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CADTH Reimbursement Review

Abiraterone Acetate and Prednisone

Nonsponsored review

Therapeutic area: High-risk nonmetastatic prostate cancer

Clinical Review

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Abbreviations

ADT	androgen deprivation therapy
AE	adverse event
CI	confidence interval
GnRH	gonadotropin-releasing hormone
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention-to-treat
LFT	liver functioning test
LHRH	luteinizing hormone-releasing hormone
MAR	missing at random
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MNAR	missing not at random
mPC	metastatic prostate cancer
NOC	Notice of Compliance
NSAID	Non-steroidal anti-inflammatory drug
nmPC	nonmetastatic prostate cancer
OL	open-label
PAG	Provincial Advisory Group
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
QoL	quality of life
RCT	randomized controlled trial
SoC	standard of care
SAE	serious adverse event
SD	standard deviation
WDAE	withdrawal due to adverse event

Executive Summary

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

Table 1: Submitted for Review

Item	Description
Drug product	Abiraterone acetate (Zytiga and generic brands), 500 mg film-coated tablets, oral; used in combination with prednisone 5 mg tablets, oral, ± enzalutamide 160 mg, oral.
Health Canada indication	Abiraterone in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer in patients who: • are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy • have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy.
Indication under consideration for reimbursement	Abiraterone in combination with prednisone, with or without enzalutamide, for the treatment of patients with high-risk nonmetastatic prostate cancer who are starting long-term ADT.
Health Canada approval status	Not approved
NOC date	NA
Requester	Provincial Advisory Group

ADT = androgen deprivation therapy; NA = not applicable; NOC = Notice of Compliance.

Introduction

Prostate cancer originates from the prostate cells, where malignant cells grow into nearby tissues and can also metastasize to other parts of the body.[1] In Canada, prostate cancer accounts for 20% of all new cancer cases in men.[2] Early stages of prostate cancer are generally asymptomatic, but as the tumour grows, symptoms may occur, such as problems in urination, erectile dysfunction, pain, and fatigue.[3,4] When detected early, the treatment goal is cure and the 5-year survival rate is 91%;[2,5] however, it is not always the case, as prostate cancer is the third leading cause of death from cancer among men.

Androgen deprivation therapy (ADT) is used in the treatment of prostate cancer to decrease androgen production in the testes. Abiraterone acts via a complementary mechanism by inhibiting the intracellular conversion of androgen precursors through inhibition of the CYP17 enzyme, hence further decreasing androgen levels available to cancer cells. Abiraterone, in combination with prednisone, has a Health Canada indication for the treatment of metastatic prostate cancer (mPC) after failure of ADT, as well as an indication for the treatment of patients with newly diagnosed hormone-sensitive high-risk mPC, in combination with ADT. The recommended dose of abiraterone is 1,000 mg orally once daily, to be given in combination with prednisone 5 mg or 10 mg orally once daily to reduce the adverse events (AEs) caused by increased mineralocorticoid production.

The Provincial Advisory Group (PAG) and clinical experts consulted by CADTH for this review indicated that there is, in clinical practice, an eagerness for treatment intensification strategies in patients with high-risk nonmetastatic prostate cancer (nmPC), for whom the treatment goal is cure. The objective of this report is

to perform a systematic review of the beneficial and harmful effects of abiraterone acetate and prednisone (or prednisolone) oral tablets, with or without enzalutamide, when added to ADT in the treatment of high-risk nmPC.

The clinical and pharmacoeconomic evidence for the review were provided through the CADTH Nonsponsored Reimbursement Review process. The review includes an appraisal of the clinical evidence and a comparison between the treatment costs associated with abiraterone and prednisolone with or without enzalutamide and those of appropriate comparators deemed to be appropriate based on feedback from clinical experts and public drug programs.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from the clinical experts consulted by CADTH for the purpose of this review.

Patient Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full patient group input is included in the Stakeholder Input section at the end of this report.

