Reimbursement Review

Enzalutamide

Nonsponsored reimbursement review
Therapeutic area: Genitourinary cancer (prostate cancer)

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Abbreviations

ADT	androgen deprivation therapy
ARPI	androgen receptor pathway inhibitor
BCR	biochemical recurrence
BICR	blinded independent central review
CDA-AMC	Canada's Drug Agency
CI	confidence interval
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FACT-P	Functional Assessment of Cancer Therapy-Prostate
HR	hazard ratio
HRQoL	health-related quality of life
ISUP	International Society of Urological Pathology
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MFS	metastasis-free survival
NCCN	National Comprehensive Cancer Network
nmCRPC	nonmetastatic castration-resistant prostate cancer
nmCSPC	nonmetastatic castration-sensitive prostate cancer
OS	overall survival
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
RP	radical prostatectomy
RT	radiotherapy
SRT	salvage radiotherapy

Executive Summary

An overview of the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Enzalutamide (Xtandi), 40 mg soft gelatin capsules, oral
Health Canada indication(s)	• In the setting of medical or surgical castration for the treatment of mCRPC in patients who are chemotherapy-naive with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy, or have received docetaxel therapy, • For the treatment of nmCRPC, • For the treatment of mCSPC, and • For the treatment of nmCSPC with biochemical recurrence at high risk for metastasis.
Indication under consideration for reimbursement	For the treatment of patients with nmCSPC with BCR at high risk of metastasis
Health Canada approval status	NOC
NOC date	January 30, 2024
Requester	Provincial Advisory Group

BCR = biochemical recurrence; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; nmCSPC = nonmetastatic castration-sensitive prostate cancer; NOC = Notice of Compliance.

Introduction

Prostate cancer is the second most common cancer worldwide and the sixth leading cause of cancer death in men.[1] The Canadian Cancer Society estimates that the 5-year net survival rate for prostate cancer in Canada is 91%.[2]

Early treatment options for prostate cancer include radical prostatectomy (RP) and radiotherapy (RT), both aiming to eradicate cancer cells and achieve long-term survival. Despite effective initial treatment, biochemical recurrence (BCR) is common, with 27% to 53% of patients experiencing rising prostate-specific antigen (PSA) levels without clinical or radiological evidence of disease within 10 years.[3,4] BCR after primary treatment serves as an early marker for potential disease progression and these patients have a higher risk of developing distant metastases and overall mortality.[3]

Survival outcomes are generally better for patients with nonmetastatic prostate cancer compared to those with metastatic disease, highlighting the importance of early detection and management of BCR.[3] Given the heterogeneity of the BCR phase, American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) recommend patients should be stratified into low- and high-risk categories before starting additional treatment.[3,4] Various guidelines support the use of salvage radiotherapy (SRT) with or without androgen deprivation therapy (ADT) for high-risk BCR patients. There is a consensus on the benefit of early intervention with ADT in high-risk patients, while active surveillance and intermittent ADT are viable options for lower-risk cases.

Enzalutamide has emerged as a potential option for patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC) with BCR at high risk of metastasis. Health Canada has recently approved enzalutamide for this indication.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of enzalutamide with or without ADT for the treatment of nmCSPC with BCR at high risk of metastasis.

Perspectives

The information in this section is a summary of input provided in response to the Canada's Drug Agency (CDA-AMC) call for input and from clinical expert(s) consulted by CDA-AMC for the purpose of this review

Patient Input

Input for this review was submitted by 1 patient group — PROCURE. The perspectives were gathered through an analysis of telephone consultations between patients and the patient group's health care professionals as well as online surveys. Patients shared their experiences with prostate cancer, highlighting concerns about treatment choices, rising PSA levels after treatment, recurrence, issues concerning hormone therapy, metastases, psychosocial impact, and quality of life. The patient group emphasized that, since individual responses to treatments vary, it is important for patients and prescribers to have access to all available new agents.

Clinician Input

Input from Clinical Experts Consulted by CDA-AMC

One clinical specialist with expertise in the diagnosis and management of prostate cancer provided the following input:

- The current standard treatment for nmCSPC is ADT, but not all patients have durable responses to ADT, with the average time to castration resistance being 18 to 24 months.
- There is an unmet need for combination treatment with ADT plus enzalutamide to delay castration resistance as well as the potential for enzalutamide alone to avoid long-term toxicities of ADT, improving quality of life and treatment outcomes.
- Enzalutamide, an established androgen receptor pathway inhibitor (ARPI), is commonly prescribed in metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC) settings. Its use in early prostate cancer could delay castration resistance, disease progression, and metastasis, while also improving quality of life and mitigating ADT-related toxicities.
- Most patients meeting the EMBARK trial inclusion criteria would benefit from enzalutamide plus ADT, while enzalutamide alone may be suitable for those intolerant to ADT or for patients who prefer to avoid ADT.
- The discrepancy in the EMBARK trial inclusion criteria, where patients' status was confirmed using conventional imaging instead of the current practice of PSMA-PET, may need to be addressed.

- Enzalutamide is not likely to benefit patients who have been on ADT for more than 3 years, though it may be reasonable to consider offering enzalutamide to those who have recently started ADT therapy (e.g., within 6 months), as they may benefit from combination treatment.

Clinician Group Input

Cancer Care Ontario, Genitourinary Cancer Drug Advisory Committee provided the following input:

- There is currently no defined treatment for patients with nmCSPC with BCR at high risk of metastasis.
- For patients in this setting, the goals of therapy are to reduce the risk of metastasis, improve overall survival (OS), and maintain quality of life.
- Patients most likely to benefit from enzalutamide with or without ADT are those with rising PSA, a doubling time of 9 months or less, and PSA above 2 after radiation or PSA above 1 after prostatectomy.

Industry Input

Astellas Pharma Canada Inc. provided input for this review, agreeing with the project scope but questioning the inclusion of abiraterone-prednisone as a comparator due to limited evidence for its use in this population. Astellas agreed with the clinically important outcomes and suggested including all the end points reported in the EMBARK trial as clinically important outcomes. Additionally, the input highlighted comments related to the health economics of this review.

Drug Program Input

The drug programs have provided the following input:

- Abiraterone, listed as a comparator in the posted project scope for this review, may not be a relevant comparator as previous funding was not established in nmCSPC with high-risk BCR.

The drug programs have raised the following questions related to policy and implementation considerations:

- Leuprolide was used as the ADT of choice in the EMBARK trial; can other ADTs be used interchangeably in this setting?
- Is the definition of high-risk disease used in the EMBARK trial consistent with how high-risk nonmetastatic prostate cancer is defined and used in clinical practice?
- The trial included patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1. Would patients with ECOG PS ≥ 2 be eligible for this treatment?
- Is there a role for re-treatment with enzalutamide when a patient's disease progresses to a more advanced stage? What treatment options are available for a patient treated with enzalutamide with or without ADT in nmCSPC should their disease progress?
- Should there be time-limited funding considerations to allow enzalutamide to be added to the treatment regimen of existing patients with nmCSPC who were recently initiated on ADT (within the last 6 months)?
- EMBARK used conventional imaging for the assessment of prostate cancer status. With PSMA-PET now available for eligible patients, what impact will this have on disease assessment?

Clinical Evidence

Protocol Selected Studies

Description of the Study

The EMBARK trial was a phase III, randomized, open-label multicentre study conducted at 244 sites across 17 countries, including Canada (27 sites). The trial aimed to evaluate the efficacy and safety of enzalutamide plus leuprolide compared to leuprolide alone, and enzalutamide alone compared to leuprolide alone, in adult patients with prostate cancer who had high-risk BCR after local therapy. The trial, which began in January 2015, included patients with histologically or cytologically confirmed adenocarcinoma of the prostate with high-risk disease, defined by a PSADT of 9 months or less and a PSA level of 2 ng/mL or more above nadir after RT or ≥ 1 ng/mL after RP (with or without postoperative RT), serum testosterone of at least 150 ng/dL, and an ECOG performance status score of 0 or 1.

Patients were randomly assigned in a 1:1:1 ratio to receive enzalutamide plus leuprolide (combination group, double-blind), placebo plus leuprolide (leuprolide-alone group, double-blind), or enzalutamide monotherapy (enzalutamide-alone group, open-label). Enzalutamide (160 mg) or placebo was taken orally once daily, and leuprolide (22.5 mg) was administered intramuscularly or subcutaneously every 12 weeks. Treatment was paused at week 37 if PSA levels were below 0.2 ng/mL and resumed when PSA levels reached at least 5.0 ng/mL (no prior prostatectomy) or 2.0 ng/mL (prior prostatectomy). Patients with detectable PSA values at week 36 continued treatment without suspension until permanent treatment discontinuation criteria were met.

The primary end point was metastasis-free survival (MFS) in the enzalutamide plus leuprolide group versus the leuprolide-alone group, with a secondary end point of MFS in the enzalutamide-alone group versus the leuprolide-alone group. MFS, defined as the time from randomization to the earliest objective evidence of radiographic progression, was independently assessed by blinded independent central review (BICR) through imaging and survival status monitoring. Other secondary end points included OS, defined as the time from randomization to death from any cause, and safety outcomes. Exploratory end points included time to PSA progression, time to development of castration resistance, and health-related quality of life outcomes (HRQoL), which were reported in a separate publication.

Critical Appraisal

The EMBARK trial was a randomized, multicentre, partially blinded study. The randomization process was clearly described, and baseline characteristics were well-balanced among the treatment groups. The primary MFS end point in all arms was assessed by BICR, which reduced detection bias. While the combination arm and leuprolide only arm were double-blinded, the enzalutamide-alone arm was open-label. However, the double-blinding of the other arms and the blinded lab and tumour assessment likely reduced the risk of performance bias in the enzalutamide-alone arm. Knowledge of treatment allocation could introduce detection bias, although this was somewhat mitigated by the BICR. Inconsistent blinding could also influence the interpretation of differences in outcomes between arms and could result in biased estimates for subjective outcomes such as safety and HRQoL. However, there was no clear evidence that this occurred in the analyses.

The trial is clinically relevant to the Canadian setting due to the inclusion of 27 Canadian sites. However, the predominantly white patient population (> 80%) and the strict inclusion criteria, such as PSADT and specific performance status requirements, might limit its generalizability to a broader patient population in Canada. The use of enzalutamide with ADT or as monotherapy is consistent with common practice, and the follow-up duration aligns with standards for monitoring high-risk prostate cancer patients. Relevant harms outcomes were reported, and HRQoL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire.

Efficacy Results

Baseline characteristics were generally balanced between the trial arms. The median age was 69 years, the median prostate-specific antigen doubling time (PSADT) was 4.9 months, and the median PSA level was 5.2 ng/mL. Most patients were white (83.2%), had ECOG 0 (92.2%), had not had previous hormonal therapy (68.9%), and had both prostatectomy and radiation therapy as primary definitive therapy (49.1%).

Patients received treatment and were monitored every 12 weeks. At week 37, treatment was suspended for patients whose PSA values were undetectable (< 0.2 ng/mL) at week 36 as determined by the central laboratory. Patients with detectable PSA values at week 36 continued treatment without suspension until permanent treatment discontinuation criteria were met. At week 36, 90.9% of patients in the enzalutamide plus leuprolide group suspended treatment, 67.8% of patients in the leuprolide group suspended treatment, and 85.9% of patients in the enzalutamide-alone group suspended treatment. At data cut-off, the median follow-up was 60.7 months.

At data cut-off, the primary end point of the blinded, independently assessed MFS in the enzalutamide-leuprolide group versus the leuprolide-alone group was for 87.3% (95% confidence interval [CI], 83.0 to 90.6) and 71.4% (95% CI, 65.7 to 76.3) respectively, translating to a hazard ratio (HR) of 0.42 (95% CI, 0.30 to 0.61; P < 0.001). The blinded independently assessed MFS for enzalutamide alone versus the leuprolide-alone group versus the leuprolide-alone group was 80.0% (95% CI, 75.0 to 84.1) and 71.4% (95% CI, 65.7 to 76.3) respectively, translating to a HR of 0.63 (95% CI, 0.46 to 0.87; P = 0.005).

The 5-year OS rates were 92.2% (95% CI, 88.7 to 94.7) for the enzalutamide-leuprolide group, 87.2% (95% CI, 83.0 to 90.4) for the leuprolide-alone group, and 89.5% (95% CI, 85.6 to 92.4) for the enzalutamide-alone group. The HR for death was 0.59 (95% CI, 0.38 to 0.91; P = 0.02) for enzalutamide plus leuprolide versus leuprolide alone, and 0.78 (95% CI, 0.52 to 1.17; P = 0.23) for enzalutamide alone versus leuprolide alone.

At data cut-off, the estimated percentage of patients free from PSA progression was 97.4% (95% CI, 94.7 to 98.8) in the enzalutamide-leuprolide group, 70.0% (95% CI, 64.1 to 75.1) in the leuprolide-alone group, and 88.9% (95% CI, 84.6 to 92.1) in the enzalutamide-alone group. Patients in both the enzalutamide-leuprolide and enzalutamide-alone groups had a significantly lower risk of PSA progression compared to the leuprolide-alone group, with HRs of 0.07 (95% CI, 0.03 to 0.14; P < 0.001) and 0.33 (95% CI, 0.23 to 0.49; P < 0.001), respectively.

Additionally, at the data cut-off, the percentage of patients who developed castration resistance was lower in the enzalutamide-leuprolide group (3.9%) compared to the leuprolide-alone group (33.5%).

More patients in the leuprolide-alone group discontinued treatment (56.8% with 24% due to radiographic or PSA progression) compared to the enzalutamide plus leuprolide group (41.4% with 7.9% due to radiographic or PSA progression) and the enzalutamide-alone group (44.4% with 11.8% due to radiographic or PSA progression).

Harms Results

More than 97% (1,035 out of 1,061) of the patients in all 3 arms had an adverse event. Any grade adverse events leading to permanent treatment discontinuation were reported in 73 of 353 patients (20.7%) in the enzalutamide plus leuprolide group, 36 of 354 patients (10.2%) in the leuprolide-alone group, and 63 of 354 patients (17.8%) in the enzalutamide-alone group.

The most common adverse events in the combination group and the leuprolide-alone group were hot flashes and fatigue. The most common adverse events in the monotherapy group were gynecomastia, hot flashes, and fatigue.

