.[3]

Chowdhury et al (2018) Indirect Comparison
The MAIC conducted by Chowdhury et al (2018)[8] has been published only as a conference abstract and the methods are sparsely reported. There are no details regarding the methodology for selecting studies for inclusion.

7.1.3 Included Studies

Submitter-Provided NMA
Nine studies met the inclusion criteria for the systematic review and five studies met the eligibility criteria for NMA.[6] In accordance with the protocol for this pCODR review, this section of the report has focussed on studies that involved enzalutamide or apalutamide. There were two studies that investigated the use of enzalutamide (PROPOSE and STRIVE) and one study that investigated the use of apalutamide (SPARTAN). The characteristics of the PROSPER trial are described in detail in section 6 of this report. STRIVE was a phase 2, multi-centre, double-blind, placebo-controlled study that compared enzalutamide (160 mg once daily) versus bicalutamide (50 mg once daily). SPARTAN was a phase 3, multicentre, double-blind, placebo-controlled RCT.[54] Both SPARTAN and PROSPER were restricted to patients with nmCRPC; whereas, the study population in STRIVE was composed primarily of patients with mCRPC (65%) with a subset of patients who had nmCRPC (35%).

Wallis et al (2018) Indirect Comparison
Similar to the submitter-provided NMA, the indirect comparison by Wallis et al (2018) included the PROSPER and SPARTAN studies.[7]

Chowdhury et al (2018) Indirect Comparison

The MAIC conducted by Chowdhury et al (2018) used individual patient-level data from the SPARTAN trial and published data from the PROSPER trial.[8]

Table 26: Study Characteristics of the PROSPER and SPARTAN trials

Characteristics	PROSPER	SPARTAN
Study design	Multinational, multicentre, phase 3, double-blind, placebo-controlled RCT	Multinational, multicentre, phase 3, double-blind, placebo-controlled RCT
Population	Patients with nmCRPC	Patients with nmCRPC
Comparators	Enzalutamide + ADT (n = 933) Placebo + ADT (n = 468)	Apalutamide + ADT (n = 806) Placebo + ADT (n = 401)
Primary Outcome	MFS defined as time from randomisation to the first date of: • radiographic progression (assessed by BICR) • appearance of 1 or more metastatic lesions on bone scan • RECIST 1.1 for soft tissue disease or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurred first	MFS defined as time from randomisation to first evidence of: • BICR-confirmed radiographically detectable bone or soft tissue distant metastasis (simply referred to as "metastasis" from this point forward) or • death due to any cause (whichever occurs earlier) + 1 day.
Secondary outcomes	• OS • Time to pain progression • Time to opiate use for prostate cancer pain • Time to pain progression or opiate use for prostate cancer pain • Time to first use of cytotoxic chemotherapy • Time to first use of new antineoplastic therapy • Time to PSA progression • PSA response rates • FACT-P • EQ-5D-5L • QLQ-PR25	• OS • Time to symptomatic progression • Time to initiation of cytotoxic chemotherapy • Radiographic PFS • Time to metastasis • FACT-P • EQ-5D

ADT = androgen deprivation therapy; **BICR** = blinded independent central review; **EQ-5D** = European Quality of Life-5 Dimensions health questionnaire; **EQ-5D-5L** = European Quality of Life-5 Dimensions-5 Levels health questionnaire; **FACT-P** = Functional Assessment of Cancer Therapy-Prostate; **MFS** = metastases-free survival; **nmCRPC** = non-metastatic castration-resistant prostate cancer; **OS** = overall survival; **PSA** = prostate specific antigen; **PFS** = progression-free survival; **RCT** = randomized controlled trial; **RECIST** = Response Evaluation Criteria in Solid Tumors

7.1.4 Patient Populations

Table 27 provides a summary of key baseline and demographic characteristics of the participants in the PROSPER and SPARTAN trials. The median age was approximately 74 years in both studies. The majority of patients were white in both PROSPER (71.9% and 68.4% with enzalutamide and placebo, respectively) and SPARTAN (65% and 68.8% with apalutamide and placebo, respectively). The SPARTAN trial included a greater proportion of patients from North America (approximately two-thirds of participants) compared with the PROSPER trial (approximately 15%). The proportion of patients with a baseline ECOG performance status of zero was slightly greater in PROSPER (80.1% to 81.6% with enzalutamide and placebo, respectively) compared with SPARTAN (77.3% to 77.8% with apalutamide and placebo, respectively). Similarly, the proportion of patients with a baseline ECOG performance status of one was slightly greater in SPARTAN compared with

PROSPER. As shown in, Table 27 the distribution of baseline Gleason scores was reported differently in the PROSPER and SPARTAN trials, making in challenging to accurately compare across the studies. The median PSA at baseline was greater in the PROSPER study (11.1 and 10.2 with enzalutamide and placebo, respectively) compared with the SPARTAN study (7.78 with apalutamide and placebo, respectively).

Table 27: Patient Characteristics of the PROSPER and SPARTAN trials

Characteristics	PROSPER		SPARTAN	
	Enzalutamide	Placebo	Apalutamide	Placebo
Age, years Median (range)	74.0 (50.0 to 95.0)	73.0 (53.0 to 92.0)	74 (48 to 94)	74 (52 to 97)
Region	Europe: 49.1% North America: 15.1% Rest of world: 35.8%	Europe: 49.6% North America: 13.5% Rest of world: 37.0%	Europe: 49.0% North America: 35.4% Asia Pacific: 15.6%	Europe: 50.9% North America: 33.4% Asia Pacific: 15.7%
Time since diagnosis of Prostate cancer (years)	Median: 7.5	Median: 7.3	Median: 7.95	Median: 7.85
Prostate cancer-related treatment history	Hormonal therapies: 96.4% Endocrine therapies: 95.8% Non-hormonal therapy: 10% BTAs: 2% Radiotherapy 46.5% Surgical procedure 52.8%	Hormonal therapies: 94.9% Endocrine therapies: 94.0% Non-hormonal therapy: 10% BTAs: 2% Radiotherapy 48.3% Surgical procedure 56.2%	Prostatectomy or radiation: 76.6% GnRH analogue agonist: 96.8% First-generation ADT: 73.4%	Prostatectomy or radiation: 76.6% GnRH analogue agonist: 96.5% First-generation ADT: 72.3%
Baseline ECOG	0: 80.1% 1: 19.8% >1: 0.0% Missing: 10.1%	0: 81.6% 1: 18.2% >1: 0.0% Missing: 0.2%	0: 77.3% 1: 22.7%	0: 77.8% 1: 22.3%
Gleason score at diagnosis	2-4: 2.3% 5-7: 52.6% 8-10: 40.8% Unknown: 4.3%	2-4: 2.6% 5-7: 49.1% 8-10: 44.2% Unknown: 4.1%	<7: 19.4% 7: 37.1% >7: 43.5%	<7: 18.6% 7: 37.7% >7: 43.7%
Baseline PSA (ng/ml) Median (range)	11.1 (0.8 to 1071.1)	10.2 (0.2 to 467.5)	7.78 (NR)	7.96 (NR)
Metastatic disease	23 (2.5%)	14 (3.0%)	Not available	Not available