One patient advocacy group, the Canadian Cancer Society, submitted patient input for this review. The Canadian Cancer Society is a national nonprofit organization committed to improving the lives of all Canadians living with all cancers across the country, through world-class research, transformative advocacy, and compassionate support. The submission was based on perspectives gathered through survey and interview responses between July 19, 2022, and August 2, 2022. Eleven patients responded to the survey. Two of the survey respondents who had direct experience with abiraterone acetate also participated in an interview.

Respondents indicated that nmPC impacts various aspects of their lives, including the ability to engage in sexual activity, work, travel, concentrate, exercise, spend time with family and friends, and maintain mental health. In addition, respondents also noted challenges with access to treatment and costs associated with treatment. Significant negative impacts due to the side effects of existing treatments were also reported.

Patients wanted to see improvements in future prostate cancer treatments to reduce side effect profiles (e.g., hot flashes and impact on sexual functioning), improve take-home cancer drug affordability, achieve more holistic care, improve communication among health care workers and patients, and improve access to imaging.

Patients who had experience with abiraterone and prednisone credited their treatment for controlling their cancer and prostate-specific antigen (PSA) levels; appreciated the ability to take abiraterone at home and did not find it difficult to take; and considered the side effects to be tolerable.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Three clinical experts provided expert knowledge regarding treatment strategies in Canada. The clinical experts reported that the treatment goals for nmPC are cure (i.e., permanent suppression of PSA), long-term suppression of PSA or prevention of metastatic disease, and maximizing quality of life (QoL). The most common treatment approaches for high-risk nmPC include external beam radiation with androgen deprivation, radical prostatectomy, and ADT. However, current standard treatments were reported to be associated with high failure rates (biochemical-free survival). There is a need for treatments that extend survival (metastasis-free survival and overall survival) in addition to maintaining or improving QoL.

Referring to the eligible patient population for the STAMPEDE trial, clinical experts noted that abiraterone plus prednisone was expected to be a suitable addition to those undergoing local therapy of the prostate cancer (for example, radiotherapy) at initial diagnosis, with no metastasis (a negative bone scan and CT scan); and as first-line treatment in this patient population considered at high risk of distant failure. However, it was noted that the study did not identify the "ideal" patient, either in terms of efficacy or tolerability or QoL metrics. Although the study protocol provided treatment of 2 years of combination treatment and 3 years of ADT, the optimal duration of treatment is not known.

The clinical experts noted that the definition of high-risk, castration-sensitive, and hormone "naive" patients varies depending on the classification system or guidelines used, such as the American Urology Association and D'Amico classification, Radiation Therapy Oncology Group guidelines, and National Comprehensive Cancer Network (NCCN) guidelines. They noted that the STAMPEDE trial's definition of "high risk" was different from the previously mentioned classification systems and guidelines, and advised the use of the definition of "high risk" from the STAMPEDE trial when defining the appropriate patient population for any reimbursement-related decision.

The outcomes used in clinical practice include metastasis-free survival, overall survival, prostate cancer–specific survival, biochemical failure-free survival, and progression-free survival, which was noted to be aligned with the primary and secondary end points of the STAMPEDE trial. The most likely reasons for treatment discontinuation were: development of castration resistance (i.e., disease progression) that was referred as development of distant metastases, rising PSA, and developing clinical symptoms. It was noted that treatment would take place in a specialist's clinic, but a specific "specialized" infrastructure is not required.

Clinician Group Input

This section was prepared by CADTH based on the input provided by clinician groups. The full clinician group input is included in the Stakeholder Input section at the end of this report.

The clinician input was submitted by Ontario Health — Cancer Care Ontario (OH-CCO)'s Genitourinary Cancer Drug Advisory Committee. OH-CCO's Drug Advisory Committees provide timely, evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug

Reimbursement Programs and the Systemic Treatment Program. Four clinicians from OH-CCO provided input for the review.