Table 2: Summary of Key Results, ITT Population

Outcome	Enzalutamide + leuprolide	Leuprolide alone	Enzalutamide alone
Efficacy (ITT population), n	**355**	**358**	**355**
Blinded, independently assessed MFS (at data cut-off) — primary end point			
Median follow-up, months	60.7	60.6	—
Imaging-based progression or death, n (%)	45 (12.7)	92 (25.7)	—
Median MFS, months	NR (NR to NR)	NR (85.1 to NR)	—
5-year MFS, % (95% CI)	87.3 (83.0 to 90.6)	71.4 (65.7 to 76.3)	—
HR (95% CI)	0.42 (0.30 to 0.61)		—
P value	P < 0.001		—
Blinded, independently assessed MFS (at data cut-off) — secondary end point			
Median follow-up, months	—	60.6	60.7
Imaging-based progression or death, n (%)	—	92 (25.7)	63 (17.7)
Median MFS, months	—	NR (85.1 to NR)	NR (NR to NR)
5-year MFS, % (95% CI)	—	71.4 (65.7 to 76.3)	80.0 (75.0 to 84.1)
HR (95% CI)	—	0.63 (0.46 to 0.87)	
P value	—	P = 0.005	
OS (at data cut-off) — secondary end point			
Median follow-up, months	66.0	66.2	64.5
Death, n (%)	33 (9.3)	55 (15.4)	42 (11.8)
5-year OS, % (95% CI)	92.2 (88.7 to 94.7)	87.2 (83.0 to 90.4)	89.5 (85.6 to 92.4)
HR (95% CI), P -value	0.59 (0.38 to 0.91), P = 0.02		—

Outcome	Enzalutamide + leuprolide	Leuprolide alone	Enzalutamide alone
	—	0.78 (0.52 to 1.17), P = 0.23	
Castration resistance (at data cut-off) — exploratory end point			
Events, n (%)	14 (3.9)	120 (33.5)	NR
HR (95% CI)	0.09 (0.05 to 0.16)		—
PSA progression (at data cut-off) — exploratory end point			
Events, n (%)	8 (2.3)	93 (26.0)	37 (10.4)
HR (95% CI), P -value	0.07 (0.03 to 0.14), P < 0.001		—
	—	0.33 (0.23 to 0.49); P < 0.001	
First deterioration in FACT-P score (at data cut-off) — secondary end point			
Events, n (%)	257 (72.4)	248 (69.3)	263 (74.1)
HR (95% CI), P value	1.14 (0.95 to 1.36)		—
	—	1.17 (0.98 to 1.39)	
As-treated population	**353**	**354**	**354**
Treatment suspension			
Duration of treatment excluding treatment suspension, median (range), months	32.4 (0.1 to 83.4)	35.4 (0.7 to 85.7)	45.9 (0.4 to 88.9)
Patients with PSA < 0.2 ng/mL at week 36 and treatment suspension, n (%)	321 (90.9)	240 (67.8)	304 (85.9)
Duration of treatment suspension, median (range), months	20.2 (5.7 to 87.9)	16.8 (3.4 to 83.0)	11.1 (2.3 to 84.9)
Did not receive treatment for > 24 months (%)	43.9	32.1	20.4
Harms			
Any grade AE, n (%)	343 (97.2)	345 (97.5)	347 (98.0)
≥ Grade 3, n (%)	164 (46.5)	151 (42.7)	177 (50.0)
Serious AE, n (%)	123 (34.8)	112 (31.6)	131 (37.0)
≥ Grade 3, n (%)	110 (31.2)	100 (28.2)	116 (32.8)
Any grade AE leading to permanent treatment discontinuation, n (%)	73 (20.7)	36 (10.2)	63 (17.8)
AE leading to death, n (%)	6 (1.7)	3 (0.8)	8 (2.3)
Notable harms			
Hot flash, n (%)	243 (68.8)	203 (57.3)	77 (21.8)
Fatigue, n (%)	151 (42.8)	116 (32.8)	165 (46.6)
Seizures, n (%)	4 (1.1)	0 (0)	3 (0.8)

AE = adverse event; CI = confidence interval; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HR = hazard ratio; ITT = intention to treat; MFS = metastasis-free survival; NR = not reported; OS = overall survival; PSA = prostate-specific antigen.

Source: Freedland et al. 2023.[4]

Other Relevant Evidence

Patient-reported outcomes for EMBARK were published separately.[13] Instruments used were the short-form Brief Pain Inventory (BPI-SF), FACT-P questionnaire, Quality of Life Questionnaire Prostate 25 (QLQ-PR25), and European Quality of Life 5-Dimension 5-Levels health questionnaire (EQ-5D-5L) scores.[5]

Cost Information

The economic review consisted of a cost comparison for enzalutamide compared with ADT for adult patients with nmCSPC with BCR at high risk of metastasis.

Based on public list prices, enzalutamide is expected to have a 28-day per patient cost of $3,270. Maintenance ADT therapies (i.e., after the initial month), range in cost from $252 per patient per 28 days (for degarelix 80 mg monthly) to $428 per patient per 28 days (for buserelin 6.3 mg every 2 months). As an add-on therapy to ADT, the incremental cost of enzalutamide is equal to its cost of $3,270 per patient per 28 days compared to ADT alone. When used without ADT, the incremental cost of enzalutamide ranges from $2,842 to $3,015 per patient per 28 days compared to maintenance ADT, depending on which ADT regimen is displaced.

Conclusions

The findings from EMBARK suggest that the combination of enzalutamide with ADT may result in a clinically meaningful delay of metastasis compared to ADT alone in patients with nmCSPC with high-risk BCR. Additionally, the findings suggest that enzalutamide monotherapy may also clinically delay metastasis relative to ADT alone. However, median survival times were not yet reached, so the magnitude of absolute differences in events between groups during the median 5-year follow-up period could not be determined. There were no direct comparisons between enzalutamide with ADT and enzalutamide alone, which precludes any conclusions about their relative efficacy. Both enzalutamide-containing arms had higher incidences of adverse events leading to treatment discontinuations compared to the leuprolide-alone group. Despite promising findings, longer follow-up is needed to evaluate long-term survival benefits and quality of life.

Results of the cost comparison of treatment costs demonstrate that, as an add-on therapy to ADT, the incremental cost of enzalutamide is $3,270 per patient per 28 days. When used without ADT, the incremental cost of enzalutamide ranges from $2,842 to $3,015 per patient per 28 days compared to maintenance ADT, depending on the ADT regimen displaced. As such, the reimbursement of enzalutamide for the treatment of adult patients with nmCSPC with BCR at high risk of metastasis is expected to increase overall drug acquisition costs, regardless of whether it is given with or without ADT.

Based on the clinical review conclusions, the combination of enzalutamide with ADT may result in clinically meaningful delay of metastasis compared to ADT alone. Additionally, enzalutamide monotherapy may also delay metastasis relative to ADT alone. Given that enzalutamide (with or without ADT) is associated with increased treatment costs and incremental benefit in terms of delay of metastasis compared to ADT alone, a cost-effectiveness analysis would be required to determine the cost-effectiveness of enzalutamide (with or without ADT) relative to ADT alone. As this was not available, the cost-effectiveness of enzalutamide (with or

without ADT) relative to ADT alone for the treatment of adult patients with nmCSPC with BCR at high risk of metastasis could not be determined.

Introduction

Disease Background

Prostate cancer is the second most common cancer worldwide and the sixth leading cause of cancer death in men.[1] The Canadian Cancer Society estimates that the 5-year net survival rate for prostate cancer in Canada is 91%.[2]

Early treatment options for prostate cancer include RP and RT, both aiming to eradicate cancer cells and achieve long-term survival. Despite effective initial treatment, BCR is common, with 27% to 53% of patients experiencing rising PSA levels without clinical or radiological evidence of disease within 10 years.[3,4] BCR after primary treatment serves as an early marker for potential disease progression, and these patients have a higher risk of developing distant metastases and overall mortality.[3]

Survival outcomes are generally better for patients with nonmetastatic prostate cancer compared to those with metastatic disease, highlighting the importance of early detection and management of BCR.[3] Given the heterogeneity of the BCR phase, the American Society of Clinical Oncology and the NCCN recommend that patients should be stratified into low- and high-risk categories before starting additional treatment.[3,4]

PSADT is currently the most reliable parameter for differentiating between low- and high-risk BCR in prostate cancer. However, additional factors such as Gleason score, clinical stage, and surgical margins can also be considered in risk calculations.[3] The American Urological Association Advanced Prostate Cancer 2020 guideline identifies high-risk BCR by a PSADT of less than 12 months, while low-risk BCR is characterized by a PSADT of 12 months or more.[6] The European Association of Urology guidelines define high-risk BCR as a PSADT of less than 12 months and/or a pathological International Society of Urological Pathology (ISUP) grade of 4 to 5, while low-risk BCR is indicated with a longer PSADT and lower ISUP grades.[7] Active surveillance is often recommended for low-risk BCR patients, focusing on regular PSA monitoring to avoid unnecessary treatments. However, high-risk BCR patients may require intensified therapy to prevent progression to metastatic disease.[3]

Standards of Therapy

NCCN guidelines recommend that patients with PSA recurrence after RP may either be observed or undergo SRT with or without ADT if no distant metastases are detected.[8] The RAVES and RADICAL trials demonstrated 5-year BCR-free survival rates of 88% with SRT for patients with PSA levels of more than 0.1 ng/mL to 0.2 ng/mL post-RP. A study by Boorjian and colleagues indicated that SRT decreased the risk of local recurrence (HR 0.13; 95% CI, 0.06 to 0.28; P < 0.0001), delayed the need for hormonal therapy (HR 0.81; 95% CI, 0.71 to 0.93; P = 0.003), and reduced systemic progression (HR 0.24; 95% CI, 0.13 to 0.45; P < 0.0001) compared to no SRT.[3]

For patients with PSA recurrence after RT and no detectable metastases confirmed by a negative biopsy, active observation or ADT are viable options, according to NCCN guidelines.[8]

Controversy remains about the timing and duration of ADT for recurrent prostate cancer. While the TOAD (Timing Of Androgen Deprivation) trial showed that immediate ADT improved 5-year OS compared to delayed ADT (91.2% versus 86.4%; log-rank P = 0.047), hormone treatment-related symptoms scores were higher and sexual activity was lower in the immediate ADT group compared to the delayed ADT group. According to an NCCN guidelines panel, the timing of ADT initiation should balance the potential benefits against the side effects, while also considering individual factors such as PSA velocity and patient life expectancy. Patients with shorter PSADT or rapid PSA velocity and a long life expectancy may be better candidates for early ADT, while older patients with prolonged PSADT may be better suited for active observation.[3,8]

Ontario Health Cancer Care Ontario guidelines define low-risk BCR after RP as PSADT greater than 1 year and pathologic Gleason score of less than 8, while high-risk BCR is identified by a PSADT of less than 1 year or a pathologic Gleason score of 8 to 10. Low-risk BCR after RT is defined by a PSADT greater than 18 months and a clinical Gleason score of less than 8, while high-risk BCR is identified by a PSADT of less than 18 months or a pathologic Gleason score of 8 to 10. Cancer Care Ontario recommends that active surveillance be offered as a treatment option for patients with low-risk BCR, while intermittent ADT could be offered as a treatment option for patients with high-risk BCR after RP and/or RT.[9]

Alberta Health Services guidelines recommend early SRT with or without ADT in select high-risk patients after biochemical failure after prostatectomy. Alberta Health Services defines BCR as a PSA nadir of + 2 ng/mL after primary RT or any rise in PSA after SRT and recommends salvage cryosurgery or salvage brachytherapy as treatment options. ADT can be an option if salvage local therapy is not an option or fails.[10]

Drug

Enzalutamide is an androgen receptor inhibitor that acts on several steps in the androgen signalling pathway. Health Canada has approved enzalutamide for the following indications:[11]

- mCRPC: in patients who are chemotherapy-naive or after docetaxel therapy
- nmCRPC
- mCSPC
- nmCSPC with BCR at high risk for metastasis (high-risk BCR) (approved in January 2024)

Data protected for enzalutamide ended on May 29, 2021.

We completed the following reimbursement reviews of enzalutamide:

- in 2013, for the treatment of patients with mCRPC who have previously received docetaxel therapy, issuing a recommendation of reimburse with clinical criteria and/or conditions
- in 2015, for the treatment of patients with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT who have not received prior chemotherapy, issuing a recommendation of reimburse with clinical criteria and/or conditions

- in 2019, for the treatment of patients with nmCRPC, issuing a recommendation of reimburse with clinical criteria and/or conditions
- in 2020, for the treatment of patients with mCSPC, issuing a recommendation of reimburse with clinical criteria and/or conditions

The Provincial Advisory Group and clinical experts consulted by us for this review expressed interest in using enzalutamide for the treatment of patients with nmCSPC with BCR at high risk for metastasis. Consequently, the Provincial Advisory Group requested that we review enzalutamide for this patient population and provide a reimbursement recommendation.

Perspectives

Patient Group Input

This section was prepared by CDA-AMC staff based on the input provided by patient groups.

The patient group input was submitted by PROCURE, which is a charitable organization that educates, supports, and informs people affected by prostate cancer and promotes and contributes to financing research. The input is based on analysis of patient calls to their specialized uro-oncology health care professionals through the toll-free line and other online surveys.

The analysis of patient calls is based on a cohort of more than 3,500 patients with localized, locally advanced, metastatic, recurrent, hormone-sensitive, or castration-resistant prostate cancer with or without metastasis. Incoming patient calls expressed the following concerns: distress, treatment choices, the rising PSA level after treatment, recurrence, hormone therapy and its side effects, and metastases.

The patient group also shared results from its online Canadian survey on the quality of life of patients treated for prostate cancer. It was conducted in May 2022 in collaboration with the firm Leger. The main challenges of treatment according to 50% of the 263 respondents included managing side effects, living with uncertainty, and maintaining a positive attitude.

In addition, PROCURE conducted an online Quebec survey in March 2018 on the needs of patients treated for a recurrence or for advanced prostate cancer. In response to the following question — “What do you hope for from future treatments for prostate cancer?” — 95% answered “slows down the progression of cancer,” 94% answered “extends life expectancy,” 98% answered “improves the quality of life,” 93% answered “helps manage or diminish side effects,” and 91% answered “decreases PSA levels.”