ADT = androgen deprivation therapy; BTA = bone-targeting agent; ECOG = Eastern Cooperative Oncology Group; GnRH = gonadotropin-releasing hormone; NR = not reported; PSA = prostate-specific antigen

7.1.5 Indirect Comparison Methods

Submitter-Provided NMA

The authors of the NMA stated that the NMA was performed in accordance with guidance from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[59,60] Prior to pooling, the similarity of the studies was assessed using guidance from the Australian Pharmaceutical Benefits Advisory Committee (PBAC) to inform their decision to pool studies.[61] These guidelines recommend that that the following five factors should be considered when assessing similarity: (1) study quality and methodology; (2) potential confounding factors related to the study populations; (3) potential confounding factors related to the circumstances of the study [e.g., trial setting and time period]; (4) differences in the treatments [e.g., dosage]; (5) differences in the outcome measures and statistical analysis.

Table 28 provides as summary of the indirect comparisons that were reported in the NMA submitted by the submitter. Analyses were performed on the following five outcomes: MFS, PFS, overall survival, time to first use of cytotoxic chemotherapy, and time to PSA progression. Log HR were calculated for all of the endpoints, citing the methods recommended in the *National Institute of Health and Care Excellence Decision Support Unit (NICE DSU) Technical Support Document 2*.

All of the analyses were conducted using fixed-effects models. The authors stated that random-effects models were not conducted because there was only one study available to inform each comparison in the networks; hence, the between-study variance could not be estimated. All of the analyses were conducted using vague prior distributions and without adjustment for any variables. Sensitivity analyses were performed for the MFS endpoint to examine the potential impact of the different MFS definitions used in the PROSPER and SPARTAN studies. Sensitivity analyses were not performed for the other endpoints.

Table 28: Overview of Methods for the Submitter-Provided NMA

Endpoint	Studies	Scale	RE or FE	Regression	Prior	Sensitivity analyses
MFS	PROSPER SPARTAN	HR	FE	None	Vague	Definitions of MFS
PFS						None
Overall survival						
Time to cytotoxic chemotherapy						
Time to PSA progression	PROSPER SPARTAN STRIVE					

FE = fixed-effects; HR = hazard ratio; MFS = metastases-free survival; PSA = prostate-specific antigen; RE = random-effects
Source: Submitter-Provided NMA[6]

Wallis et al (2018) Indirect Comparison

Wallis et al (2018) conducted indirect comparisons for seven outcomes (three efficacy and four safety).[7] All analyses were conducted using the Bucher method (Table 29). Hazard ratios were conducted for the efficacy endpoints (MFS, time to PSA progression, and overall survival). Odds ratios were calculated for the safety endpoints (total adverse events, grade 3-4 adverse events, withdrawals due to adverse events, fatal adverse events). A sensitivity analysis was performed for

MFS that was restricted to patients with N0 disease; there were no other sensitivity analyses or subgroup analyses.

Table 29: Overview of Methods for the Wallis et al (2018) Indirect Comparison

Endpoint	Studies	Scale	Sensitivity analyses
MFS	PROSPER SPARTAN	HR	Restricted to patients with N0 disease
Time to PSA progression			No sensitivity analysis
Overall survival			
Any AEs		OR	
Grade 3-4 AEs			
WDAE			
AEs leading to death			
AE = adverse events; FE = fixed-effects; HR = hazard ratio; MFS = metastases-free survival; N/A = not applicable; OR = odds ratio; WDAEs = withdrawals due adverse events			

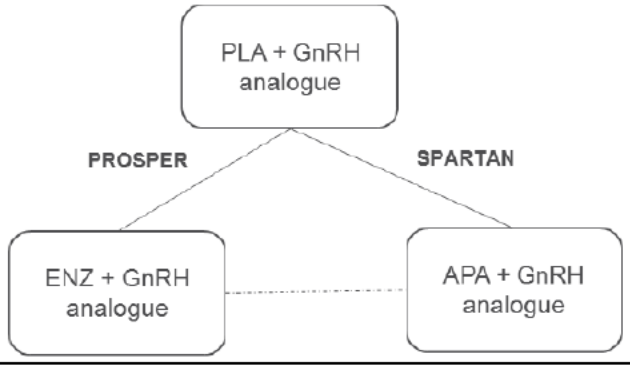
Chowdhury et al (2018) Indirect Comparison

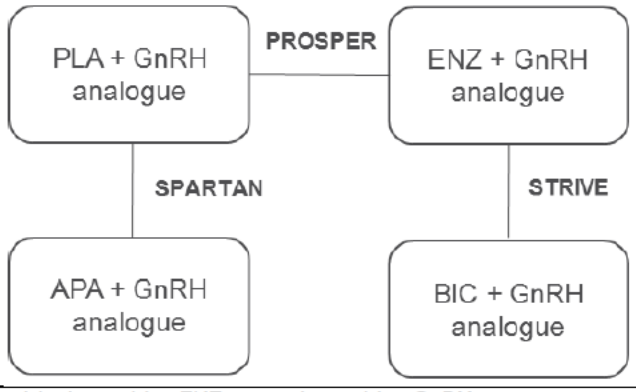
The MAIC conducted by Chowdhury et al (2018)[8] has been published only as a conference abstract and the methods are sparsely reported. The authors reported that they used individual patient-level data from the SPARTAN trial and published data from the PROSPER trial to conduct an anchored MAIC. Patients from the SPARTAN trial were matched to the baseline characteristics reported for PROSPER (age, Gleason Score, ECOG score, PSA, PSA doubling time, use of bone targeting agents, and surgical prostate cancer procedures. The authors then re-estimated the hazard ratios for MFS and OS from the SPARTAN trial using weighted Cox proportional hazards models and indirectly compared apalutamide to enzalutamide for MFS and OS using a Bayesian NMA.[8]

7.1.6 Evidence Network

The evidence networks used in the submitter-provided NMA are provided in Table 30. Two studies (PROSPER and SPARTAN) were included in the analyses for MFS, PFS, overall survival, and time to first use of cytotoxic chemotherapy. The analysis for time to PSA progression included PROSPER, SPARTAN, as well as the STRIVE study. Evidence network diagrams were not provided in the publication by Wallis et al (2018); however, PROSPER and SPARTAN were the only included studies.