Given that there are no systemic therapies approved in high-risk nmPC, the group emphasized the need for better treatment options beyond ADT alone. As such, abiraterone with prednisone would be a first systemic therapy option, in addition to ADT, in men with high-risk nmPC.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may affect their ability to implement a recommendation. For the CADTH review of abiraterone and prednisolone in nmPC, the drug plans provided questions pertaining to the variation in definition of "high-risk nmPC" between clinical trial and clinical settings, eligibility for re-treatment, appropriate time to initiate therapy, and treatment algorithm, and also raised concerns about additional resource requirements.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

One published open-label (OL) randomized controlled trial (RCT), the STAMPEDE trial (N = 1,974),[6] was included in the systematic review. The STAMPEDE trial was a multiarm, multistage, platform RCT comparing various treatment options to standard of care (SoC) in patients starting long-term ADT for high-risk nmPC. Among the treatment comparisons assessed in the trial, 2 were included in this review. The first evaluated the impact of adding the combination of abiraterone and prednisone to ADT and SoC on the primary outcome of metastasis-free survival. The second treatment comparison was similar to the first, except that enzalutamide was also part of the combination therapy. Abiraterone 1,000 mg and prednisone or prednisolone 5 mg, with or without enzalutamide 160 mg, were administered orally once daily for 2 years or until disease progression. ADT was mandatory for every patient enrolled in the trial; SoC included radiotherapy.

Included patients of any age had histologically confirmed prostate adenocarcinoma of high-risk presentation, no evidence of metastases in conventional imaging, and intended to use long-term ADT for the first time. In the trial, a high-risk presentation was defined as **a node-positive cancer**; a **node-negative cancer with at least 2 risk factors** (clinical tumour stage T3 or T4, Gleason sum score 8 to 10, and/or PSA ≥ 40 ng/mL); or a **node-negative relapsing cancer** with high-risk features.

Efficacy Results

The use of abiraterone and prednisone, when assigned alone or in combination with enzalutamide, was consistently associated with hazard ratios (HRs) in favour of active treatment versus control (ADT alone) for analyses of metastasis-free survival, relapse-free survival, and progression-free survival. Detailed results and HRs for each of these outcomes are presented in Table 2. Although the median survivals were not yet reached, the magnitude of the absolute differences in events during the median 6-year follow-up

time between groups was considered clinically meaningful by the clinical experts consulted by CADTH for this review. This suggests that intensifying ADT treatment with abiraterone and prednisone results in metastasis-free, relapse-free, and progression-free survival benefits in patients starting long-term ADT for high-risk nmPC. There were no direct comparisons between the abiraterone and prednisone combination and the abiraterone, prednisone, and enzalutamide triple therapy groups. However, the magnitude of the benefit appeared only somewhat larger when enzalutamide was added to abiraterone and prednisone, and when combined with what appeared to be more AEs with the enzalutamide therapy, the data suggest that there was no added clinically important benefit with the triple therapy versus dual therapy. The authors of the study drew a similar conclusion, which aligned with their previous research that also did not suggest added benefit with this triple therapy regimen.

Although the HRs for overall survival and prostate cancer–specific survival favoured the abiraterone combination treatments versus ADT alone, there is uncertainty about the results. It was unclear whether the proportional hazards assumption for the adjusted analyses was met. The STAMPEDE protocol indicated that other survival analysis methods (e.g., restricted mean survival time) would be used in the case of nonproportional hazards; however, presumably based on the Schoenfeld test results that indicated no evidence of nonproportional hazards, other methods to validate these survival results were not reported. In addition, the authors of the study acknowledged that it is unclear what impact treatment modifications may have had on these survival analyses. It was also noted that the number of deaths as a percentage of events contributing to the metastasis-free survival analyses was higher in the abiraterone combination groups than in the control groups (93 deaths out of 180 events [52%] versus 117 deaths out of 306 events [38%]). Therefore, although the overall survival and prostate cancer–specific survival results are promising, a concrete conclusion cannot be made based on the results of the STAMPEDE trial alone.