The patient group submission has also highlighted the following key areas or concepts in terms of the disease experience:

- Physical impact: Side effects are a significant burden for patients
- Significant psychological impact
- Partners unintentionally become caregivers

- Recurrence significantly impacts patients both physically and emotionally
- Advanced cancer creates anxiety within the couple, not knowing how much time they have ahead of them
- Quality of life

The patient group has also indicated that because patients do not all respond the same way to treatments, including new drugs or combination treatments, it is important for patients and specialists to have access to all new agents and new indications that have demonstrated their effectiveness with minimal side effects while maintaining stable PSA levels and providing good quality of life.

Based on their surveys, patients also have the following expectations related to the new treatments:

- Stabilize or control the cancer
- Delay the onset or eliminate metastases
- Decrease or keep PSA levels stable over a long period (a source of anxiety)
- Prolong life and quality of life
- Be heard and taken seriously

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

All CDA-AMC review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management prostate cancer.

Unmet Needs

In the setting of nmCSPC, the current standard treatment is ADT. However, 1 clinical expert emphasized that not all patients will have durable tumour responses to ADT alone. The clinical expert estimated that on average, patients may have durable response with time to castration resistance in 18 to 24 months. Recognizing there is heterogeneity on this range to response, there will be patients who progress quickly. For these patients, the ability to receive combination treatment with ADT plus enzalutamide to delay the development of castration resistance would potentially fill an unmet need and achieve an outcome that is meaningful to patients.

Another expert noted that there currently are no available systemic therapies that have a curative intent and that early ARPI-targeting therapies may only delay disease progression.

In addition, a clinical expert highlighted that all patients become refractory to ADT at some point. Further, the concept of treatment intensification is not new and well established to be beneficial in advanced disease setting (e.g., mCSPC). Hence, applying this concept in nmCSPC means shifting the treatment paradigm to

allow patients to have access to treatment intensification earlier in the same disease, which could improve treatment outcomes.

The clinical expert also highlighted that while ADT is the current standard of treatment for patients with nmCSPC, it is associated with toxicities (such as increased risk of cardiovascular events and bone fracture) that have longer-term health implications and impacts on patients' HRQoL. Hence a potential treatment option without ADT, such as using enzalutamide alone may be a favourable option for patients who value the ability to maintain their androgen levels, while still having the option to treat the disease.

Place in Therapy

One clinical expert noted that most practitioners may consider the combination therapy (enzalutamide plus ADT) in early setting as a treatment intensification strategy to delay the development of castration resistance, to delay disease progression, or to delay metastasis. However, the use of enzalutamide without ADT is an option as well as it offers an alternative for patients especially to avoid ADT-related adverse effects.

Patient Population

One clinical expert suggested to align the patient population with the inclusion and exclusion criteria of the EMBARK trial, which would include higher risk biochemical recurrent patients with nonmetastatic prostate cancer. The clinical expert noted that the study's inclusion criteria included patients with nonmetastatic prostate cancer as confirmed by conventional imaging (e.g., CT, MRI, or bone scans), whereas patients in current practice settings may receive PSMA-PET imaging to identify potential metastasis. The expert indicated that while conventional imaging is still the default in current Canadian practice, PSMA-PET imaging, where available, is seeing an increase in use. If there is discordance between the imaging results from the conventional imaging and PSMA-PET imaging (e.g., negative for metastasis on conventional imaging but positive on PSMA-PET imaging), there may be a need to align the practice approach as to how to define patients suitable for these treatments (e.g., enzalutamide plus ADT, or enzalutamide monotherapy).

Which patients should receive treatment for enzalutamide alone is unclear. It may be reserved for patients who have experienced intolerance and/or adverse effects to ADT or may be due to patients' preferences to avoid ADT. The clinical expert suggested that the inclusion criteria for the EMBARK study would apply to this patient population.

The clinical expert also noted that the least suitable patients for enzalutamide or enzalutamide plus ADT would include those with a hypersensitivity to enzalutamide and/or patients with pre-existing seizure disorders or who have other medical conditions or on medications that can lower the seizure threshold (the enzalutamide product monograph includes a serious warnings and precautions box about clinically significant seizures associated with enzalutamide).

In addition, the clinical expert noted that adding enzalutamide is unlikely to be beneficial for patients who have been receiving ADT for more than 3 years, suggesting that the patients may be responding adequately to ADT monotherapy alone. However, it was the clinical expert's opinion that it would be reasonable to offer enzalutamide to those who have recently initiated ADT therapy (e.g., within 6 months) to potentially benefit from the combination treatment.

Assessing Response to Treatment

In this population for patients with high-risk biochemical recurrent nonmetastatic prostate cancer, 1 clinical expert noted that response to treatment can be evaluated with a stabilization or decrease in PSA level. In addition, treatment response can be evaluated with imaging. However, there is heterogeneity in the frequency of imaging to assess response in different practice settings.

The clinical expert has noted that there are adverse events to monitor for this treatment. Many clinicians would have experience with monitoring the effects of enzalutamide and ADT. Specific to enzalutamide, clinicians should screen for potential drug interactions and increased seizure risk. Other adverse events to monitor include dysgeusia, neurocognitive issues, fatigue, concentration, short-term memory loss, hypertension, abnormalities with liver function tests. Enzalutamide may increase risk of seizure only in patients with pre-existing factors for seizure or on medications that lower seizure thresholds.

Another expert noted early systemic therapy may increase time on treatment and associated toxicities, such as fatigue, sexual dysfunction, and gynecomastia, without clear evidence of long-term benefits.

Discontinuing Treatment

One clinical expert noted that treatment should be discontinued or adjusted if a patient experiences clinically important adverse effects. Upon disease progression to metastasis, treatment should be discontinued as well. However, if there is only progression reflected by rising PSA with no evidence of metastasis, treatment may be continued at the discretion of the physician in collaboration with the patient.

Prescribing Conditions

One clinical expert has emphasized that specialists with training in medical oncology, urology-oncology, or radiation-oncology would be required to prescribe enzalutamide or enzalutamide plus ADT. The clinical expert noted that enzalutamide, as an ARPI is not a new drug. The noted oncologists would have experience working with an ARPI including enzalutamide specifically and understand the effects of these drugs in treating prostate cancer in mCSPC and mCRPC.

Additional Considerations

The clinical experts were consulted on the efficacy outcomes of interest in the inclusion criteria of the systematic review. One expert agreed that MFS, OS, progression-free survival, and HRQoL were appropriate outcomes of interest and suggested that time to castration resistance would also be a reasonable outcome to include. Regarding MFS as an efficacy outcome, an expert noted that, while MFS has not been validated as a surrogate for OS in this setting, the PROSPER[12] and SPARTAN[13] trials have shown an association between MFS and OS in nonmetastatic prostate cancer. Another expert also indicated that the FDA recognizes MFS as a surrogate for OS in the nmCRPC setting, though the expert acknowledges that this reflects a policy decision rather than statistical validation of surrogacy and that delaying MFS may not necessarily translate into meaningful improvements in OS.

Clinician Group Input

This section was prepared by CDA-AMC staff based on the input provided by clinician groups.

Clinician group input was received from the Cancer Care Ontario Genitourinary Cancer Drug Advisory Committee, on behalf of 6 clinicians. The group identified that there is no defined treatment in this setting for patients with nmCSPC with BCR at high risk of metastasis. The goal is to reduce the risk of metastasis, improve OS, and maintain quality of life. The clinician group input has highlighted that this treatment under review would benefit patients with a rising PSA, a doubling time of 9 months or less, and PSA above 2 after radiation or PSA above 1 after prostatectomy.

Industry Input

Industry input was submitted by Astellas Pharma Canada Inc. The input indicates that the project scope aligns with the population, which is in patients with nonmetastatic prostate cancer who are at a high risk of BCR. The input also agrees with the intervention evaluating enzalutamide plus ADT or enzalutamide monotherapy as compared with ADT alone. The input raises the question of abiraterone-prednisone as a comparator, citing there is limited evidence to support its use in patients at a high risk of BCR. The input also commented on the outcome and recognized that the project scope outlined all clinically important outcomes including MFS. Other suggested end points for consideration include time to PSA progression, first use of new antineoplastic therapy, the percentage of patients who achieved undetectable PSA, the median duration of treatment suspension, the proportion of patients who remain treatment-free 2 years after suspension of study drug treatment, time to resumption of any hormonal therapy following treatment suspension, time to castration resistance, and HRQoL. This industry input has also highlighted additional comments related to health economics evaluation of this review.

Drug Program Input

The drug programs provide input on each drug being reviewed through CDA-AMC's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation.

The drug programs have highlighted that while abiraterone was listed as a comparator in the posted project scope for this review, it may not be a relevant comparator since previous funding was not established for its use in nmCSPC with high-risk BCR.

The drug programs highlighted several policy and implementation considerations and questions. One question was whether other ADTs can be used interchangeably with leuprolide in clinical practice. Other questions revolved around the consistency of the definition of high-risk disease as applied in clinical practice, whether patients with an ECOG status greater than 2 could be eligible for enzalutamide with or without ADT, the potential for downstream re-treatment with enzalutamide, and the treatment options available after enzalutamide. Additionally, they inquired whether there should be time-limited funding considerations to add enzalutamide to the treatment regimen of nmCSPC patients who were recently started on ADT within the last 6 months. The drug programs also sought clarification on the impact of using conventional imaging for the assessment of prostate cancer status in the EMBARK trial, now that PSMA-PET is available.

Other implementation questions and corresponding responses from the clinical experts consulted by CDA-AMC are summarized in the Drug Plan Input published on "Responses to Questions from the Drug Programs."

Clinical Evidence

The clinical evidence included in the review of enzalutamide is presented in 3 sections. The first section, the systematic review, includes studies that were selected according to an a priori protocol.

Systematic Review

Objectives

To perform a systematic review of the beneficial and harmful effects of enzalutamide for the treatment of patients with nmCSPC with BCR at high risk for metastasis.

Methods

Studies selected for inclusion in the CDA-AMC systematic review included those meeting the selection criteria presented in Table 3.Outcomes included in the CDA-AMC review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 3: Inclusion Criteria for the Systematic Review

Criteria	Description
Population	Patients with nmCSPC with BCR at high risk for metastasis
Intervention	Enzalutamide 160 mg orally once daily, with or without ADT
Comparator	ADT (LHRH agonist with or without first-generation antiandrogen, LHRH antagonist, bilateral orchiectomy)
Outcomes	**Efficacy outcomes:** • Metastasis-free survival • Overall survival • Progression-free survival • Time to development of castration resistance • HRQoL **Harms outcomes:** • AEs, SAEs, WDAEs, deaths as AEs **Harms of interest:** • Seizures • Dysgeusia
Study Designs	Published and unpublished phase III and IV RCTs

ADT = androgen deprivation therapy; AE = adverse event; BCR = biochemical recurrence; HRQoL = quality of life; LHRH = luteinizing hormone-releasing hormone; nmCSPC = nonmetastatic castration-sensitive prostate cancer; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[14]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search

concepts were developed based on the elements of the PICOS (participants, intervention, comparator or control, outcomes, and study design) framework and research questions. The main search concepts were enzalutamide and biochemically recurrent, nonmetastatic prostate cancer. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

Search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. Retrieval was limited to documents published since January 1, 2016. Retrieval was not limited by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on May 21, 2024. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee on September 19, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Practical Tool for Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts.

Two CDA-AMC clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

A focused literature search for indirect treatment comparisons dealing with enzalutamide and biochemically recurrent, nonmetastatic prostate cancer was run in MEDLINE on May 21, 2024. The search was limited to documents published since January 1, 2016.

Findings From the Literature

A total of 292 studies were identified from the literature search, and 1 study was selected for inclusion in the systematic review (refer to Figure 3 in Appendix 2). The included study is summarized in Table 4.

Of note, no indirect evidence was identified from the literature that met the selection criteria specified in the review, and no additional relevant studies were identified that may address important gaps in the evidence included in the systematic review.

Protocol Selected Studies

Characteristics of the Included Studies

The characteristics of the EMBARK trial are summarized in Table 4.

Table 4: Details of the Included Trial

Detail	EMBARK 2023[4]
Design and population	
Study design	Phase III, multicentre, randomized controlled trial
Locations	244 sites across 17 countries including Canada (27 sites)
Patient enrolment dates	Between January 2015 and August 2018
Randomized (N)	1,068 patients
Inclusion criteria	• 18 years of age and older • histologically or cytologically confirmed adenocarcinoma of the prostate at initial biopsy, without neuroendocrine differentiation, signet-cell, or small-cell features • prostate cancer initially treated by RP or RT (including brachytherapy) or both, with curative intent — prostate cryoablation was not considered definitive therapy for this study, but its prior use is not exclusionary • PSADT ≤ 9 months • Screening PSA ≥ 1 ng/mL for patients with RP (with or without RT) as primary treatment and screening PSA of at least 2 ng/mL above the nadir for patients who had RT only as primary treatment • Serum testosterone ≥ 150 ng/dL at screening • ECOG PS of 0 or 1 • Anticipated life expectancy of ≥ 12 months • Adequate bone marrow/hematologic function: Hgb ≥ 10.0 g/dL, ANC ≥ 1.5 × 10^9 per litre, platelet count ≥ 100 × 10^9 per litre, may not have received growth factors or blood transfusions within 7 days before hematology values obtained at screening • Adequate renal function: serum creatinine ≥ • 2.0 mg/dL at screening • Adequate hepatic function: total bilirubin < 1.5 x ULN or alanine aminotransferase/aspartate aminotransferase < 2.5 x ULN at screening, albumin ≥ 3.0 g/dL at screening
Exclusion criteria	• Prior cytotoxic chemotherapy • History of seizures or a condition that may confer a predisposition to seizures. • Evidence of distant metastatic disease on conventional imaging (e.g., CT, MRI, bone scans) • If after RP were considered eligible for SRT by investigators • Prior hormonal therapy except for the following indications: neoadjuvant or adjuvant therapy at the time of definitive radiation therapy for no more than 36 months and at least 9 months before randomization or a single dose or short course (≤ 6 months) of hormonal therapy administered for rising PSA levels at least 9 months before randomization
Drugs	
Intervention(s)	• Enzalutamide 160 mg (administered as 4 x 40 mg capsules) by mouth once daily with or without food plus leuprolide acetate 22.5 mg IM or SC once every 12 weeks (double-blinded) • Enzalutamide 160 mg (administered as 4 x 40 mg capsules) by mouth once daily with or without food (open-label)
Comparator	Placebo capsules by mouth once daily plus leuprolide acetate 22.5 mg IM or SC once every 12 weeks (double-blinded)

Detail	EMBARK 2023[4]
Duration	
Follow-up	Treatment was suspended at week 37 if PSA level < 0.2 ng/mL and restarted when PSA level was ≥ 5.0 ng/mL (if no prior RP) or ≥ 2.0 ng/mL (if had prior RP)[a]
Outcomes	
Primary end point	MFS (enzalutamide plus leuprolide vs. leuprolide alone), assessed by blinded central radiological review[b]
Secondary and exploratory end points	Secondary: MFS (enzalutamide alone vs. leuprolide alone), OS[c] Exploratory: PSA progression, development of castration resistance, HRQoL[d]
Notes	
Publications	Freedland et al. *N Engl J Med.* 2023;389(16):1453 to 1465.[4] Freedland et al. *NEJM Evid. 2023;2(12):EVIDoa2300251.*[e]

ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRQoL = health-related quality of life; IM = intramuscular; MFS = metastasis-free survival; OS = overall survival; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; RP = radical prostatectomy; RT = radiotherapy; SC = subcutaneous; SRT = salvage radiotherapy; ULN = upper limit of normal.