Table 30: Evidence Networks in the Submitter-Provided NMA

Outcomes	Network diagram
• MFS • PFS • Overall survival • Time to first use of cytotoxic chemotherapy	

• Time to PSA progression	

APA = apalutamide; BIC = bicalutamide; ENZ = enzalutamide; GnRH = gonadotropin-releasing hormone; MFS = metastases-free survival; PLA = placebo; PSA = prostate-specific antigen
Source: Submitter-Provided NMA[6]

7.1.7 Indirect Comparison Results

Submitter-Provided NMA

Results for the submitter-provided NMA are summarized in **Table 31**. There was no difference between enzalutamide and apalutamide for the primary analysis MFS and all of the sensitive analyses. Similarly, there was no difference between enzalutamide and apalutamide in overall survival (HR: 1.14 [95% CI, 0.68 to 1.89]); time to initiating treatment with cytotoxic chemotherapy (HR: 0.86 [95% CI, 0.52 to 1.42]); or time to PSA progression (HR: 1.10 [95% CI, 0.81 to 1.50]). The direct and indirect estimates for enzalutamide versus placebo were identical to those reported in the PROSPER study for all endpoints.

Table 31: Results for the Submitter-Provided NMA

Endpoint	Comparison	Direct HR (95% CI)	Indirect Median HR (95% CrI)
MFS (primary analysis)	ENZ vs. Placebo	0.29 (0.24 to 0.35)	0.29 (0.24 to 0.35)
	APA vs. Placebo	0.28 (0.23 to 0.38)	0.28 (0.22 to 0.36)
	ENZ vs. APA	N/A	1.04 (0.76 to 1.43)
MFS (sensitivity analysis 1)	ENZ vs. Placebo	0.30 (0.25 to 0.36)	0.30 (0.25 to 0.36)
	APA vs. Placebo	0.28 (0.23 to 0.38)	0.28 (0.22 to 0.36)
	ENZ vs. APA	N/A	1.06 (0.77 to 1.45)
MFS (sensitivity analysis 2)	ENZ vs. Placebo	0.29 (0.24 to 0.35)	0.29 (0.24 to 0.35)
	APA vs. Placebo	0.29 (0.24 to 0.36)	0.29 (0.24 to 0.36)
	ENZ vs. APA	N/A	1.01 (0.76 to 1.33)
MFS (sensitivity analysis 3)	ENZ vs. Placebo	0.30 (0.25 to 0.36)	0.30 (0.25 to 0.36)
	APA vs. Placebo	0.29 (0.24 to 0.36)	0.29 (0.24 to 0.36)
	ENZ vs. APA	N/A	1.02 (0.77 to 1.34)
Overall survival	ENZ vs. Placebo	0.80 (0.58 to 1.09)	0.80 (0.58 to 1.09)
	APA vs. Placebo	0.70 (0.47 to 1.04)	0.70 (0.47 to 1.04)
	ENZ vs. APA	N/A	1.14 (0.68 to 1.89)
Time to cytotoxic chemotherapy	ENZ vs. Placebo	0.38 (0.28 to 0.51)	0.38 (0.28 to 0.51)
	APA vs. Placebo	0.44 (0.29 to 0.66)	0.44 (0.29 to 0.66)
	ENZ vs. APA	N/A	0.86 (0.52 to 1.42)
Time to PSA progression	ENZ vs. Placebo	0.07 (0.05 to 0.08)	0.07 (0.05 to 0.08)
	APA vs. Placebo	0.06 (0.05 to 0.08)	0.06 (0.05 to 0.08)
	ENZ vs. APA	N/A	1.10 (0.81 to 1.50)

Endpoint	Comparison	Direct HR (95% CI)	Indirect Median HR (95% CrI)
APA = apalutamide; CI = confidence interval; CrI = credible interval; ENZ = enzalutamide; HR = hazard ratio; MFS = metastases-free survival; N/A = not applicable; PSA = prostate-specific antigen Source: Submitter-Provided NMA[6]			

Wallis et al (2018) Indirect Comparison

Efficacy results

Results for the indirect comparison are summarized in . There were no differences between enzalutamide and apalutamide for any of the efficacy endpoints (enzalutamide versus apalutamide): MFS (HR: 1.04 [95% CI, 0.78 to 1.37]), time to PSA progression (HR: 1.17 [95% CI, 0.84 to 1.63]), or overall survival (HR: 1.14 [95% CI, 0.69 to 1.90]).[7]

Safety results

There were no differences between enzalutamide and apalutamide for any of the endpoints (enzalutamide versus apalutamide): total adverse events (OR: 0.96 [95% CI, 0.53 to 1.73]); grade 3-4 adverse events (OR: 0.83 [95% CI, 0.60 to 1.15]); WDAEs (OR: 1.03 [95% CI, 0.55 to 1.93]); and adverse events leading to death (OR: 1.09 [95% CI, 0.10 to 11.81]).

Chowdhury et al (2018) Indirect Comparison

The MAIC conducted by Chowdhury et al (2018)[8] has been published only as a conference abstract and the results are sparsely reported (Table 32).