The STAMPEDE criteria for high-risk prostate cancer differed from the Canadian definition of high-risk disease. Patients with node-positive cancer were included in the STAMPEDE trial as a high-risk population. In Canada, these patients would not be considered within the high-risk nonmetastatic category; instead, they would be considered to have a level of risk that is higher than those patients included in the high-risk strata. Patients with node-positive disease were well represented in the STAMPEDE trial, and efficacy in these patients was confirmed by a preplanned subgroup analysis for the outcome of metastasis-free survival. As for patients with node-negative disease, the inclusion criteria in the trial required them to have at least 2 risk factors to meet the trial's high-risk definition; in Canada, the high-risk definition would include only 1 of the following risk factors: tumour stage T3 or T4, Gleason sum score 8 to 10, or PSA greater than or equal to 40 ng/mL. Therefore, in terms of the Canadian risk definition, patients from the STAMPEDE trial would be considered at highest risk or at very high risk. It is unknown if the magnitude of treatment effect would be similar if abiraterone and prednisone were administered in patients with a risk that is lower than that of patients included in the trial. The authors of the article emphasized that the results were only generalizable to the population enrolled in the trial, and the clinical experts consulted by CADTH agreed.

The STAMPEDE trial was not informative regarding the impact of abiraterone and prednisone on health-related quality of life (HRQoL) or other patient-reported efficacy outcomes because data for these were not reported.

Harms Results

The proportions of patients who experienced AEs were low, especially considering the high treatment discontinuation rates due to AEs, and they were numerically higher in patients receiving active treatment versus those in the control group. The clinical experts consulted by CADTH indicated that it is common for patients to experience numerous AEs. In the trial, however, patients and clinicians were aware of the treatment strategy received, which may have introduced bias in these subjectively measured outcomes. Potential abiraterone-related harms, as well as corticosteroid-related AEs, were reported in a small proportion of patients, but were also numerically higher in patients receiving active treatment versus those in the control group. The differences between treatment groups were more apparent with the addition of enzalutamide. The observed types of AEs were consistent with what is expected with these 3 drugs. The patient input provided to CADTH for this review highlighted that AEs for abiraterone and prednisone may be tolerable considering the potential benefits of the drugs.

Table 2: Summary of Key Results From the STAMPEDE Trial — Treatment Comparisons Presented Separately (Preplanned Subgroup Analysis)

	Abiraterone and prednisolone or prednisone comparison		Abiraterone, prednisolone or prednisone, and enzalutamide comparison	
Outcome	Abiraterone and prednisolone or prednisone n = 459 (efficacy) n = 451 (safety)	Control n = 455	Abiraterone, prednisolone or prednisone, and enzalutamide n = 527 (efficacy) n = 513 (safety)	Control n = 533
Overall survival				
Number of events	95	142	52	94
Median (IQR if estimable)	Median not reached		Median not reached	
HR (95% CI)	0.63 (0.48 to 0.82)		0.54 (0.39 to 0.76)	
Prostate cancer–specific survival				
Number of events	48	86	25	56
Median (IQR if estimable)	Median not reached		Median not reached	
HR (95% CI)	0.52 (0.36 to 0.75)		0.44 (0.28 to 0.71)	
Metastasis-free survival				
Number of events	111	183	69	123
Median (IQR if estimable)	Median not reached		Median not reached	
HR (95% CI)	0.54 (0.43 to 0.68)		0.53 (0.39 to 0.71)	
Progression-free survival				
Number of events	84	166	54	111
Median (IQR if estimable)	Median not reached		Median not reached	
HR (95% CI)	0.43 (0.33 to 0.56)		0.45 (0.32 to 0.63)	

Outcome	Abiraterone and prednisolone or prednisone comparison		Abiraterone, prednisolone or prednisone, and enzalutamide comparison	
	Abiraterone and prednisolone or prednisone n = 459 (efficacy) n = 451 (safety)	Control n = 455	Abiraterone, prednisolone or prednisone, and enzalutamide n = 527 (efficacy) n = 513 (safety)	Control n = 533
Patients with ≥ 1 grade 3 or worse AEs over the first 24 months (planned duration of combination therapy)				
n (%)	169 (37)	130 (29)	298 (57)	172 (32)

AE = adverse event; CI = confidence interval; HR = hazard ratio; IQR = interquartile range.

Notes:

Metastasis-free survival was defined as time from randomization to death from any cause or to distant metastases confirmed by imaging.

Overall survival was defined as time from randomization to death.

Prostate cancer–specific survival was defined as time from randomization to death from prostate cancer.

Progression-free survival was defined as time from randomization to local progression, distant metastases, or death from prostate cancer.