[a]PSA was monitored throughout the study, and at week 37, treatment was suspended for patients whose PSA values were undetectable (PSA level < 0.2 ng/mL) at week 36. PSA and testosterone were measured every 3 months thereafter. Radiographic assessments were conducted approximately every 6 months from randomization until radiographic progression.

[b]MFS was defined as the time in months between randomization and the earliest objective evidence of radiographic progression by central imaging or death on study (death within 168 days after permanent treatment discontinuation), whichever occurs first.

[c]OS was defined as the time from the date of randomization to the date of death.

[d]HRQoL was evaluated using Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score.

[e]Patient-reported outcomes were reported in a separate publication. Instruments used were the short-form Brief Pain Inventory (BPI-SF), Quality of Life Questionnaire Prostate 25 (QLQ-PR25), and European Quality of Life 5-Dimensions 5-Levels health questionnaire (EQ-5D-5L).

Source: Freedland et al. 2023.[4]

Study Design

The EMBARK trial was a phase III, randomized, multicentre trial conducted at 244 sites across 17 countries, including Canada (27 sites). The objective of the trial was to evaluate the efficacy and safety of enzalutamide plus leuprolide to leuprolide alone, and enzalutamide alone to leuprolide alone, in adult patients with prostate cancer who had high-risk BCR after local therapy.

Patients were randomly assigned in a 1:1:1 ratio using central randomization to receive enzalutamide plus leuprolide, enzalutamide monotherapy, or placebo plus leuprolide.

The trial began in January 2015, with the primary data cut-off date on January 31, 2023. The data cut-off for the final MFS analysis and interim OS analysis occurred when at least 197 MFS events, based on independent central review, had occurred across the 3 treatment arms. The final OS analysis occurred when 271 OS events had occurred across the 3 treatment arms. The trial was funded by Pfizer and Astellas Pharma.

Eligibility Criteria

Adult patients with prostate cancer who had BCR after local therapy were eligible for the EMBARK trial if they had histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet-cell features, or small-cell features at the time of the initial biopsy before primary definitive therapy. At screening, patients had to have high-risk disease, defined by a PSA doubling time of

months or less and a PSA level of 2 ng/mL or more above nadir after radiation therapy or ≥ 1 ng/mL after RP (with or without postoperative radiation therapy). Additionally, patients needed a serum testosterone level of at least 150 ng/dL and an ECOG performance status score of 0 or 1.

Patients were excluded from the trial if they had undergone prior cytotoxic chemotherapy, had a history of seizures or a condition predisposing them to seizures, showed evidence of distant metastatic disease on conventional imaging (CT, MRI, or bone scans), or were considered candidates for SRT after they had undergone RP. Previous hormonal therapy was also an exclusion criterion, except for neoadjuvant or adjuvant therapy at the time of definitive radiation therapy for no more than 36 months and at least 9 months before randomization, or a single dose or short course (≤ 6 months) of hormonal therapy for rising PSA levels at least 9 months before randomization.

Interventions

Patients were randomly assigned in a 1:1:1 ratio to receive enzalutamide plus leuprolide (combination group, double-blind), placebo plus leuprolide (leuprolide-alone group, double-blind), or enzalutamide monotherapy (enzalutamide-alone group, open-label). Enzalutamide (160 mg) or placebo was taken orally once daily, and leuprolide (22.5 mg) was given intramuscularly or subcutaneously every 12 weeks. Treatment was paused at week 37 if PSA levels at week 36 were below 0.2 ng/mL and resumed when PSA levels reached at least 5.0 ng/mL (no prior prostatectomy) or 2.0 ng/mL (prior prostatectomy). Patients with detectable PSA values at week 36 continued treatment without suspension until permanent treatment discontinuation criteria were met. Patients continued their assigned treatments until imaging-based disease progression confirmed by central review, an unacceptable adverse event, seizure, death, protocol violation, or a decision by the patient or physician to stop the regimen.

Outcomes

A list of efficacy end points identified in the CDA-AMC review protocol that were assessed in the clinical trials included in this review is provided in Table 5 and is further summarized in the following paragraphs.

Table 5: Summary of Outcomes of Interest Identified in the CDA-AMC Review Protocol

Outcome measure	EMBARK
Blinded, independently assessed MFS (combination group vs. leuprolide alone)	Primary
Blinded, independently assessed MFS (monotherapy group vs. leuprolide alone)	Secondary
OS	Secondary
PFS	Not evaluated
Safety	Secondary
PSA progression	Exploratory
Development of castration resistance	Exploratory
HRQoL	Exploratory

CDA-AMC = Canada's Drug Agency; HRQoL = health-related quality of life; MFS = metastasis-free survival; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen.

The primary end point was MFS in the enzalutamide plus leuprolide group versus leuprolide-alone group and a secondary end point was MFS in the enzalutamide-alone group versus leuprolide-alone group.

MFS was defined as the time from randomization to the date of earliest objective evidence of imaging-based progression or death from any cause. Imaging, as defined by Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1, was reviewed by a BICR using conventional CT or MRI and whole-body radionuclide bone scans. Baseline evaluations occurred within 4 weeks before starting trial treatment, and progression assessments were conducted approximately every 6 months after randomization. PSA and testosterone levels were measured by a central laboratory, with patients and site investigators blinded to PSA levels during treatment. Trial sites were notified if PSA levels were considered undetectable (< 0.2 ng/mL at week 36) or met PSA progression criteria, defined as a PSADT of 10 months or less.

Other secondary end points included:

- OS, which was defined as the time from randomization to death from any cause
- time to PSA progression, which was defined as the time from randomization to date of first PSA value demonstrating progression while patients are on study treatment and confirmed at least 3 weeks later, although outcome reported was number of patients with PSA progression
- time to development of castration resistance, which was defined as the time from randomization to the first castration-resistant event (first occurrence of radiographic disease progression, PSA progression, or symptomatic skeletal event with castration levels of testosterone [< 50 ng/dL]), although outcome reported was number of patients that developed castration resistance
- HRQoL outcomes
- safety outcomes.

Adverse events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

HRQoL was evaluated as an exploratory end point using the FACT-P questionnaire. The FACT-P questionnaire is a self-reported, quality of life instrument designed for use in prostate cancer that was completed by patients at the beginning of study visits. It includes 27 core items that evaluate physical, social/family, emotional, and functional well-being over the past 7 days, along with 12 items specific to prostate-related symptoms. Each item is rated on a 0 to 4 scale, and the scores are combined to produce subscale scores for each domain and a global quality of life score, with higher scores indicating better quality of life. Time to first deterioration of FACT-P Total Score was defined as the time from randomization to first assessment with at least a 10-point decrease from baseline on the total score.

Statistical Analysis

Power Calculation

For the primary end point of MFS, it was calculated that with a target enrolment of 1,068 patients, the occurrence of at least 197 events (metastasis or death) across the 3 groups combined would provide the trial

with 90% power to detect a HR of 0.58 for metastasis or death for the enzalutamide plus leuprolide group compared to the leuprolide-alone group, at a two-sided alpha level of 0.05.

Statistical Tests

All efficacy analyses in the EMBARK trial were conducted in the intention-to-treat population, which included all randomized patients regardless of whether they received the allocated treatment or had any efficacy assessments collected. Supportive analyses of the primary and secondary end points were performed using the per-protocol population, defined as patients who were treated according to the protocol without major deviations. As per the trial protocol, unless otherwise specified, all data were evaluated as observed and no imputation of missing values was used.

The distribution of MFS was estimated using the Kaplan-Meier method, and the comparison of MFS between treatment arms was performed using a stratified log-rank test. The stratification factors included PSA level at screening (≤ 10 ng/mL or > 10 ng/mL), PSADT (≤ 3 months or > 3 months to ≤ 9 months), and previous hormonal therapy (yes or no), as reported in an interactive web-response system. This stratified approach aimed to ensure balanced comparisons across treatment groups.

Both interim and final analyses of OS was planned for EMBARK. The interim analysis occurred at the same time as MFS, which was expected after approximately 260 death events in the 2 blinded groups combined. The final OS analysis (not reported) will be conducted after about 465 death events. An O'Brien-Fleming stopping boundary was used for the interim analysis.

HRs were estimated based on a stratified Cox regression model with the trial group as the only covariate, while accounting for the stratification factors. The 2-sided P-values were calculated using a log-rank test, while accounting for the stratification factors. The analyses for MFS, OS, and PSA progression used a hierarchical testing plan to control the potential of inflated type I error. The hierarchical testing strategy began with the comparison of MFS between the enzalutamide plus leuprolide group and the leuprolide-alone group and, if statistically significant, the hierarchal testing would proceed to key secondary end points in a prespecified order. The analyses of development of castration resistance were descriptive.

Safety analyses were conducted on the as-treated population, which included all patients who received at least 1 dose of the study drug. The safety profile was evaluated by the occurrence of serious adverse events, incidence and severity of adverse events, incidence of permanent treatment discontinuation due to adverse events, and incidence of new clinically significant changes in clinical laboratory values and vital signs.

HRQoL was assessed at randomization and every 12 weeks thereafter. The key HRQoL end point was the time to a 10-point decline in the global score of the FACT-P questionnaire. The time to decline in the global FACT-P score was compared between treatment groups using a 2-sided log-rank test.

Critical Appraisal

Internal Validity

Study Design, Intervention, and Comparators

The EMBARK trial was a phase III, randomized, multicentre trial designed to evaluate the efficacy and safety of enzalutamide plus leuprolide versus leuprolide alone using a double-blind design for the primary end point. Additionally, a secondary end point was to evaluate the efficacy and safety of enzalutamide alone versus leuprolide alone, with the enzalutamide-alone arm unblinded.

Patients were randomly assigned in a 1:1:1 ratio using central randomization to receive enzalutamide plus leuprolide, enzalutamide alone, or placebo plus leuprolide. Patients were monitored every 12 weeks. At week 37, treatment was suspended for patients whose PSA values were undetectable (< 0.2 ng/mL) at week 36 as determined by the central laboratory. Patients with detectable PSA values at week 36 continued treatment without suspension until permanent treatment discontinuation criteria were met. Safety follow-up occurred approximately 30 days after treatment was discontinued.

The primary MFS end point in all arms was assessed by BICR, which reduced detection bias. While the combination arm and leuprolide only arm were double-blinded, the enzalutamide-alone arm was open-label. However, the double-blinding of the other arms and the blinded lab and tumour assessment likely reduced the risk of performance bias in the enzalutamide-alone arm. Knowledge of treatment allocation could introduce detection bias, although this was somewhat mitigated by the BICR. Inconsistent blinding could also influence the interpretation of differences in outcomes between arms and could result in biased estimates for subjective outcomes such as safety and HRQoL. However, there was no clear evidence that this occurred in the analyses. The trial did not report on whether participants and investigators were surveyed after the trial to assess their awareness of treatment allocation, which could be a limitation.

Selection, Allocation, and Disposition of Patients

Randomization was conducted using central randomization to ensure unbiased allocation and balance across the 3 treatment arms. The baseline characteristics were well-balanced among the treatment groups indicating that the randomization method was appropriate.

Details of patient disposition are reported in Table 6. The overall discontinuation rates were higher in the leuprolide monotherapy group (56%) compared to the enzalutamide plus leuprolide (41%) and enzalutamide monotherapy groups (44%). Discontinuations due to adverse events were more frequent in both enzalutamide groups and leuprolide group (21% in the enzalutamide and leuprolide group versus 10% in the leuprolide-alone group and 18% in the enzalutamide-alone group). During the randomization period, 2 patients in the enzalutamide plus leuprolide group, 4 patients in the leuprolide-alone group, and 1 patient in the enzalutamide-alone group were randomly assigned but did not receive treatment. The treated populations were 99.4% for the enzalutamide plus leuprolide group, 99.7% for the enzalutamide monotherapy group, and 98.8% for the placebo plus leuprolide group.

Outcome Measures

The primary end point of MFS for enzalutamide plus leuprolide versus leuprolide alone was determined by imaging-based assessment and monitoring of survival status. Imaging assessments, based on RECIST v1.1 criteria, were performed by BICR using conventional CT or MRI and whole-body radionuclide bone scans to identify bone disease. Baseline imaging was conducted 4 weeks before trial start, with progression assessed every 6 months after randomization. The authors justified the use of MFS as a valid and reliable measure of clinical benefit by citing 2 studies[15,16] showing that delays in metastases correlate with prolonged OS in patients with high-risk nonmetastatic prostate cancer and localized prostate cancer.

A clinical expert consulted by CDA-AMC noted that there is uncertainty about the correlation between MFS and OS in the target population for this review, although the expert indicated that MFS has been used as a surrogate end point for OS in the nmCRPC setting (as seen in the PROSPER[12] and SPARTAN[13] trials). However, the validity of MFS as a surrogate for OS in biochemically recurrent prostate cancer remains unclear because it has not been validated in this specific setting. Another expert noted that 1[15] of the studies cited by the authors is a summary analysis of 2 randomized controlled trial from different sites within the STAMPEDE trial and does not aim to establish a direct correlation between MFS and OS. The expert also indicated that while the FDA recognizes MFS as a surrogate for OS in the nmCRPC setting,[17] this recognition is a policy decision rather than statistical validation of surrogacy.