Table 32: Efficacy Results for the Chowdhury et al., 2018 Indirect Comparison

Endpoint	Comparison	Direct HR (95% CI)	HR (95% CrI)
MFS	ENZ vs. Placebo	NR	NR
	APA vs. Placebo	NR	0.27 (0.21 to 0.34)
	APA vs. ENZ	NR	0.92 (0.69 to 1.24)
Overall survival	ENZ vs. Placebo	NR	NR
	APA vs. Placebo	NR	0.62 (0.41 to 0.94)
	APA vs. ENZ	NR	0.77 (0.46 to 1.30)
APA = apalutamide; CI = confidence interval; CrI = credible interval; ENZ = enzalutamide; HR = hazard ratio; MFS = metastases-free survival; NR = not reported Source: Chowdhury et al., 2018[8]			

7.1.8 Critical Appraisal of the Indirect Comparisons

The methods and reporting of the indirect comparisons were assessed according the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[62] Systematic review methodology was assessed according to recommendations in AMSTAR2.[63]

Submitter-Provided NMA

The literature search for the systematic review was comprehensive, involved multiple databases, and the search methodology was well reported in the NMA and systematic review reports (i.e., sources, restrictions, dates, search terms and complete strategy). At pCODR's request, the submitter provided the complete systematic review report.[57] Methodology for study selection,

data extraction, and quality assessment were appropriate and well-reported (i.e., performed by a single reviewer with a process for quality assessment and resolving discrepancies). The systematic review methodology was rigorous and well-reported by the study authors. Research questions and eligibility criteria were clearly stated in the report (including a comprehensive PICOS statement). A detailed study selection flow chart was provided in the report. A list of excluded studies was not reported for the systematic review; only a list of studies that were included in the systematic review, but subsequently excluded from the NMA was report.[6,57]

The submitter's NMA was conducted using the relevant patient population (i.e., patients with high risk nmCRC). The patient populations of the PROSPER and SPARTAN studies aligned with the indication under review (i.e., patients with nmCRPC). The STRIVE study was included in one of the indirect comparisons. This study enrolled patients with both mCRPC (65%) and nmCRPC (35%), but reported subgroup results for those with non-metastatic disease. The study authors included a range of relevant efficacy outcomes (including MFS, overall survival, time to first use of cytotoxic chemotherapy, and time to PSA progression), but there were no analyses conducted for any safety endpoints. The submitter-provided NMA was limited to the use of fixed-effects models. The use of a random-effects model would likely result in greater uncertainty in the estimates of effect. Since there was no difference observed between enzalutamide and apalutamide with the fixed-effect estimates, the use of a random effects approach would be unlikely to alter the conclusions of the indirect comparison (i.e., no observable difference in the efficacy of enzalutamide and apalutamide).

The studies included in the networks (PROSPER and SPARTAN) were multinational trials that were well-conducted and well-reported. The study authors used the NICE checklist to assess the quality of all the trials that met their inclusion criteria, and reported that the results of their quality appraisal did not reveal low quality studies within the NMAs. There was no selective reporting of outcomes in the PROSPER and SPARTAN trials. In order to show between-study similarities, the submitter-provided NMA report and systematic review report described the distribution of seven key baseline characteristics of the study populations (median age at baseline, gender, race, smoking history, disease stage, histology, and performance status) along with a description of study design characteristics. However, no quantitative measures of between-study heterogeneity were provided to justify the similarity assumption (no treatment-covariate interactions) between the included trials.

The NMA used the standard model that assumes constant, proportional hazards for all included studies. This assumption was assessed and reported as not having been met for all endpoints in PROSPER (with the exception of overall survival). The impact on the risk of bias on the estimates of effect is unclear. Overall survival data were immature for both the PROSPER and SPARTAN trials. The NMA appears to have used the first-interim analysis for PROSPER rather than the more recent second-interim analysis.

There were differences in the proportion of patients who initiated treatment with cytotoxic chemotherapy during the PROSPER (9.1% and 20.5% with enzalutamide and placebo, respectively) and SPARTAN (5.7% and 11.0% with apalutamide and placebo, respectively). The pCODR methods team identified potential differences in the subsequent antineoplastic therapies that were used by patients in the PROSPER and SPARTAN trials. The protocol for the SPARTAN study clearly stated

that patients with radiographic progression would be offered treatment with abiraterone + prednisone (both apalutamide and abiraterone acetate are currently marketed by the same manufacturer [i.e., Janssen]). For those who initiated subsequent treatment, the proportion of patients who received abiraterone acetate was greater in the SPARTAN trial (72.5% versus 71.4% in the placebo and apalutamide groups, respectively) compared with the PROSPER study (36% versus 38% in the placebo and enzalutamide groups, respectively). However, this is only an approximate comparison as there were differences in how the proportions were reported in the PROSPER and SPARTAN trials. In contrast, the use of docetaxel was more commonly reported in the PROSPER trial (27% and 22% in the enzalutamide and placebo, respectively) compared with the SPARTAN trial (8.6% and 8.1% in the apalutamide and placebo, respectively). This large difference in the proportion of patients who initiated treatment with docetaxel reduces confidence in the indirect comparison for time to initiation with cytotoxic chemotherapy. In addition, it is unclear if these differences have the potential to impact the results for overall survival.

Wallis et al Indirect Comparison

There were few details provided regarding the literature search strategy and no details regarding the study selection process. Similarly, there were no methodological details reported regarding data extraction and it was not reported if a risk of bias assessment was performed by the study authors. Despite these limitations, the relevant studies identified by Wallis et al (2018) are identical to those identified by the pCODR Methods Team and by the authors of the submitter-provided indirect comparison. Therefore, there are no concerns regarding missing studies from this analysis or the absence of formal risk of bias assessment (this is available in the submitter's NMA report for the PROSPER and SPARTAN studies).

The indirect comparison was focused on the relevant patient population (i.e., patients with high risk nmCRC) and the included studies accurately reflect this target population (i.e., SPARTAN and PROSPER). The indirect comparison included the two pharmaceutical treatments that are approved for nmCRPC in Canada (enzalutamide and apalutamide). As noted above, the PROSPER and SPARTAN studies were well conducted multinational trials with strong internal validity. The authors did not report a critical appraisal of the studies; however, the same studies were included in the NMA provided by the submitter and there were no serious limitations identified in the assessment performed using the NICE checklist.