Source: Attard et al. (2022)[6] (including supplementary appendix).[7]

Critical Appraisal

The STAMPEDE trial may be considered methodologically rigorous. However, findings from the trial are generalizable to a population with a higher level of risk than what is considered a high-risk patient according to the Canadian definition. The lack of detail regarding SoC received during the treatment period and upon disease progression precludes assessment of the impact of these co-interventions on survival findings. Being an OL study, the STAMPEDE trial was susceptible to assessment and reporting biases, the impact or direction of which are uncertain. High proportions of patients discontinued active treatment, highlighting the importance of perceived balance between the impact of the drug on disease progression versus the numerous AEs.

Cost Information

As CADTH does not have access to an economic model to address the specified research question, the economic review included a comparison between the treatment costs of abiraterone with prednisone (with or without enzalutamide) and those of comparators deemed to be appropriate based on clinical expert consultations and drug plans.

Based on publicly available list prices, abiraterone with prednisone is expected to have a 28-day cost of $2,916, whereas abiraterone with prednisone and enzalutamide is expected to have a 28-day cost of $6,186. As both regimens would be used as add-on therapy to ADTs, all costs are expected to be incremental.

Conclusions

Findings from the STAMPEDE trial suggest that treatment intensification of ADT with abiraterone and prednisone may result in clinically meaningful prevention of metastasis and disease relapse versus ADT alone, in patients starting long-term ADT for high-risk nmPC. The overall survival and prostate cancer–specific survival benefits of abiraterone and prednisone added on to ADT could not be determined because of a lack of reporting of important methods and statistical analysis details. Median survival times

were not estimable for any of the analyses. The trial definition for "high-risk" differed from the Canadian definition; these patients would instead be considered at very high risk or at highest risk in clinical practice. Enzalutamide, when added to abiraterone and prednisone, did not appear to add clinically meaningful benefit but seemed to increase toxicity. Despite small proportions of patients reporting AEs, high discontinuation rates due to AEs were observed in the trial. However, patient input suggests that AEs may be acceptable in light of the potential benefits of the treatment regimen.

As a cost-effectiveness analysis was not submitted, the cost-effectiveness of treatment intensification of ADT with abiraterone and prednisone compared with ADT alone in patients with high-risk nmPC could not be determined. Results of the cost comparison of treatment costs demonstrate that, over a 28-day cycle, abiraterone and prednisone added on to ADT is $2,916 more costly than ADT alone. Abiraterone with prednisone and enzalutamide is $6,186 more costly per 28-day cycle than ADT alone. As both regimens would be used as add-on therapy to ADTs, the reimbursement of abiraterone with prednisone for high-risk nmPC is expected to increase overall treatment costs. Other costs, such as administration costs, were not considered as part of the cost comparison. To consider this alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of treatment intensification of ADT with abiraterone and prednisone compared with ADT alone would be required.

Introduction

Disease Background

Prostate cancer originates from the prostate cells, part of the male reproductive organ and urinary system, where malignant cells grow into nearby tissues and can also metastasize to other parts of the body.[1] In Canada, prostate cancer accounts for 20% of all new cancer cases in men; Canadian Cancer Statistics estimated that 24,600 men were diagnosed with prostate cancer and 4,600 died from the disease in 2021.[2] Common risk factors for prostate cancer include age older than 50 years, Black African or Caribbean ancestry, family history of prostate cancer, overweight or obesity, and inherited gene mutations.[8]

Early stages of prostate cancer are generally asymptomatic, but as the tumour grows, symptoms may occur, such as problems in urination, erectile dysfunction, pain, and fatigue.[3,4] PSA testing and digital rectal exams are routine tests for early prostate cancer detection.[9] A PSA elevation above 0.75 ng/mL/year (or above the range for the patient's age cohort), as well as an abnormality on digital rectal exam accompanied with adjunctive evaluation tools, may arise suspicion of cancer. The diagnosis of prostate cancer can then be made through the histology of tissue obtained on a prostate biopsy.[3,10]

Most patients with prostate cancer are diagnosed with localized disease, for which the 5-year survival rate is 91% in Canada.[2,5] When detected early, the treatment goal is cure; however, it is not always the case, as prostate cancer is the third leading cause of death from cancer among men.