Statistical Analysis

The analyses for MFS, OS, and PSA progression used a hierarchical testing plan to control the potential of inflated type I error. The hierarchical testing strategy began with the comparison of MFS between the enzalutamide plus leuprolide group and the leuprolide-alone group and, if statistically significant, the hierarchal testing would proceed to key secondary end points in a prespecified order. The lack of multiplicity adjustment in the statistical analyses of secondary end points cannot rule out the possibility of type I errors, which could lead to an overestimation of difference between treatment groups.

The authors did not report whether the proportional hazards assumption was evaluated before conducting the Cox proportional hazards analyses, which raises uncertainty in the reliability of the HRs and 95% CIs reported for MFS and other time-to-event end points. The Kaplan-Meier curves showed crossover at several points for the MFS analyses, though the curves showed clear separation from month 24 for the enzalutamide + leuprolide versus leuprolide comparison, and from month 30 for the enzalutamide monotherapy versus leuprolide comparison. Later separation of the survival curves is not unusual in trials of interventions versus active comparators in patients with earlier stage cancers. Thus, while information regarding whether the proportion hazards assumption was met — including sensitivity analysis using approaches that do not rely on the proportional hazards assumption — should have been provided, CDA-AMC reviewers' visual inspection of the Kaplan-Meier curves did not indicate a clear violation of the assumption.

External Validity

Patient Selection, Treatment Regimen, Length of Follow-Up, and Outcome Measures

The EMBARK trial is clinically relevant to the Canadian setting due to the inclusion of 27 Canadian sites. However, the predominantly white patient population (> 80%) and the strict inclusion criteria, such as PSADT

and specific performance status requirements, might limit its generalizability to a broader patient population in Canada. The use of enzalutamide in combination with ADT or as monotherapy is consistent with clinical practice, as both medications are approved and used in Canada for the treatment of prostate cancer. The regimens studied in the trial align with current practice. The duration of follow-up aligns with standards for monitoring high-risk prostate cancer patients; however, MFS and OS were not mature at the data cut-off. Progression-free survival, which was identified by CDA-AMC experts and reviewers as a key outcome of interest, was not evaluated in the trial. No comparison between enzalutamide combination therapy and enzalutamide monotherapy was made, limiting the ability to determine which treatment might be preferable and which patient subgroups might benefit from 1 approach over the other. Relevant harm outcomes were reported. HRQoL was assessed using the FACT-P questionnaire, with additional patient-reported outcomes measures reported separately.[5]

Results

Patient Disposition

Of the 1,068 patients enrolled and randomized into the study, 355 patients were assigned to the combination group, 358 into the leuprolide-alone group, and 355 into the enzalutamide-mono group (Table 6). During the randomization period, 2 patients in the enzalutamide plus leuprolide group, 4 patients in the leuprolide-alone group, and 1 patient in the enzalutamide along group were randomly assigned but not treated. More patients in the leuprolide-alone group discontinued treatment (56.2%) compared to the enzalutamide plus leuprolide group (41.1%) and the enzalutamide-alone group (44.2%). In the leuprolide-alone group, more patients discontinued treatment due to progression: radiographic progression (18.4%), PSA progression (5.6%), and development of castration resistance (0.6%). More patients in the enzalutamide plus leuprolide group (20.6%) and the enzalutamide-alone group (17.7%) discontinued treatment due to adverse events compared to the leuprolide-alone group (10.1%).

Baseline Characteristics

The baseline characteristics of the 3 treatment arms are listed in Table 7. They were generally balanced between the 3 arms. The median age was 69 years (range, 49.0 to 93.0), the median PSADT was 4.9 months (range, 0.9 to 18.9), and the median PSA level was 5.2 ng per mL (range, 1.0 to 308.3). Most patients were white (83.2%), had ECOG 0 (92.2%), and had not had previous hormonal therapy (68.9%).

Table 6: Patient Disposition

Disposition	EMBARK		
	Enzalutamide + leuprolide	Leuprolide alone	Enzalutamide alone
Screened, N	1,813		
Randomized, N	1,068		
Started, N	355	358	355
Treated, N (%)	353 (99.4)	354 (98.9)	354 (99.7)
Randomly assigned but not treated, N (%)	2 (0.6)	4 (1.1)	1 (0.3)

Disposition	EMBARK		
	Enzalutamide + leuprolide	Leuprolide alone	Enzalutamide alone
Continued to receive treatment, N (%)	207 (58.3)	153 (42.7)	197 (55.5)
With treatment suspension and reinitiation	168 (47.3)	114 (31.8)	171 (48.2)
With treatment suspension but no reinitiation	34 (9.6)	14 (3.9)	13 (3.7)
Without treatment suspension	5 (1.4)	25 (7.0)	13 (3.7)
Discontinued treatment, N (%)	146 (41.1)	201 (56.2)	157 (44.2)
Reason for discontinuation, N (%)			
Adverse events	73 (20.6)	36 (10.1)	63 (17.7)
Withdrew consent	26 (7.3)	32 (8.9)	25 (7.0)
Had radiographic progression	26 (7.3)	66 (18.4)	37 (10.4)
Had castration resistance	0 (0)	2 (0.6)	0 (0)
PSA progression	2 (0.6)	20 (5.6)	5 (1.4)
Protocol deviation	2 (0.6)	2 (0.6)	1 (0.3)
Lost to follow-up	0 (0)	1 (0.3)	0 (0)
Site closure	0 (0)	1 (0.3)	0 (0)
Other	17 (4.8)	41 (12.8)	26 (7.3)
ITT, N	355	358	355
Safety, N	353	354	354

ITT = intention to treat; PSA = prostate-specific antigen.

Source: Freedland et al. 2023.[4]

Table 7: Summary of Baseline Characteristics

Characteristic	Enzalutamide + leuprolide (n = 355)	Leuprolide alone (n = 358)	Enzalutamide alone (n = 355)
Age in years, median (range)	69 (51 to 87)	70 (50 to 92)	69 (49 to 93)
Age group, n (%)			
< 65 years	81 (22.8)	91 (25.4)	91 (25.6)
65 to < 75 years	201 (56.6)	180 (50.3)	174 (49.0)
≥ 75 years	73 (20.6)	87 (24.3)	90 (25.4)
Race or ethnic group, n (%)			
White	293 (82.5)	301 (84.1)	295 (83.1)
Asian	26 (7.3)	26 (7.3)	26 (7.3)
Black	16 (4.5)	16 (4.5)	15 (4.2)
American Indian or Alaska Native	4 (1.1)	1 (0.3)	0

Characteristic	Enzalutamide + leuprolide (n = 355)	Leuprolide alone (n = 358)	Enzalutamide alone (n = 355)
Native Hawaiian or other Pacific Islander	1 (0.3)	0	0
Other	5 (1.4)	9 (2.5)	5 (1.4)
Not reported	10 (2.8)	5 (1.4)	14 (3.9)
Geographic region, n (%)			
North America	144 (40.6)	137 (38.3)	133 (37.5)
Europe	130 (36.6)	128 (35.8)	146 (41.1)
Rest of the world	81 (22.8)	93 (26.0)	76 (21.4)
ECOG PS, n (%)			
0	328 (92.4)	336 (93.9)	321 (90.4)
1	26 (7.3)	21 (5.9)	34 (9.6)
> 1	1 (0.3)	0	0
Missing data	0	1 (0.3)	0
PSA doubling time, n (%)			
≤ 3 months	69 (19.4)	80 (22.3)	76 (21.4)
> 3 to 6 months	187 (52.7)	142 (39.7)	164 (46.2)
> 6 to 9 months	98 (27.6)	135 (37.7)	114 (32.1)
Missing data	1 (0.3)	1 (0.3)	1 (0.3)
PSADT in months, median (range)	4.6 (0.9 to 9.6)	5.0 (1.1 to 10.8)	5.0 (1.0 to 18.9)
Serum PSA level (ng/mL), median (range)	5.0 (1.0 to 308.3)	5.5 (1.1 to 163.3)	5.3 (1.1 to 37.0)
Previous hormonal therapy, n (%)			
Yes	107 (30.1)	113 (31.6)	112 (31.5)
No	248 (69.9)	245 (68.4)	243 (68.5)
Primary definitive therapy, n (%)			
Prostatectomy alone	90 (25.4)	75 (20.9)	99 (27.9)
Radiation therapy alone	86 (24.2)	104 (29.1)	90 (25.4)
Prostatectomy and radiation therapy	179 (50.4)	179 (50.0)	166 (46.8)

ECOG PS = Eastern Cooperative Oncology Group Performance Status; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time.

Source: "From N Engl J Med. Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. 2023;389(16):1458. Copyright © 2023 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society."[4]

Exposure to Study

The median duration of treatment excluding treatment suspension was 38.7 months. At week 36, 90.9% of patients in the enzalutamide plus leuprolide group had a PSA of < 0.2 ng/mL and suspended treatment for a median of 20.2 months. 67.8% of patients in the leuprolide-alone group suspended treatment for a median of

16.8 months while 85.9% of patients in the enzalutamide-alone group suspended treatment for a median of 11.1 months. Refer to Table 8.

Table 8: Treatment Exposure — EMBARK

Treatment exposure	Enzalutamide + leuprolide (n = 355)	Leuprolide alone (n = 358)	Enzalutamide alone (n = 355)
Duration of treatment in months, excluding treatment suspension, median (range)		38.7 (0.1 to 88.9)	
Duration of treatment in months, excluding treatment suspension, median (range)	32.4 (0.1 to 83.4)	35.4 (0.7 to 85.7)	45.9 (0.4 to 88.9)
Patients with PSA < 0.2 ng/mL at week 36 and treatment suspension, n (%)	321 (90.9)	240 (67.8)	304 (85.9)
Duration of treatment suspension in months, median (range)	20.2 (5.7 to 87.9)	16.8 (3.4 to 83.0)	11.1 (2.3 to 84.9)
Did not receive treatment for > 24 months (%)	43.9	32.1	20.4

PSA = prostate-specific antigen.

Source: Freedland et al. 2023.[4]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported in this section. Refer to Table 9.

At data cut-off (January 31, 2023), the median follow-up for MFS for all groups was 60.7 months (60.7 months in the enzalutamide plus leuprolide group, 60.6 months in the leuprolide group, and 60.7 months in the enzalutamide-alone group) while the median follow-up for OS was 66.0 months in the enzalutamide plus leuprolide group, 66.2 months in the leuprolide-alone group, and 64.5 months in the enzalutamide-alone group.

Metastasis-Free Survival

Blinded, Independently Assessed MFS (Enzalutamide Plus Leuprolide Versus Leuprolide Alone)

At data cut-off, 45 patients (12.7%) in the enzalutamide-leuprolide group had experienced an MFS event compared to 92 patients (25.7%) in the leuprolide-alone group. The 5-year MFS rate was 87.3% (95% CI, 83.0 to 90.6) for the combination group and 71.4% (95% CI, 65.7 to 76.3) for the leuprolide-alone group. The HR favoured treatment with combination therapy as compared to leuprolide alone for MFS (HR, 0.42; 95% CI, 0.30 to 0.61; P < 0.001).

Blinded, Independently Assessed MFS (Enzalutamide Alone Versus Leuprolide Alone)

A total of 63 patients (17.7%) in the enzalutamide-alone group experienced an MFS event at data cut-off. The 5-year MFS rate was 80.0% (95% CI, 75.0 to 84.1) in the enzalutamide-alone group. The HR for MFS favoured treatment with enzalutamide monotherapy as compared to leuprolide alone (HR, 0.63; 95% CI, 0.46 to 0.87; P = 0.005).

Overall Survival

Interim analysis of OS was conducted concurrently with the primary analysis of MFS. At interim analysis, 130 of 271 patients (48.0%) had died: 33 patients in the enzalutamide-leuprolide group, 55 in the leuprolide-alone group, and 42 in the enzalutamide-alone group. The 5-year OS rates were 92.2% (95% CI, 88.7 to 94.7) for the enzalutamide-leuprolide group, 87.2% (95% CI, 83.0 to 90.4) for the leuprolide-alone group, and 89.5% (95% CI, 85.6 to 92.4) for the enzalutamide-alone group. The HR for death was 0.59 (95% CI, 0.38 to 0.91; P = 0.02) for enzalutamide plus leuprolide versus leuprolide alone, and 0.78 (95% CI, 0.52 to 1.17; P = 0.23) for enzalutamide alone versus leuprolide alone.

PSA Progression

At data cut-off, the estimated percentage of patients free from PSA progression was 97.4% (95% CI, 94.7 to 98.8) in the enzalutamide-leuprolide group, 70.0% (95% CI, 64.1 to 75.1) in the leuprolide-alone group, and 88.9% (95% CI, 84.6 to 92.1) in the enzalutamide-alone group. Patients in both the enzalutamide-leuprolide and enzalutamide-alone groups had a significantly lower risk of PSA progression compared to the leuprolide-alone group (HR for the enzalutamide-leuprolide group, 0.07; 95% CI, 0.03 to 0.14; P < 0.001; HR for the enzalutamide-alone group, 0.33; 95% CI, 0.23 to 0.49; P < 0.001).

Development of Castration Resistance

At data cut-off, the percentage of patients that developed castration resistance was lower in the enzalutamide-leuprolide group (3.9%) than the leuprolide-alone group (33.5%). Development of castration resistance was not reported in the enzalutamide-alone group.

Health-Related Quality of Life

At data cut-off, there was no significant difference in the incidences of time to first deterioration of FACT-P total scores between the enzalutamide-leuprolide group (72.4%), the enzalutamide-alone group (74.1%), and the leuprolide-alone group (69.3%).

Patient-reported outcomes for EMBARK were published separately.[5] Instruments used were the BPI-SF, FACT-P questionnaire, QLQ-PR25, and European Quality of Life 5-Dimension 5-Levels health questionnaire (EQ-5D-5L) scores.