The study authors included slightly fewer efficacy endpoints compared with the submitter's NMA (including MFS, overall survival, and time to PSA progression). However, in contrast to the submitter's NMA, Wallis et al included the following safety endpoints: total adverse events, grade 3–4 adverse events, WDAEs and adverse events leading to death. The pCODR Methods Team noted that the proportion of placebo-treated patients who experienced at least one adverse event was considerably higher in the SPARTAN trial compared with those in the PROSPER study (93% versus 77%). Similarly, the proportion of patients who reported at least one serious adverse event was greater in the placebo group of SPARTAN compared with the placebo group of PROSPER (34% versus 23%). The rationale for this difference is unclear, but it raises questions about the comparability of the adverse event data from the PROSPER and SPARTAN trials.[7]

Similar to the method used in the submitter-provided NMA, the Bucher method assumes constant, proportional hazards for the included studies. As noted previously, this assumption was assessed

and reported as not having been met for all endpoints in PROSPER (with the exception of overall survival). The impact on the risk of bias on the estimates of effect is unclear. As with the submitter-provided NMA, overall survival data were immature for both the PROSPER and SPARTAN trials; there were differences in the proportion of patients who initiated treatment with cytotoxic chemotherapy; and there were potential differences in the subsequent antineoplastic therapies that were used by patients in the PROSPER and SPARTAN trials.

Chowdhury et al Indirect Comparison

The MAIC conducted by Chowdhury et al (2018)[8] was reported only as a conference abstract and the pCODR Methods Team was unable to conduct a rigorous evaluation of the conduct and reporting of this analysis. The funding source for the analysis was not reported but several of the authors were from Janssen, the manufacturer of apalutamide. The authors noted that the analysis was conducted with immature overall survival data for PROSPER and SPARTAN.[8]

Table 33: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Submitter-Provided NMA	Wallis et al
1. Is the population relevant?	Yes. The patient populations of the PROSPER and SPARTAN studies aligned with the indication under review (i.e., patients with nmCRPC). The STRIVE study was included in one of the indirect comparisons. This study enrolled patients with both mCRPC (65%) and nmCRPC (35%), but reported subgroup results for those with non-metastatic disease.	Yes. The patient populations of the PROSPER and SPARTAN studies aligned with the indication under review (i.e., patients with nmCRPC).
2. Are any critical interventions missing?	No. Both indirect comparisons included ENZ and APA (i.e., the pharmaceutical treatments that are approved for nmCRPC in Canada).	
3. Are any relevant outcomes missing?	Yes. The study authors included all relative efficacy outcomes for this patient population. However, there were no analyses conducted for any safety endpoints and no analyses conducted for quality of life endpoints,	Yes. The study authors included relevant efficacy and safety outcomes for this patient population, but time to cytotoxic chemotherapy was excluded as were all endpoints for quality of life.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes. The clinical setting of both the PROSPER and SPARTAN studies were considered to be appropriate and generalizable to the Canadian context.	
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. The submitter provided a detailed systematic literature review report that was used to identify the studies that were included in the NMA. The systematic review methods were appropriate and well-reported.	Unclear. The methodology used to identify studies was poorly reported; however, there does not appear to be any relevant studies missing based on the systematic reviews conducted by the pCODR Methods Team and submitted by the submitter.
6. Do the trials for the interventions of interest form one connected network of RCTs?	Yes. The evidence networks for each outcome included the interventions of interest for this pCODR review (i.e., enzalutamide and apalutamide).	

ISPOR Questions	Submitter-Provided NMA	Wallis et al
7. Is it apparent that poor quality studies were included thereby leading to bias?	**No.** The studies included in the networks were multinational trials that were well-conducted and well-reported. The study authors used the NICE checklist to assess the quality of all the trials that met their inclusion criteria, and reported that the results of their quality appraisal did not reveal low quality studies within the NMAs.	**No.** The studies included in the networks were multinational trials that were well-conducted and well-reported. The authors did not perform a critical appraisal of the studies. However, the same studies were included in the NMA submitted by the submitter and there were no serious limitations identified in the assessment performed using the NICE checklist.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**No.** There was no selective reporting of outcomes in the PROSPER and SPARTAN trials.	
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Unclear.** In order to assess between-study similarities, the submitter-provided NMA report and systematic review report described the distribution of key baseline characteristics of the study populations (age at baseline, region, time since diagnosis of Prostate cancer, prostate cancer-related treatment history, ECOG performance status at baseline, Gleason score at diagnosis, PSA at baseline, and the proportion of patients with metastatic disease at baseline). The pCODR Methods Team noted that there were differences in the proportion of patients who initiated treatment with cytotoxic chemotherapy during the PROSPER trial (9.1% and 20.5% with enzalutamide and placebo, respectively) and SPARTAN (5.7% and 11.0% with apalutamide and placebo, respectively). This difference in the proportion of patients who initiated treatment with docetaxel reduces confidence in the indirect comparison for time to initiation with cytotoxic chemotherapy. In addition, it is unclear if these differences have the potential to impact the results for overall survival.	
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**No.** There were no analyses conducted to investigate the impact of potential differences in patient characteristics.	**Partially.** The authors performed a single sensitivity analysis that limited the analysis to patients with N0 disease. As PROSPER was limited to patients with N0 disease, this analysis would have excluded a subset of patients in the SPARTAN trial who had N1 disease at baseline. The CGP noted that N0 versus N1 would not typically be considered an important risk factor for disease progression in this patient population.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	**Yes.** The submitter submitted a Bayesian NMA (standard approach) to analyze data on outcomes of interest from the included RCTs. However, the NMA used the standard model that assumes constant, proportional hazards for all included studies. This assumption was assessed and reported as not having been met for all endpoints in PROSPER (with the exception of overall survival). The impact on the risk of bias of the estimates is unclear.	**Yes.** The submitter submitted an indirect comparison using the Bucher method. However, the indirect comparison is based on the assumption of proportional hazards for all included studies. This assumption was assessed and reported as not having been met for all endpoints in PROSPER (with the exception of overall survival). The impact on the risk of bias of the estimates is unclear.