Two different systems are used to evaluate the progression of prostate cancer. The first, the Gleason Classification System, is used for grading and aims to differentiate the pattern or arrangement of the cancer

cells. The Gleason score ranges from 1 to 10 and helps to determine how quickly the cancer is likely to grow and spread. The second is the TNM (tumour, node, metastasis) staging system; it is commonly used to classify disease extent. Staging can be clinical — if based on results of a digital rectal exam, PSA test, Gleason score, and imaging — or staging can be pathological, if based directly on pathological tissue from the prostate and regional lymph.

Table 3: Summary of TNM Staging System

Staging system	T	N	M
Definition	Tumour description and growth, including to the surrounding tissues	Spread of the cancer to surrounding lymph nodes	Spread of the cancer to other parts of the body (metastasis)
Stages	T category from 1 to 4, further divided into a, b, and c	N0 = no spread N1 = spread to lymph node	M0 = none M1 = metastasis

M = metastasis, N = node; T = tumour.

Other terms are also used to describe the growth and spread of cancer, such as "localized" (limited to the prostate), "locally advanced" (spread outside of the prostate but not metastatic) and "metastatic" (spread beyond the tissues surrounding the prostate to lymph nodes or other parts of the body, such as the lungs, liver, or bones).[11-13]

Standards of Therapy

Treatments for prostate cancer include both local and systemic options, or the combination of both. Surgery and radiation therapy are used to treat local cancer in a specific, limited area of the body. Systemic treatments options include hormonal therapy, targeted therapy, chemotherapy, immunotherapy, radiopharmaceuticals, or bone-modifying drugs.[14] Appropriate treatment in early stages of prostate cancer aims to eliminate the cancer completely.[14]

According to the clinical experts consulted for this review, treatment of nmPC depends on risk categorization of the disease at diagnosis. "Risk" refers to probability of metastasis, risk of recurrence, and risk of death due to prostate cancer. The clinical experts noted that the criteria are based on PSA values, Gleason Score, and clinical T stage.

Table 4: Risk Categorization of Prostate Cancer

Risk level definition	Low	Intermediate	High
PSA	0 to 10 ng/mL	10 to 20 ng/mL	> 20 ng/mL
Gleason Score	≤ 6	7	8 to 10
Clinical T Stage	cT1 to T2a	cT2b	cT2c[3]

PSA = prostate-specific antigen; T = tumour.

Aligning with the guidelines, clinical experts noted that patients with very low-risk and low-risk prostate cancer are treated with surgery or radiation therapy, and if it shows signs of getting worse, patients are initially managed through active surveillance. Active surveillance involves periodic repeat biopsies, digital

rectal exams, and PSA tests.[14] As per the clinical experts, the most common treatment approaches for intermediate-risk prostate cancer include active surveillance, radiation therapy with or without ADT, radical prostatectomy, or high-intensity focused ultrasound.

Approaches for high-risk nonmetastatic disease, according to the clinical experts, are external beam radiation therapy (EBRT) with ADT and radical prostatectomy. Experts noted that there is variability in clinical practice as to when to start ADT, mainly due to the perceived balance between the impact of the drug on disease progression versus its numerous adverse effects. However, men with high-risk features are recommended ADT with a luteinizing hormone-releasing hormone (LHRH) antagonist or agonist. The NCCN guidelines suggest that ADT combined with radiation therapy is associated with improved disease-specific survival and overall survival and is an effective primary treatment for patients at high risk or very high risk for prostate cancer.[15]

The clinical experts Indicated that the current goal of treatment for nmPC is cure; treatments aim to provide permanent or long-term suppression of PSA, prevent metastatic disease, and maximize QoL. Clinical experts noted that therapies for curative intent are usually performed in men with a life expectancy of more than 10 years.

The clinical experts outlined that current standard treatments are associated with high failure rates based on biochemical-free survival, and additional treatments to improve clinical outcomes (i.e., metastasis-free survival and overall survival) are required. Optimal treatments for high-risk nonmetastatic prostate cancer should include those that extend survival in addition to maintaining or improving HRQoL.