Table 9: EMBARK Efficacy Outcomes

Efficacy outcome	Enzalutamide + leuprolide, n = 355	Leuprolide alone, n = 358	Enzalutamide alone, n = 355
Blinded, independently assessed MFS (at data cut-off) — primary end point			
Median follow-up, months	60.7	60.6	—
Imaging-based progression or death, n (%)	45 (12.7)	92 (25.7)	—
Median MFS, months	NR (NR to NR)	NR (85.1 to NR)	—
5-year MFS, % (95% CI)	87.3 (83.0 to 90.6)	71.4 (65.7 to 76.3)	—
HR (95% CI)	0.42 (0.30 to 0.61)		—

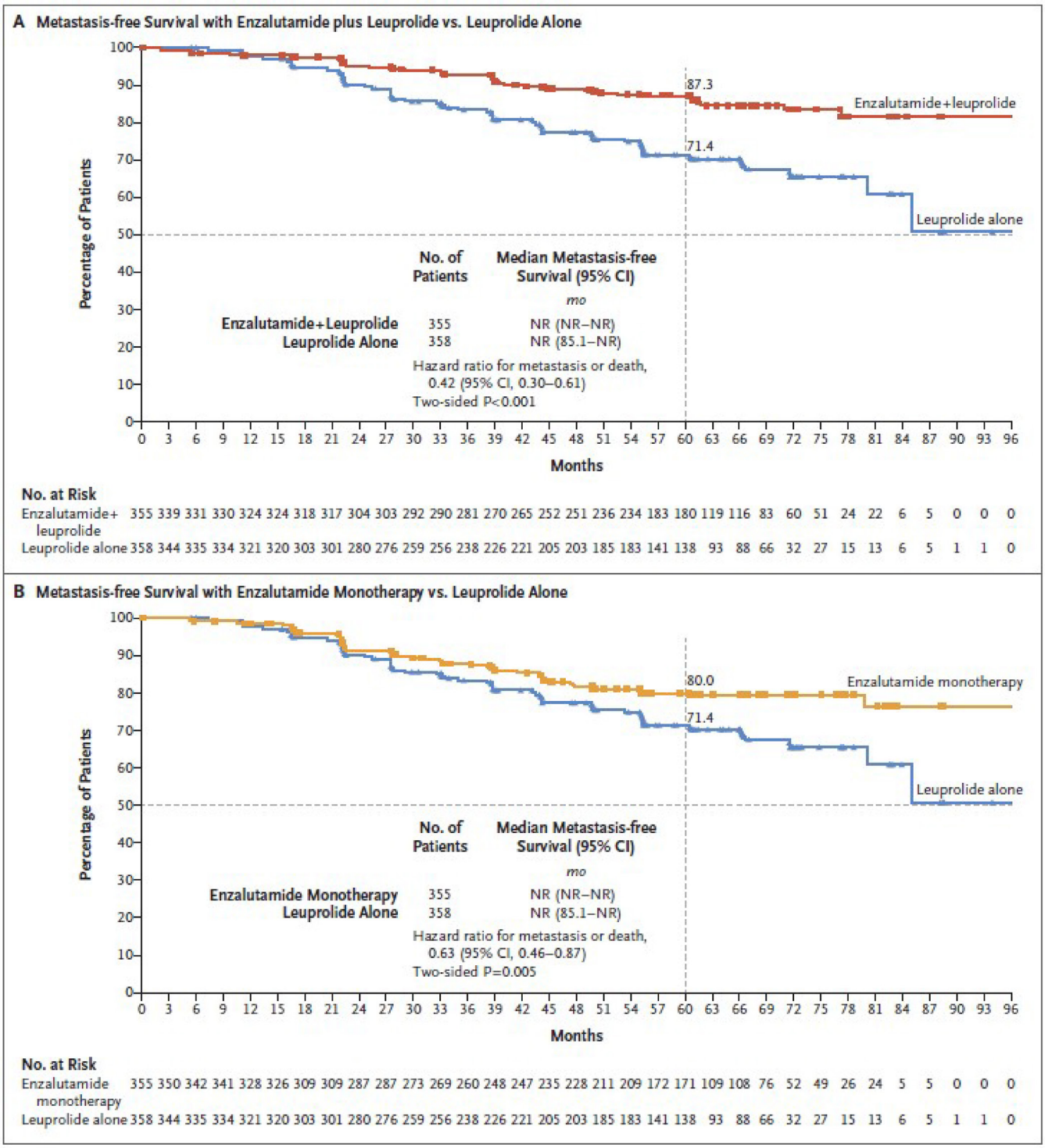
Efficacy outcome	Enzalutamide + leuprolide, n = 355	Leuprolide alone, n = 358	Enzalutamide alone, n = 355
P value	P < 0.001		—
Blinded, independently assessed MFS (at data cut-off) — secondary end point			
Median follow-up, months	—	60.6	60.7
Imaging-based progression or death, n (%)	—	92 (25.7)	63 (17.7)
Median MFS, months	—	NR (85.1 to NR)	NR (NR to NR)
5-year MFS, % (95% CI)	—	71.4 (65.7 to 76.3)	80.0 (75.0 to 84.1)
HR (95% CI)	—	0.63 (0.46 to 0.87)	
P value	—	P = 0.005	
OS (at data cut-off) — secondary end point			
Median follow-up, months	66.0	66.2	64.5
Death, n (%)	33 (9.3)	55 (15.4)	42 (11.8)
5-year OS, % (95% CI)	92.2 (88.7 to 94.7)	87.2 (83.0 to 90.4)	89.5 (85.6 to 92.4)
HR (95% CI), P value	0.59 (0.38 to 0.91), P = 0.02		—
	—	0.78 (0.52 to 1.17), P = 0.23	
Castration resistance (at data cut-off) — exploratory end point			
Events, n (%)	14 (3.9)	120 (33.5)	—
HR (95% CI)	0.09 (0.05 to 0.16)		—
PSA progression (at data cut-off) — exploratory end point			
Events, n (%)	8 (2.3)	93 (26.0)	37 (10.4)
HR (95% CI), P value	0.07 (0.03 to 0.14), P < 0.001		—
	—	0.33 (0.23 to 0.49); P < 0.001	
First deterioration in FACT-P score (at data cut-off) — secondary end point			
Events, n (%)	257 (72.4)	248 (69.3)	263 (74.1)
HR (95% CI), P value	1.14 (0.95 to 1.36)		—
	—	1.17 (0.98 to 1.39)	

CI = confidence interval; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HR = hazard ratio; ITT = intention to treat; MFS = metastasis-free survival; NR = not reported; OS = overall survival; PSA = prostate-specific antigen.

[a]Blinded, independently assessed.

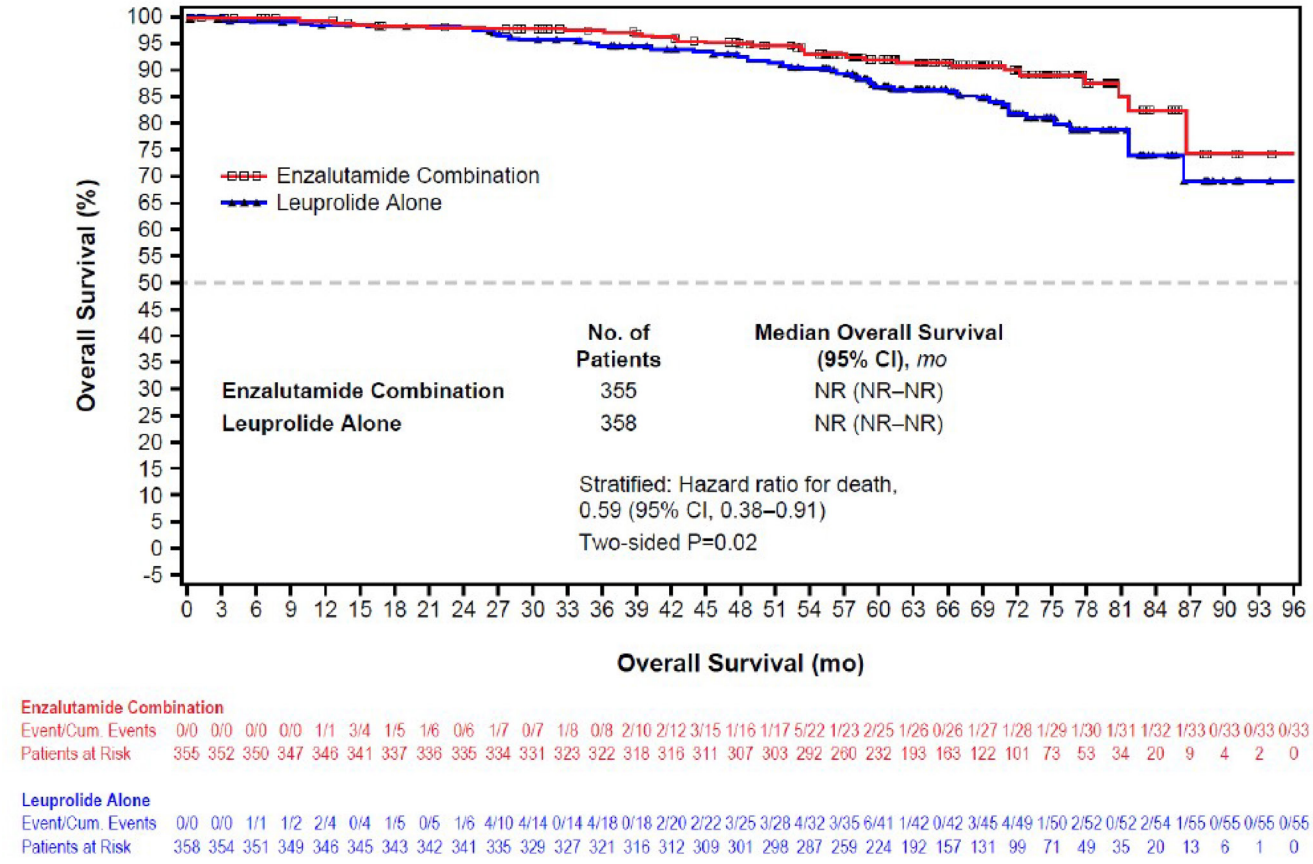
Source: Freedland et al.[4]

Figure 1: Metastasis-Free Survival (ITT Population)



Source: "From N Engl J Med. Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. 2023;389(16):1460. Copyright © 2023 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society."[4]

Figure 2: Overall Survival (ITT Population) Enzalutamide Plus Leuprolide Versus Leuprolide Alone



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Harms

Only those harms identified in the review protocol are reported in the following paragraphs. Refer to Table 10 for detailed harms data.

Adverse Events

Adverse events occurred in more than 97% of patients across all groups. Treatment discontinuation due to adverse events was noted in 73 of 353 patients (20.7%) in the enzalutamide plus leuprolide group, 36 of 354 patients (10.2%) in the leuprolide-alone group, and 63 of 354 patients (17.8%) in the enzalutamide-alone group. The most common adverse event leading to discontinuation was fatigue, affecting 12 patients (3.4%) in the combination group, 4 patients (1.1%) in the leuprolide-alone group, and 8 patients (2.3%) in the monotherapy group.

Adverse events leading to death were not considered treatment-related by the site investigators in any group.

Notable Harms

Despite the exclusion of patients with a history of seizures, seizures occurred more frequently in the combination group compared to the leuprolide-alone group. Investigators determined the overall seizure rate to be low (1.1%; 0.3% per 100 patient-years), consistent with rates observed in previous trials of enzalutamide.

Table 10: Summary of Harms

AEs	Enzalutamide + leuprolide (n = 353)	Leuprolide alone (n = 354)	Enzalutamide alone (n = 354)
Any grade AE, n (%)	343 (97.2)	345 (97.5)	347 (98.0)
≥ Grade 3, n (%)	164 (46.5)	151 (42.7)	117 (50.0)
Serious AE, n (%)	123 (34.8)	112 (31.6)	131 (37.0)
≥ Grade 3, n (%)	110 (31.2)	100 (28.2)	116 (32.8)
AE leading to dose reduction, n (%)	25 (7.1)	16 (4.5)	56 (15.8)
AE leading to permanent treatment discontinuation, n (%)	73 (20.7)	36 (10.2)	63 (17.8)
AE leading to death, n (%)	6 (1.7)	3 (0.8)	8 (2.3)
AEs of interest, n (%)			
Hot flash	243 (68.8)	203 (57.3)	77 (21.8)
Fatigue	151 (42.8)	116 (32.8)	165 (46.6)
Arthralgia	97 (27.5)	75 (21.2)	81 (22.9)
Hypertension	82 (23.2)	69 (19.5)	67 (18.9)
Fracture	65 (18.4)	48 (13.6)	39 (11.0)
Back pain	60 (17.0)	54 (15.3)	62 (17.5)
Hematuria	42 (11.9)	44 (12.4)	45 (12.7)
Urinary incontinence	34 (9.6)	28 (7.9)	36 (10.2)
Urinary tract infection	27 (7.6)	26 (7.3)	37 (10.5)
Gynecomastia	29 (8.2)	32 (9.0)	159 (44.9)
Ischemic heart disease	19 (5.4)	20 (5.6)	32 (9.0)
Other selected cardiovascular events[a]	18 (5.1)	17 (4.8)	13 (3.7)
Seizures	4 (1.1)	0 (0)	3 (0.8)

AE = adverse event.

[a]Other selected cardiovascular events include hemorrhagic central nervous system vascular conditions, ischemic central nervous system vascular conditions, and cardiac failure.

Source: "From N Engl J Med. Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. 2023;389(16):1463. Copyright © 2023 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society."[4]

Indirect Evidence

No indirect treatment comparisons were identified for this review.

Other Relevant Evidence

Additional quality of life data for EMBARK was published separately[5] and discussed in the Health-Related Quality of Life section.

Economic Evidence

The economic review consisted of a cost comparison for enzalutamide (with and without ADT) compared with ADT alone for adult patients with nmCSPC with BCR at high risk of metastasis.

CDA-AMC Analyses

The comparators presented in Table 11 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on public cancer agency regimen monographs and validated by clinical experts. If discrepancies in dosing between the monograph and Canadian clinical practice exist, the dose specified by clinical experts was used. Pricing for comparator products was based on publicly available list prices.

The recommended dose of enzalutamide is 160 mg daily. At $29.20 per 40 mg capsule, the cost of treatment with enzalutamide is $116.78 daily, or $3,270 per patient per 28 days. While the EMBARK trial studied enzalutamide with or without leuprolide compared to leuprolide alone, according to clinical expert input obtained by CDA-AMC, for patients who receive enzalutamide in addition to ADT, the choice of ADT in clinical practice is unlikely to change due to the addition of enzalutamide. The incremental cost of enzalutamide as an add-on therapy to ADT (including leuprolide) is equal to its cost of $3,270 per patient per 28 days. According to clinical expert input obtained by CDA-AMC, the option to avoid ADT therapy is likely to be attractive to some patients. For patients receiving enzalutamide alone, the incremental cost of treatment with enzalutamide is $2,388 to $3,015 per patient per 28 days compared to ADT, depending on ADT regimen displaced. Note that results may differ by jurisdiction if there are differences in their list prices for the drugs under review compared to those presented in Table 11.