ISPOR Questions	Submitter-Provided NMA	Wallis et al
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	**Not applicable.** There were no closed loops in the networks used in the submitter-provided indirect comparison.	**Not applicable.** The authors did not conduct an NMA.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the NMA?	**Not applicable.** There were no closed loops in the networks.	**Not applicable.** The authors did not conduct an NMA.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	**Partially.** There were no subgroup analyses or meta-regressions performed based on patient characteristics. Sensitivity analyses were performed to examine the potential impact of having different definitions for MFS in the PROSPER and SPARTAN studies.	**Partially.** The authors performed a single sensitivity analysis that limited the analysis to patients with N0 disease. As PROSPER was limited to patients with N0 disease, this analysis would have excluded a subset of patients in the SPARTAN trial who had N1 disease at baseline (results were reported to be similar to the primary analysis).
15. Was a valid rationale provided for the use of random effects or fixed effect models?	**Yes.** In order to estimate between-study variance, the network must include at least one comparison that is informed by multiple studies.	**No.** The authors did not discuss their rationale for applying the Bucher method to conduct the indirect comparison.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	**Not applicable:** The authors only performed fixed-effects analyses for all outcomes.	**Not applicable:** The authors only performed fixed-effects analyses for all outcomes.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	**Unclear.** It is unclear if the sensitivity analysis was pre-specified by the authors.	**Unclear.** It is unclear if the sensitivity analysis was pre-specified by the authors.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	**Yes.** Evidence network diagrams were provided for all of the endpoints.	**No.** However, there are only two studies (PROSPER and SPARTAN) and these are addressed in the NMA submitted by the submitter.
19. Are the individual study results reported?	**Yes.** Individual study results were reported for the endpoints of interest.	**Partially.** Individual study results were reported for nearly all of the endpoints of interest; however, confidence intervals were not reported for the individual study endpoints (only p values). In addition, the individual study results were not reported for the sensitivity analysis based on N0 patients.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or NMA?	**Yes.** Both the submitter's NMA report and the publication by Wallis et al (2018) provide direct and indirect estimates of effect (when available).	

ISPOR Questions	Submitter-Provided NMA	Wallis et al
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	**Yes.** Measures of uncertainty were reported for the direct estimates of effect (95% CI) and for the indirect estimates (95% credible intervals) reported in the submitter-provided NMA.	**Partially.** Measures of uncertainty were reported for the indirect estimates of effect (i.e., 95% CI); however, the confidence intervals were not reported for the individual study endpoints.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	**Not applicable.** Ranks were not reported for the Bayesian NMA provided in the submitter-provided indirect comparison.	**Not applicable.** Wallis et al (2018) performed an indirect comparison using the Bucher method.
23. Is the impact of important patient characteristics on treatment effects reported?	**Not reported**	**Not reported**
24. Are the conclusions fair and balanced?	The author's conclusions of the indirect comparisons accurately reflect the results (i.e., no statistically significant differences between ENZ and APA). The claims in the submitter-provided indirect comparison regarding 'numerical' differences are not typically considered to be valid by pCODR's Methods Team. The pCODR Methods Team noted that analyses for the efficacy endpoints were conducted using methods that assumed proportionality of 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 and/or reported. The potential risk of bias with this limitation is unclear and the results should be interpreted with caution. The data for overall survival data 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 overall survival.	The authors concluded that apalutamide and enzalutamide are likely to be associated with similar efficacy and safety. However, the indirect comparisons were limited to aggregate measures of adverse events, which do not provide insight into the unique adverse event profiles of enzalutamide and apalutamide (e.g., risk of seizures). Furthermore, the included trials were not designed or powered to examine safety endpoints. The pCODR Methods Team noted that analyses for the efficacy endpoints were conducted using methods that assumed proportionality of hazards for the included studies. This assumption was not valid for MFS and time to PSA progression. The potential risk of bias with this limitation is unclear and the results should be interpreted with caution. The data for overall survival data 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 overall survival.
25. Were there any potential conflicts of interest?	The NMA is unpublished and was prepared by a consultant for the submitter of enzalutamide.	Conflicts of interest were declared in the publication. One author had received speaker bureau honoraria from Astellas (i.e., the submitter of enzalutamide).

ISPOR Questions	Submitter-Provided NMA	Wallis et al
26. If yes, were steps taken to address these?	Not applicable	The authors declared that the sponsor that no role in funding or supporting the study.

APA = apalutamide; **ENZ** = enzalutamide; **CI** = confidence interval; **CrI** = credible interval; **NMA** = network-meta-analysis; **nmCRPC** = non-metastatic castration-resistant prostate cancer; **RCT** = randomized controlled trial

† Adapted from Jansen et al., 2014[62]

TABLE 34: APPRAISAL OF POTENTIAL EFFECT MODIFIERS IN THE NMA

Characteristics	Appraisal of Heterogeneity
Dosing of comparators	• Enzalutamide and apalutamide were both administered in a manner that is consistent with recommendations in the Canadian product monographs.[51,64]
Compliance with treatments	• Compliance with the study treatments was greater in the PROSPER study (96.0% and 98.3% in the enzalutamide and placebo groups, respectively) compared with the SPARTAN trial (88% and 93% with apalutamide and placebo, respectively).[1,55]
Disease severity	• The SPARTAN trial included a subset of patients with N1 disease at diagnosis (approximately 15%); whereas, PROSPER was limited to patients with N0 disease. The CGP noted that N0 versus N1 would not typically be considered an important risk factor for progression to metastatic disease in this patient population. The indirect comparison by Wallis et al (2018) included a sensitivity analysis that was restricted to patients with N0 disease reported that the results were similar to the primary analysis. • Baseline disease severity was similar based on ECOG performance status. The median baseline PSA was greater in the PROSPER trial (11.1 and 10.2 in the enzalutamide and placebo groups, respectively) compared with the SPARTAN trial (7.78 and 7.96 in the apalutamide and placebo, respectively). The CGP noted that this could be indication that those in the PROSPER trial had slightly more severe disease at baseline, but the clinical relevance of this difference would be minimal.
Concomitant treatments	• The use of bone-targeting agents was similar in the PROSPER and SPARTAN studies.
Event rate in the placebo groups (efficacy)	• The proportion of patients who experienced disease progression or death (i.e., the events used to determine MFS), was similar in the placebo groups of both PROSPER (48.7%) and SPARTAN (48.4%).[4,55] • There were differences in the proportion of patients who initiated treatment with cytotoxic chemotherapy during the PROSPER (9.1% and 20.5% with enzalutamide and placebo, respectively) and SPARTAN (5.7% and 11.0% with apalutamide and placebo, respectively).
Event rate in the placebo groups (safety)	• The proportion of placebo-treated patients who experienced at least one adverse event was considerably higher in the SPARTAN trial compared with those in the PROSPER study (93% versus 77%). Similarly, the proportion of patients who reported at least one serious adverse event was greater in the placebo group of SPARTAN compared with the placebo group of PROSPER (34% versus 23%). The rationale for this difference is unclear, but it raises questions about the comparability of the adverse event data from the PROSPER and SPARTAN.[7]
Definitions and timing of endpoint evaluation	The definition of MFS differed between the PROSPER and SPARTAN trials: • **PROSPER:** Time from randomisation to the first date of: ▪ BICR-confirmed radiographic progression ▪ appearance of 1 or more metastatic lesions on bone scan ▪ RECIST 1.1 for soft tissue disease or death on study (death within 112 days of treatment discontinuation without evidence of radiographic progression), whichever occurred first • **SPARTAN:** Time from randomisation to first evidence of: ▪ BICR-confirmed radiographically detectable bone or soft tissue distant metastasis or ▪ death due to any cause (whichever occurs earlier) + 1 day. The authors conducted sensitivity analyses to investigate the potential impact of the different definitions used in the PROSPER and SPARTAN studies.
Withdrawal rates	• The proportion of patients who discontinued the study treatments was greater in the SPARTAN study (70% and 39% in the placebo and apalutamide groups, respectively) compared with the PROSPER study (62% and 32% in the placebo and enzalutamide groups, respectively). The difference appears to be primarily attributable to more withdrawals due to progressive disease in SPARTAN (52% and 19% in the placebo and apalutamide groups, respectively) compared with PROSPER (44.2% and 14.8% in the placebo and enzalutamide groups, respectively).
Risk of seizure	• Seizures were specified by the manufacturer as an adverse event of special interest in the PROSPER study and these events were identified by the Clinical Guidance Panel as an event of particular interest for this pCODR review. Both PROSPER and SPARTAN trials excluded patients if they had a history of seizure or a condition that could pre-dispose them to seizures.