Drug

Abiraterone and enzalutamide are antiandrogen drugs (Table 5). Abiraterone acts by inhibiting the intracellular conversion of androgen precursors and decreases androgen levels by competitive inhibition of the CYP17 enzyme. Enzalutamide competitively inhibits binding of androgens to androgen receptors, which inhibits translocation of androgen receptors and the interaction of androgen receptors with DNA.

Abiraterone, in combination with prednisone, and enzalutamide have Health Canada–approved indications for the treatment of select patients with metastatic castration-resistant prostate cancer (mCRPC) (Table 5).

The PAG and clinical experts consulted by CADTH for this review indicated that there is an interest in clinical practice for treatment intensification strategies in patients with high-risk nmPC, for whom the treatment goal is cure. The PAG requested that CADTH review abiraterone in combination with prednisolone (with or without enzalutamide) when added to ADT for patients with high-risk nmPC and provide a reimbursement recommendation.

Table 5: Summary of Key Characteristics of Abiraterone, Enzalutamide, and Comparators

Item	Abiraterone	Enzalutamide	LHRH agonists for ADT (e.g., goserelin)	LHRH antagonists for ADT (e.g., degarelix)
Mechanism of action	An androgen biosynthesis inhibitor that selectively inhibits the enzyme CYP17, required for androgen biosynthesis in testicular, adrenal, and prostatic tumour tissues.	An androgen receptor inhibitor that inhibits translocation of androgen receptors and interaction of androgen receptors with DNA.	A synthetic analogue of GnRH or LHRH that inhibits gonadotropin production, resulting in gonadal and accessory sex organ regression.	A selective GnRH receptor antagonist that competitively and reversibly binds to the pituitary GnRH receptors, reducing the release of gonadotropins LH and FSH, and thereby reducing the secretion of testosterone by the testes.
Indication[a]	For the treatment of mCRPC (in combination with prednisone) in patients who are asymptomatic or mildly symptomatic after failure of ADT or have received prior chemotherapy containing docetaxel after failure of ADT.	For the treatment of patients with mCRPC[c] who are chemotherapy-naive with asymptomatic or mildly symptomatic disease after failure of ADT or have received docetaxel therapy. For the treatment of patients with mCSPC. For the treatment of patients with nmCRPC.[b]	For the palliative treatment of patients with hormone-dependent advanced carcinoma of the prostate[d] (Stage M1 according to the TNM classification system, or Stage D2 according to the AUA classification). For use in combination with a nonsteroidal antiandrogen and radiation therapy for the management of locally advanced (T3, T4) or bulky Stage T2b, T2c carcinoma of the prostate.[e] As adjuvant hormone therapy to external beam irradiation for patients with locally advanced prostate cancer (Stage T3 to T4).	For testosterone suppression in patients with advanced hormone-dependent prostate cancer.
Route of administration	Oral	Oral	Subcutaneous injection (into the anterior abdominal wall)	Subcutaneous administration
Recommended dose	Abiraterone: 1 g (two 500 mg tablets or four 250 mg tablets) as a single daily dose.[f] Prednisone: 10 mg (mCRPC) and 5 mg (newly diagnosed high-risk mPC).	160 mg (four 40 mg capsules) as a single daily dose.	3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by the long-acting dose of 10.8 mg depot. Or: Four injections of 3.6 mg	Starting dose: 240 mg given as 2 doses every 28 days of 120 mg at a concentration of 40 mg/mL. Maintenance dose[g]: 80 mg as 1 dose at a

Item	Abiraterone	Enzalutamide	LHRH agonists for ADT (e.g., goserelin)	LHRH antagonists for ADT (e.g., degarelix)
			depot at 28-day intervals (2 depots preceding and 2 during radiotherapy until completion of the radiation therapy).	concentration of 20 mg/mL, monthly.
Serious adverse effects or safety issues	Risk of hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess. Should be used with caution in patients with a history of cardiovascular disease. Contraindicated in patients with severe and moderate hepatic impairment, as hepatotoxicity (including fatal cases) has been observed.	Risk of seizures and posterior reversible encephalopathy syndrome.	Risk of tumour flare reaction, osteoporosis, injection site injuries, and vascular injuries.	Risk of QT prolongation and osteoporosis.