Table 11: CDA-AMC Cost Comparison Table for High-Risk Biochemically Recurrent, Nonmetastatic, Castration-Sensitive Prostate Cancer

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	Cost per 28 days
Enzalutamide (Xtandi)	**40 mg**	**Capsule**	**29.1954**	**160 mg orally once daily**	**116.78**	**3,270**
Enzalutamide plus leuprolide					**125.88 to 129.54**	**3,525 to 3,627**
Enzalutamide plus any ADT (maintenance)					**128.88 to 132.06**	**3,525 to 3,698**
LHRH agonists						
Buserelin (Suprefact Depot)	6.3 mg 9.45 mg	Implant	929.2348 1376.9938	6.3 mg SC implanted every 2 months or 9.45	15.09 to 15.28	423 to 428

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	Cost per 28 days
				mg SC implanted every 3 months[18,19]		
Leuprolide (Eligard)	7.5 mg 22.5 mg 30 mg 45 mg	Prefilled, dual chambered syringe with powder for reconstitution	310.7200 891.0000 1,285.2000 1,659.9000	7.5 mg SC monthly, 22.5 mg SC every 3 months, 30 mg SC every 4 months, or 45 mg SC every 6 months[20,21]	9.10 to 10.56	255 to 296
Leuprolide (Lupron Depot)	7.5 mg 22.5 mg 30 mg	Prefilled, dual chambered syringe with powder for reconstitution	387.9700 1,071.0000 1,428.0000	7.5 mg IM monthly, 22.5 mg IM every 3 months, or 30 mg IM every 4 months[20,21]	11.74 to 12.76	329 to 357
Goserelin (Zoladex, Zoladex LA)	3.6 mg 10.8 mg	Depot for SC injection	422.6778 1,204.7322	3.6 mg SC every 4 weeks or 10.8 mg SC every 3 months (13 weeks)[22,23]	13.24 to 15.10	371 to 423
Triptorelin (Trelstar, Trelstar LA)	3.75 mg 11.25 mg 22.5 mg	Powder for injectable suspension	346.3100 1,038.9700 1,659.9000	3.75 mg IM monthly or 11.25 mg IM every 3 months, or 22.5 mg IM every 6 months[24,25]	9.10 to 11.39	255 to 319
First-generation antiandrogens						
Bicalutamide (generics)	50 mg	Tablet	1.2690	50 mg orally once daily[18,20,22,25,26]	1.27	36
Flutamide (generic)	250 mg	Tablet	1.8255	250 mg orally every 8 hours[27]	5.48	153
Nilutamide (Anandron)	50 mg	Tablet	2.7051	300 mg orally once daily for 1 month, then 150 mg once daily thereafter[28]	First month: 16.23 Thereafter: 8.12	First cycle: 454 Thereafter: 227
LHRH agonist plus first-generation antiandrogen combination regimens						
LHRH agonist plus first-generation antiandrogen (continuous)[a]					First month: 10.36 to 31.51 Thereafter: 10.36 to 23.39	First cycle: 290 to 882 Thereafter: 290 to 655
LHRH agonist (continuous) plus first-generation antiandrogen (1 month only)[ab]					First month: 10.36 to 31.51 Thereafter: 9.10 to 15.28	First cycle: 290 to 882 Thereafter: 255 to 428

Treatment	Strength / concentration	Form	Price	Recommended dosage	Daily cost	Cost per 28 days
LHRH antagonist						
Degarelix (Firmagon)	80 mg 120 mg	Powder for injection	274.1760 370.9440	240 mg SC initially, then 80 mg SC monthly[29]	First month: 24.39 Thereafter: 9.01	First cycle: 683 Thereafter: 252

ADT = androgen deprivation therapy; CDA-AMC = Canada's Drug Agency; IM = intramuscular; LA = long-acting; LHRH = luteinizing hormone-releasing hormone; SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2024)[30] unless otherwise indicated and do not include dispensing fees. A year was assumed to last 365 days, and a month was assumed to be 365/12 days.

[a]The Cancer Care Ontario regimen database lists funded LHRH agonist plus antiandrogen regimens only for bicalutamide in combination with buserelin, goserelin, leuprolide, or triptorelin. However, clinical expert opinion obtained by CDA-AMC indicates that clinicians often use any LHRH agonist in combination with any first-generation antiandrogen. As both drug classes are listed as general benefits in some jurisdictions (e.g., Ontario[30]), the cost range presented here assumes all combinations of an LHRH agonist and a first-generation antiandrogen are possible.

[b]Clinical expert opinion obtained by CDA-AMC indicates that first-generation antiandrogens are often prescribed for 1 month only, with patients continuing on an LHRH agonist alone thereafter.[4,5]

Issues for Consideration

- Health Canada currently lists 3 generic enzalutamide submissions under review.[31] Should any or all of these submissions receive regulatory approval and become available in Canada, the cost of enzalutamide would be lower than estimated in this review. According to the pan-Canadian Pharmaceutical Alliance Tiered Pricing Framework,[32] the price of a single source generic product would be reduced to 55% of the brand reference after 3 months of funding, whereas when 3 or more generics are available on the Canadian market, the price would be 25% of the brand reference price (assuming an oral solid product such as enzalutamide). Therefore, should generic enzalutamide become available in Canada, the cost per 40 mg capsule could range from $7.30 to $16.06, depending on the number of generic products available, corresponding to a cost of $817 to $1,798 per patient per 28 days.
- According to clinical expert input obtained by CDA-AMC, patients who receive enzalutamide with or without ADT for the treatment of high-risk BCR nmCSPC are unlikely to be treated with enzalutamide again should they progress while receiving it (i.e., to metastatic disease and/or castration-resistant prostate cancer). As such, the funding of enzalutamide for high-risk BCR nmCSPC may potentially be partially offset by reductions in its use in later lines of therapy.
- According to clinical expert input obtained by CDA-AMC, monitoring costs such as physician assessments, nursing care, or pharmacy assessments may be higher with enzalutamide than ADT alone. However, due to potential delays in progression to castration-resistant and/or metastatic disease, the higher costs involved in managing more severe disease are also expected to be delayed and potentially reduced. Insufficient data were available to estimate such differences.
- Within the EMBARK trial, more patients within the enzalutamide plus leuprolide group achieved a PSA < 0.2 ng/mL at week 36 and were able to suspend treatment for longer than either the leuprolide-alone or enzalutamide-alone groups[5] (Table 8: Treatment Exposure). If patients in clinical practice are similarly more likely to achieve PSA < 0.2 ng/mL and suspend therapy for longer periods

of time with enzalutamide plus ADT than enzalutamide alone, the overall treatment cost of treatment with enzalutamide plus ADT may be lower than that of enzalutamide alone.

- No Canadian cost-effectiveness studies were identified based on a literature search conducted on August 2, 2024.

Discussion

Summary of Available Evidence

The main evidence base for this review was the EMBARK trial, a phase III, randomized, multicentre study conducted at 244 sites across 17 countries. Patients with prostate cancer who had high-risk BCR after local therapy were randomized to receive enzalutamide plus leuprolide (n = 355), enzalutamide monotherapy (n = 355), or placebo plus leuprolide (n = 358). The median duration of treatment in all groups was 38.7 months.

The primary end point was independently assessed MFS in the enzalutamide plus leuprolide group versus the leuprolide-alone group. Other end points included independently assessed MFS in the enzalutamide monotherapy group versus the leuprolide-alone group, OS, PSA progression, development of castration resistance, HRQoL, and safety. The median age was 69 years (range, 49 to 93), the median PSADT was 4.9 months (range, 0.9 to 18.9), and the median PSA level was 5.2 ng per mL (range, 1.0 to 308.3). The distributions by race were 83.2% white, 7.3% Asian, 4.4% Black, 0.5% American Indian or Alaska Native, 0.09% Native Hawaiian or other Pacific Islander, 1.8% other, and 2.7% not reported. 99.8% of patients reported ECOG PS of 0 or 1.

Interpretation of Results

Efficacy

At the data cut-off date on January 31, 2023, the median follow-up in all 3 groups was 60.7 months. At week 36, 90.9% of patients in the enzalutamide plus leuprolide group had a PSA of < 0.2 ng/mL and suspended treatment for a median of 20.2 months. 67.8% of patients in the leuprolide-alone group suspended treatment for a median of 16.8 months while 85.9% of patients in the enzalutamide-alone group suspended treatment for a median of 11.1 months. A clinical expert consulted by CDA-AMC considered this a relevant outcome, as a treatment-free period for patients who have fairly well-controlled disease would mean less exposure to treatment-associated toxicities. The investigators posited that the shorter duration of suspension in the enzalutamide monotherapy group could likely be attributed to the absence of testosterone suppression, whereas ADT can sustain testosterone suppression for months to years after treatment cessation, which the expert agreed was a reasonable assumption.

At 5 years, the blinded, independently assessed MFS of the enzalutamide plus leuprolide group versus the leuprolide-alone group was 87.3% (95% CI, 83.0 to 90.6) and 71.4% (95% CI, 65.7 to 76.3) respectively, translating to a HR of 0.42 (95% CI, 0.30 to 0.61; P < 0.001). At 5 years, the blinded independently assessed MFS for the enzalutamide alone versus the leuprolide-alone group versus the leuprolide-alone group was

80.0% (95% CI, 75 to 84.1) and 71.4% (95% CI, 65.7 to 76.3) respectively, translating to a HR of 0.63 (95% CI, 0.46 to 0.87; P = 0.005).

The 5-year OS rates were 92.2% (95% CI, 88.7 to 94.7) for the enzalutamide-leuprolide group, 87.2% (95% CI, 83.0 to 90.4) for the leuprolide-alone group, and 89.5% (95% CI, 85.6 to 92.4) for the enzalutamide-alone group. The HR for death was 0.59 (95% CI, 0.38 to 0.91; P = 0.02) for enzalutamide plus leuprolide versus leuprolide alone, and 0.78 (95% CI, 0.52 to 1.17; P = 0.23) for enzalutamide alone versus leuprolide alone.

MFS and OS were not mature at data cut-off. Although a minimal clinically important difference threshold for MFS in nmCSPC has not been established, a clinical expert consulted by CDA-AMC suggested that the 15.9% difference in MFS between the enzalutamide plus leuprolide and leuprolide-alone groups could be deemed clinically significant. For enzalutamide alone versus leuprolide alone, a 7.5% difference in MFS may be considered clinically significant.

Similarly, while a minimal clinically important difference OS in nmCSPC has not been determined, the expert indicated that a 5% difference in OS between the enzalutamide plus leuprolide and leuprolide-alone groups might suggest a clinically significant improvement favouring the combination group. However, the 2.3% difference in OS between enzalutamide alone and leuprolide alone is unlikely to reflect a clinically meaningful improvement. Caution is warranted when interpreting these results due to the immaturity of the OS data, the relatively small number of events, and the fact that the EMBARK trial was not optimally designed to assess OS.

At data cut-off, the estimated percentage of patients free from PSA progression was 97.4% (95% CI, 94.7 to 98.8) in the enzalutamide-leuprolide group, 70.0% (95% CI, 64.1 to 75.1) in the leuprolide-alone group, and 88.9% (95% CI, 84.6 to 92.1) in the enzalutamide-alone group. Patients in both the enzalutamide-leuprolide and enzalutamide-alone groups had a significantly lower risk of PSA progression compared to the leuprolide-alone group, with HRs of 0.07 (95% CI, 0.03 to 0.14; P < 0.001) and 0.33 (95% CI, 0.23 to 0.49; P < 0.001), respectively.

Additionally, at the data cut-off, the percentage of patients who developed castration resistance was lower in the enzalutamide-leuprolide group (3.9%) compared to the leuprolide-alone group (33.5%). A clinical expert consulted by CDA-AMC suggested that the 29.6% difference in castration resistance represents a clinically significant improvement with enzalutamide plus leuprolide compared to leuprolide alone. This outcome is relevant because the development of castration resistance is associated with an increased risk of metastatic disease, which in turn correlates with poorer oncologic outcomes. However, caution should be exercised when interpreting these results due to the descriptive nature of the analysis.

The analyses for MFS, OS, and PSA progression used a hierarchical testing plan to control the potential of inflated type I error, while there was lack of multiplicity adjustment in the statistical analyses of secondary end points which cannot rule out the possibility of type I errors.

At data cut-off, HRQoL results using the FACT-P questionnaire trended in favour of leuprolide alone, though the differences were not statistically significant.

Limitations of the EMBARK trial included the lack of blinding in the enzalutamide-alone arm, underrepresentation of patients from racial or ethnic groups other than white, and the lack of comparative analyses between both enzalutamide-containing arms.

Harms

More than 97% (1,035 out of 1,061) of the patients in all 3 arms had an adverse event. Any grade adverse events leading to permanent treatment discontinuation were reported in 73 of 353 patients (20.7%) in the enzalutamide plus leuprolide group, 36 of 354 patients (10.2%) in the leuprolide-alone group, and 63 of 354 patients (17.8%) in the enzalutamide-alone group.

The most common adverse events in the combination group and the leuprolide-alone group were hot flashes and fatigue. The most common adverse events in the monotherapy group were gynecomastia, hot flashes, and fatigue.

Fatigue was a notable harm across all arms, occurring in 42.8% of patients in the combination group, 32.8% in the leuprolide-alone group, and 46.6% in the monotherapy group. Despite excluding patients with a history of seizures from the trial, seizures were reported in 1.1% of patients in the combination group and 0.8% in the monotherapy group. No seizures were reported in the leuprolide-alone group. Other notable harms included gynecomastia, nipple pain, and breast tenderness, which were more common in the enzalutamide monotherapy group.

Adverse events leading to death were reported in 6 patients (1.7%) in the combination group, 3 patients (0.8%) in the leuprolide-alone group, and 8 patients (2.3%) in the monotherapy group, though none of these was considered to be related to treatment by the trial investigator. As per the expert consulted by CDA-AMC, this is a reasonable assumption, as deaths from ADTs and ARPIs are rare.