Characteristics	Appraisal of Heterogeneity
Overall survival	• Overall survival data were immature for both the PROSPER and SPARTAN trials.
Subsequent treatments	• The proportion of patients who initiated treatment with at least one post-baseline systematic therapy for prostate cancer was similar in the placebo groups of the PROSPER and SPARTAN trials (55.5% versus 55.4%, respectively). However, the proportion of patients in the active treatment groups who initiated subsequent treatment was greater in the PROSPER study compared with the SPARTAN study (26.2% versus 21.7%, respectively). • Abiraterone was cited by the CGP as a common therapeutic choice for patients who have progressed from nmCRPC to mCRPC. The proportion of patients who received abiraterone acetate was greater in the SPARTAN trial (72.5% versus 71.4% in the placebo and apalutamide groups, respectively) compared with the PROSPER study (36% versus 38% in the placebo and enzalutamide groups, respectively). In contrast, the use of docetaxel was more common in the PROSPER trial (27% and 22% in the enzalutamide and placebo, respectively) compared with the SPARTAN trial (8.6% and 8.1% in the apalutamide and placebo, respectively). This is likely attributable to the protocol for SPARTAN which stated that patients with radiographic progression would be offered treatment with abiraterone + prednisone (both apalutamide and abiraterone acetate are currently marketed by the same manufacturer [i.e., Janssen]).
BICR = blinded independent central review; **CGP** = Clinical Guidance Panel; **ECOG** = Eastern Cooperative Oncology Group; **mCRPC** = Metastatic castration-resistant prostate cancer; **MFS** = Metastasis-free survival; **nmCRPC** = non-metastatic castration-resistant prostate cancer; **RECIST** = Response Evaluation Criteria in Solid Tumors	

7.1.9 Conclusion

The pCODR Methods Team identified three indirect comparisons of enzalutamide and apalutamide: an unpublished Bayesian NMA provided by the submitter, a published indirect comparison using Bucher methodology, and a conference abstract reporting a matching-adjusted indirect comparison. All three of the indirect comparisons were focussed on the PROSPER and SPARTAN studies (placebo-controlled RCTs involving enzalutamide and apalutamide in combination with ADT, respectively).[6-8] The submitter-provided NMA only included efficacy endpoints and reported no statistically significant difference between two treatments for the following endpoints (enzalutamide versus apalutamide): MFS (HR: 1.04 [95% CrI, 0.76 to 1.43]), overall survival (HR: 1.14 [95% CrI, 0.68 to 1.89]), time to cytotoxic chemotherapy (HR: 0.86 [95% CrI, 0.52 to 1.42]), and time to PSA progression (HR: 1.10 [95% CrI, 0.81 to 1.50]).[6] The Bucher indirect comparison reported no differences between the treatments (enzalutamide versus apalutamide) for: MFS (HR: 1.04 [95% CI, 0.78 to 1.37]), time to prostate-specific antigen progression (HR: 1.17 [95% CI, 0.84 to 1.63]), and overall survival (HR: 1.14 [95% CI, 0.69 to1.90]).[7] The MAIC published as a conference abstract also demonstrated no significant difference (apalutamide versus enzalutamide) for MFS (0.77 [95% CrI, 0.46 to 1.30]) and overall survival (0.92 [95% CrI, 0.69 to 1.24]).[8]

The submitter-provided NMA only included efficacy endpoints and reported no statistically significant difference between two treatments for the following endpoints (enzalutamide versus apalutamide): MFS (HR: 1.04 [95% CrI, 0.76 to 1.43]), overall survival (HR: 1.14 [95% CrI, 0.68 to 1.89]), time to cytotoxic chemotherapy (HR: 0.86 [95% CrI, 0.52 to 1.42]), and time to PSA progression (HR: 1.10 [95% CrI, 0.81 to 1.50]).[6] The Bucher indirect comparison reported no differences between the treatments (enzalutamide versus apalutamide) for: MFS (HR: 1.04 [95% CI, 0.78 to 1.37]), time to prostate-specific antigen progression (HR: 1.17 [95% CI, 0.84 to 1.63]),

and overall survival (HR: 1.14 [95% CI, 0.69 to1.90]).[7] The MAIC published as a conference abstract also demonstrated no significant difference (apalutamide versus enzalutamide) for MFS (0.77 [95% CrI, 0.46 to 1.30]) and overall survival (0.92 [95% CrI, 0.69 to 1.24]).