According to the expert consulted by CDA-AMC, some long-term side effects associated with enzalutamide are cardiovascular toxicity, seizures, and osteoporosis. These harms have been reported in EMBARK and are presented in Table 10.

Based on the reported harms outcomes, enzalutamide plus leuprolide and enzalutamide monotherapy were associated with higher incidences of adverse events compared with leuprolide alone, though longer follow-up may be necessary to fully determine the long-term consequences of prolonged enzalutamide exposure.

Costs

Based on public list prices, enzalutamide is expected to have a 28-day per patient cost of $3,270. Maintenance ADT therapies (i.e., after the initial month), range in cost from $252 per patient per 28 days (for degarelix 80 mg monthly) to $428 per patient per 28 days (for buserelin 6.3 mg every 2 months). As an add-on therapy to ADT, the incremental cost of enzalutamide is equal to its cost of $3,270 per patient per 28 days compared to ADT alone. When used without ADT, the incremental cost of enzalutamide ranges from $2,842 to $3,015 per patient per 28 days compared to maintenance ADT, depending on which ADT regimen is displaced.

Conclusions

The findings from EMBARK suggest that the combination of enzalutamide with ADT may result in a clinically meaningful delay of metastasis compared to ADT alone in patients with nmCSPC with high-risk BCR. Additionally, the findings also suggest that enzalutamide monotherapy may also clinically delay metastasis relative to ADT alone. However, median survival times were not yet reached, so the magnitude of absolute differences in events between groups during the median 5-year follow-up period could not be determined. There were no direct comparisons between enzalutamide with ADT and enzalutamide alone, which precludes any conclusions about their relative efficacy. Both enzalutamide-containing arms had higher incidences of adverse events leading to treatment discontinuations compared to the leuprolide-alone group. Despite promising findings, longer follow-up is needed to evaluate long-term survival benefits and quality of life.

Results of the cost comparison of treatment costs demonstrate that, as an add-on therapy to ADT, the incremental cost of enzalutamide is $3,270 per patient per 28 days. When used without ADT, the incremental cost of enzalutamide ranges from $2,842 to $3,015 per patient per 28 days compared to maintenance ADT, depending on the ADT regimen displaced. As such, the reimbursement of enzalutamide for the treatment of adult patients with nmCSPC with BCR at high risk of metastasis is expected to increase overall drug acquisition costs, regardless of whether it is given with or without ADT.

Based on the clinical review conclusions, the combination of enzalutamide with ADT may result in a clinically meaningful delay of metastasis compared to ADT alone. Additionally, enzalutamide monotherapy may also delay metastasis relative to ADT alone. Both enzalutamide-containing arms had higher incidences of adverse events leading to treatment discontinuations compared to the leuprolide-alone group. Given that enzalutamide (with or without ADT) is associated with increased treatment costs and some incremental benefit in terms of delay of metastasis compared to ADT alone, a cost-effectiveness analysis would be required to determine the cost-effectiveness of enzalutamide (with or without ADT) relative to ADT alone. As this was not available, the cost-effectiveness of enzalutamide (with or without) ADT relative to ADT alone for the treatment of adult patients with nmCSPC with BCR at high risk of metastasis could not be determined. CDA-AMC consulted clinical experts as part of this review, and feedback indicated there may be differences in monitoring costs (which are potentially increased) and subsequent therapy costs (potentially decreased) and delays in the cost of managing more severe disease between enzalutamide with or without ADT and ADT. To consider this alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of enzalutamide with or without ADT would be required.

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Appendix 1: Literature Search Strategy

Please note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: May 21, 2024

Alerts: Biweekly search updates until project completion

Search filters applied: Randomized controlled trials and controlled clinical trials.

Limits:

- Publication date limit: 2016-present
- Language limit: none
- Conference abstracts: excluded

Table 12: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word

Syntax	Description
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multidatabase Strategy

1 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
2 Randomized Controlled Trial/
3 exp Randomized Controlled Trials as Topic/
4 “Randomized Controlled Trial (topic)”/
5 Controlled Clinical Trial/
6 exp Controlled Clinical Trials as Topic/
7 “Controlled Clinical Trial (topic)”/
8 Randomization/
9 Random Allocation/
10 Double-Blind Method/
11 Double Blind Procedure/
12 Double-Blind Studies/
13 Single-Blind Method/
14 Single Blind Procedure/
15 Single-Blind Studies/
16 Placebos/
17 Placebo/
18 Control Groups/
19 Control Group/
20 (random* or sham or placebo*).ti,ab,hw,kf.
21 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
22 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
23 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
24 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.

25 allocated.ti,ab,hw.

26 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.

27 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.

28 (pragmatic study or pragmatic studies).ti,ab,hw,kf.

29 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.

30 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.

31 (phase adj3 (III or “3”) adj3 (study or studies or trial*)).ti,hw,kf.

32 or/1-31

33 (aludel or anamide or azel or bdenza or capmide or dizalet or ensuvanza or enzalunix or enzalutamida or enzalutamide or enzamide or enzana or enzastik or enzavitae or enzuta or enzutix or enzyl or glenza or karkino or midalune or obnyx or samenza or samluta or xalut or xtandi or xylutide or zalutex or asp 9785 or asp9785 or mdv 3100 or mdv3100 or “pf 04998299” or pf04998299 or ro 5251782 or ro5251782 or 93T0T9GKNU).ti,ab,kf,ot,hw,rn,nm.

34 (CSPC or nmCSPC or HSPC or ((castrat* or hormone or androgen) adj2 (sensitiv* or naive or dependent))).ti,ab,kf.

35 Neoplasm recurrence, local/ or ((biochemical* or prostate specific antigen or PSA or neoplasm) adj2 (recurren* or failure)).ti,ab,kf.

36 (non-metastatic or nonmetastatic or “not metastatic” or non-advanc* or nonadvanc* or “not advanc*” or non-malignant or nonmalignant or “not malignant”).ti,ab,kf.

37 33 and (34 or 35 or 36)

38 32 and 37

39 limit 38 to yr=”2016 -Current”

40 39 use medall

41 *enzalutamide/ or (aludel or anamide or azel or bdenza or capmide or dizalet or ensuvanza or enzalunix or enzalutamida or enzalutamide or enzamide or enzana or enzastik or enzavitae or enzuta or enzutix or enzyl or glenza or karkino or midalune or obnyx or samenza or samluta or xalut or xtandi or xylutide or zalutex or asp 9785 or asp9785 or mdv 3100 or mdv3100 or “pf 04998299” or pf04998299 or ro 5251782 or ro5251782).ti,ab,kf,dq.

42 (CSPC or nmCSPC or HSPC or ((castrat* or hormone or androgen) adj2 (sensitiv* or naive or dependent))).ti,ab,kf,dq.

43 biochemical recurrence/ or ((biochemical* or prostate specific antigen or PSA or neoplasm) adj2 (recurren* or failure)).ti,ab,kf,dq.

44 (non-metastatic or nonmetastatic or “not metastatic” or non-advanc* or nonadvanc* or “not advanc*” or non-malignant or nonmalignant or “not malignant”).ti,ab,kf,dq.

45 41 and (42 or 43 or 44)

46 32 and 45

47 46 not (conference review or conference abstract).pt.

48 limit 47 to yr="2016 -Current"

49 48 use oemezd

or/40,49

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search — Phase III and Phase IV trials | 01/01/2014-current | enzalutamide OR xtandi OR ASP 9785 OR ASP9785 OR MDV 3100 OR MDV3100 OR "PF 04998299" OR PF04998299 OR RO 5251782 OR RO5251782]

WHO ICTRP

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

[Search terms — aludel OR anamide OR azel OR bdenza OR capmide OR dizalet OR ensuvanza OR enzalunix OR enzalutamida OR enzalutamide OR enzamide OR enzana OR enzastik OR enzavitae OR enzuta OR enzutix OR enzyl OR glenza OR karkino OR midalune OR obnyx OR samenza OR samluta OR xalut OR xtandi OR xylutide OR zalutex OR ASP 9785 OR ASP9785 OR MDV 3100 OR MDV3100 OR "PF 04998299" OR PF04998299 OR RO 5251782 OR RO5251782]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search 01/01/2014-current | enzalutamide OR xtandi]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms — aludel OR anamide OR azel OR bdenza OR capmide OR dizalet OR ensuvanza OR enzalunix OR enzalutamida OR enzalutamide OR enzamide OR enzana OR enzastik OR enzavitae OR enzuta OR enzutix OR enzyl OR glenza OR karkino OR midalune OR obnyx OR samenza OR samluta OR xalut OR xtandi OR xylutide OR zalutex OR "ASP 9785" OR ASP9785 OR "MDV 3100" OR MDV3100 OR "PF 04998299" OR PF04998299 OR "RO 5251782" OR RO5251782]

EU Clinical Trials Information System

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms — aludel OR anamide OR azel OR bdenza OR capmide OR dizalet OR ensuvanza OR enzalunix OR enzalutamida OR enzalutamide OR enzamide OR enzana OR enzastik OR enzavitae OR enzuta OR enzutix OR enzyl OR glenza OR karkino OR midalune OR obnyx OR samenza OR samluta OR xalut OR xtandi OR xylutide OR zalutex OR “ASP 9785” OR ASP9785 OR “MDV 3100” OR MDV3100 OR “PF 04998299” OR PF04998299 OR “RO 5251782” OR RO5251782]

Grey Literature

Search dates: May 8, 2024 – May 25, 2024

Keywords: [enzalutamide, xtandi, aludel, anamide, azel, bdenza, capmide, dizalet, ensuvanza, enzalunix, enzalutamida, enzamide, enzana, enzastik, enzavitae, enzuta, enzutix, enzyl, glenza, karkino, midalune, obnyx, samenza, samluta, xalut, xylutide, zalutex, CSPC, nmCSPC, HSPC, castrate sensitive, castrate naive, castrate dependent, castration sensitive, castration naive, castration dependent, hormone sensitive, hormone naive, hormone dependent, androgen sensitive, androgen naive, androgen dependent, non-metastatic, nonmetastatic, not metastatic, non-advanced, nonadvanced, non-advancing, nonadvancing, non-malignant, nonmalignant, not malignant]

Limits: Publication years: none

Relevant websites from the following sections of the grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

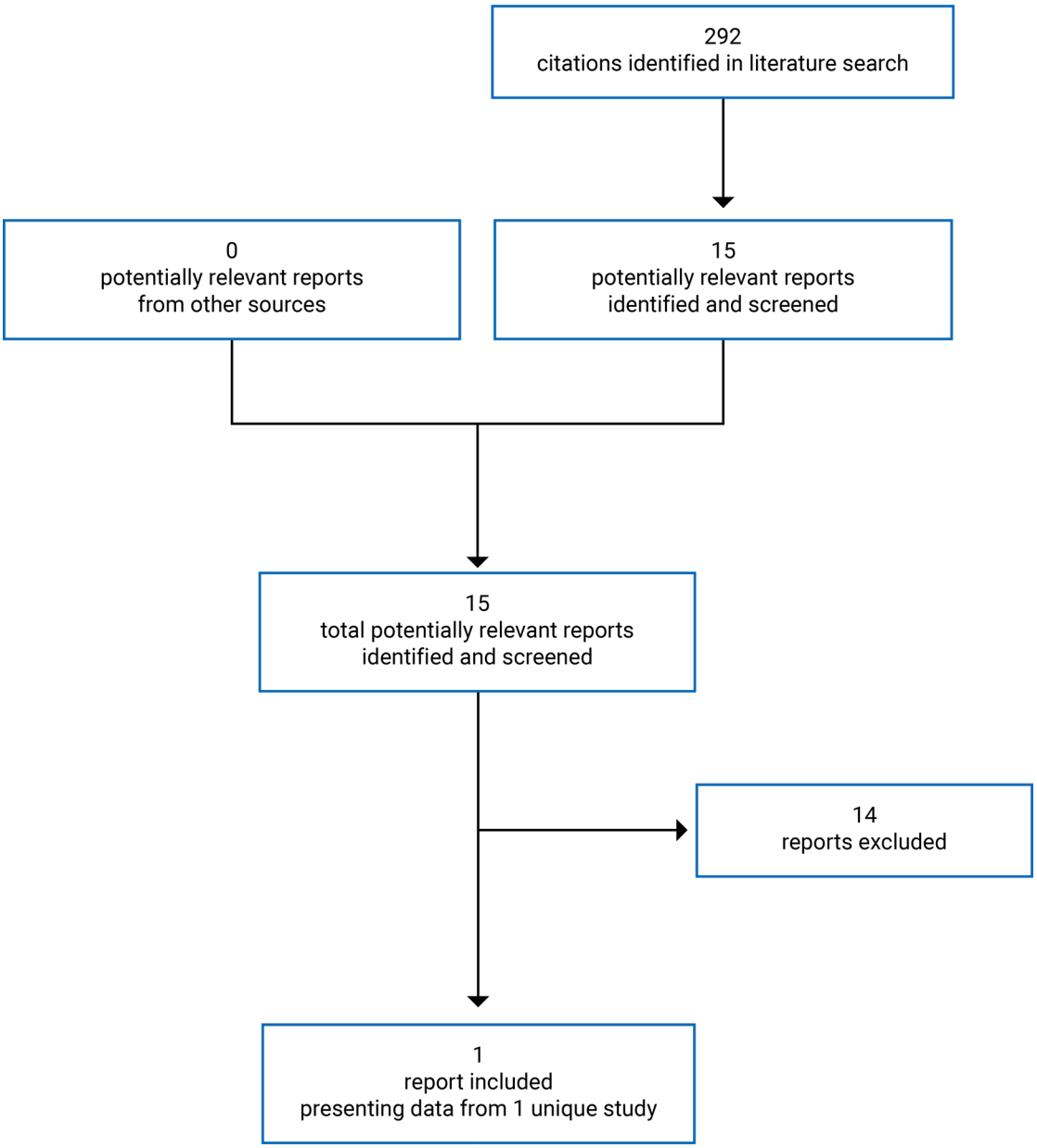
Appendix 2: Study Selection

Please note that this appendix has not been copy-edited.

Findings From the Literature

A total of 292 studies were identified from the literature for inclusion in the systematic review (Figure 3).

Figure 3: Flow Diagram for Inclusion and Exclusion of Studies



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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.