The submitter-provided NMA and the MAIC did not evaluate any safety endpoints; however, the published indirect comparison reported no difference between enzalutamide and apalutamide for total adverse events, grade 3–4 adverse events, withdrawals due to adverse events, or adverse events leading to death. The pCODR Methods Team noted that adverse events and serious adverse events were more commonly reported in the placebo group of the SPARTAN trial compared with the PROSPER study; raising questions about the comparability of the safety data from those two trials. Indirect comparisons on aggregate measure of adverse events can provide useful information regarding comparative safety, but do not provide insight into the unique adverse event profiles of enzalutamide and apalutamide (e.g., risk of seizures). There were no indirect comparisons that investigated potential differences between enzalutamide and apalutamide in the risk of seizures, an adverse event of special interest for this pCODR review.

The pCODR Methods Team was unable to critically appraise the MAIC due to the absence of a publication and identified several important limitations with the submitted-provided NMA and the Bucher indirect comparison of enzalutamide and apalutamide. Most notably, the analyses for the efficacy endpoints 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 and/or reported. The potential risk of bias with this limitation is unclear and the results should be interpreted with caution. The data for overall survival data 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 overall survival.

8 COMPARISON WITH OTHER LITERATURE

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

9 ABOUT THIS DOCUMENT

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

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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

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

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials August 2018, Embase 1974 to 2018 October 1, Ovid MEDLINE(R) ALL 1946 to October 01, 2018

#	Searches	Results
1	(enzalutamide* or xtandi* or kstandi* or MDV3100 or MDV-3100 or ASP-9785 or ASP9785 or 93T0T9GKNU).ti,ab,ot,kf,kw,hw,nm.	6174
2	Prostatic Neoplasms, Castration-Resistant/ or (((((androgen* or castrat*) adj2 (independent* or insensitive* or resist*)) or (hormon* adj2 (refractory or relaps* or resist*))) adj5 prostat* adj5 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or metasta* or neoplas* or sarcoma* or tumo?r*)) or CRPC or nmCRPC or nm-CRPC or nCRPC or n-CRPC).ti,ab,kf,kw.	30760
3	1 and 2	4289
4	3 use medall	1101
5	3 use cctr	294
6	*Enzalutamide/ or (enzalutamide* or xtandi* or kstandi* or MDV3100 or MDV-3100 or ASP-9785 or ASP9785).ti,ab,kw,dq.	4789
7	Castration Resistant Prostate Cancer/ or (((((androgen* or castrat*) adj2 (independent* or insensitive* or resist*)) or (hormon* adj2 (refractory or relaps* or resist*))) adj5 prostat* adj5 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or metasta* or neoplas* or sarcoma* or tumo?r*)) or CRPC or nmCRPC or nm-CRPC or nCRPC or n-CRPC).ti,ab,kw,dq.	31953
8	6 and 7	3744
9	8 use oemezd	2455
10	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1102463
11	Randomized Controlled Trial/	983438
12	exp Randomized Controlled Trials as Topic/	277593
13	"Randomized Controlled Trial (topic)"/	149193
14	Controlled Clinical Trial/	550704
15	exp Controlled Clinical Trials as Topic/	288751
16	"Controlled Clinical Trial (topic)"/	9561
17	Randomization/	175449
18	Random Allocation/	192277
19	Double-Blind Method/	394113
20	Double Blind Procedure/	153174
21	Double-Blind Studies/	258391
22	Single-Blind Method/	74541
23	Single Blind Procedure/	32455
24	Single-Blind Studies/	76488
25	Placebos/	324449
26	Placebo/	323483
27	Control Groups/	111321
28	Control Group/	111229
29	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3944316
30	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	772069

31	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2912
32	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2570993
33	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	93429
34	allocated.ti,ab,hw.	174143
35	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	112388
36	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	24260
37	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	924
38	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	10768
39	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	16956
40	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	125102
41	or/10-40	5646787
42	4 and 41	240
43	9 and 41	889
44	43 and (conference review or conference abstract).pt.	395
45	limit 44 to english language	395
46	limit 45 to yr="2013 -Current"	368
47	43 not (conference review or conference abstract).pt.	494
48	5 or 42 or 47	1028
49	limit 48 to english language	955

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

#	Query	Items found
#5	Search #1 AND #2 AND #3 Filters: English	61
#4	Search #1 AND #2 AND #3	61
#3	Search publisher[sb]	530390
#2	Search ((((androgen*[tiab] OR castrat*[tiab]) AND (independent*[tiab] OR insensitive*[tiab] OR resist*[tiab])) OR (hormon*[tiab] AND (refractory[tiab] OR relaps*[tiab] OR resist*[tiab]))) AND prostat*[tiab] AND (cancer*[tiab] OR carcinoid*[tiab] OR carcinoma*[tiab] OR carcinogen*[tiab] OR adenocarcinoma*[tiab] OR adeno-carcinoma*[tiab] OR malignan*[tiab] OR metasta*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR tumo*[tiab])) OR CRPC[tiab] OR nmCRPC[tiab] OR nm-CRPC[tiab] OR nCRPC[tiab] OR n-CRPC[tiab]	15557
#1	Search enzalutamide*[tiab] OR xtandi*[tiab] OR kstandi*[tiab] OR MDV3100[tiab] OR MDV-3100[tiab] OR ASP-9785[tiab] OR ASP9785[tiab] OR 93T0T9GKNU[tiab] OR 93T0T9GKNU[rn]	1319

3. Cochrane Central Register of Controlled Trials (Central)

- Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

- U.S. NIH ClinicalTrials.gov: http://www.clinicaltrials.gov/
- Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials: http://www.canadiancancertrials.ca/

Search: XTANDI/enzalutamide, castration-resistant prostate cancer

Select international agencies including:

- Food and Drug Administration (FDA):http://www.fda.gov/
- European Medicines Agency (EMA): http://www.ema.europa.eu/

Search: XTANDI/enzalutamide, castration-resistant prostate cancer

Conference abstracts:

- American Society of Clinical Oncology (ASCO): http://www.asco.org/
- European Society for Medical Oncology (ESMO): https://www.esmo.org/

Search: XTANDI/enzalutamide, castration-resistant prostate cancer – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (August 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were XTANDI/enzalutamide and castration-resistant prostate cancer.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of January 31, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Detailed Methodology of Literature Review

Study Selection

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

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

Quality Assessment

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

Data Analysis

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

Writing of the Review Report

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

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

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