ADT = androgen deprivation therapy; AUA = American Urologic Association; CYP17 = 17-alpha-hydroxylase, C17,20-lyase; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; LHRH = luteinizing hormone-releasing hormone; M = metastasis; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; mPC = metastatic prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; NoC = Notice of Compliance; T = tumour; TNM = tumour, node, metastasis.

[a]Health Canada–approved indication. Abiraterone has not received a Health Canada NoC for nonmetastatic prostate cancer.

[b]Not studied in patients with nmCRPC at low risk of developing metastatic disease. The benefit and risk profile in these patients is unknown.

[c]In the setting of medical or surgical castration.

[d]Stage M1 according to the TNM classification system or Stage D2 according to the AUA classification.

[e]Treatment with goserelin and a nonsteroidal antiandrogen should start 8 weeks before initiating radiation therapy and continue until completion of the radiation therapy.

[f]Must be taken on an empty stomach. No solid or liquid food should be consumed for at least 2 hours before the dose and for at least 1 hour after the dose.

[g]The first maintenance dose should be given 1 month after the starting dose.

Source: Product monograph for abiraterone,[16] enzalutamide,[17] goserelin,[18] and degarelix.[19]

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full patient group input is included in the Stakeholder Input section at the end of this report.

One patient advocacy group, the Canadian Cancer Society, submitted input for this review. Input was based on perspectives gathered through survey and interview responses between July 19, 2022, and August 2, 2022. The survey and interview opportunity with patients and their caregivers was shared through Cancer Connection forums, social media, various support groups, and prostate cancer–treating clinicians who agreed to share it with their patients. Eleven patients responded to the survey (10 patients with high-risk nmPC and 1 patient previously diagnosed with metastatic castration-sensitive prostate cancer (mCSPC) that

is now in remission. Two of the survey respondents who had direct experience with abiraterone acetate also participated in an interview (1 patient with nmPC, and 1 patient with mCSPC that is now in remission).

Respondents indicated that the physical manifestation of nmPC impacts various aspects of their lives, including engaging in sexual activity, work, travel, concentration, exercise, relationships with family and friends, and their mental health. Respondents noted the following barriers to treatment: long wait times to receive tests or treatments, costs associated with complementary medicines that were recommended by their health care team, lack of familiarity with navigating the health care system, transportation costs to attend appointments, costs associated with take-home cancer drugs, costs related to lodging and accommodations when receiving treatment, loss of income due to absence from work, and difficulty attending appointments due to disability or mobility issues.

Many of the respondents indicated they had undergone 3 or more lines of therapy, including EBRT, surgery, LHRH agonists, corticosteroids, and/or an antiandrogen drug. With regard to current treatment-related side effects, respondents reported the following had significant negative impacts: changes in libido and sexual function, fatigue, hot flashes, appetite changes, anemia, loss of muscle mass, weight changes, body hair loss, and rash or skin irritation. Respondents noted that they would like to see improvements in future prostate cancer treatments to reduce side effect profiles (e.g., hot flashes and impact on sexual functioning), improve take-home cancer drug affordability, achieve more holistic care, improve communication among health care workers and patients, and improve access to imaging.

Interview respondents credited their treatment — which included abiraterone acetate — for controlling their cancer and PSA levels. Respondents indicated that they appreciated the ability to take abiraterone at home and the ease of administration. The most important aspects of the treatment were identified as lengthening of life, access to treatment, and the ability to enjoy life. Patients considered the side effects tolerable and identified that they would recommend abiraterone acetate to others. However, there were concerns about their ability to access abiraterone acetate in the future and respondents advocated for government funding.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH 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 3 clinical specialists with expertise in the diagnosis and management of prostate cancer.

Unmet Needs

The clinical experts reported that the treatment goals for nmPC are cure (i.e., permanent suppression of PSA), long-term suppression of PSA, or prevention of metastatic disease, and maximizing QoL. It was noted that treatment in healthy patients is dependent on risk categorization of the disease at diagnosis, referring to probability of metastasis, risk of recurrence, and risk of death due to prostate cancer. The criteria for risk

categorization are based on PSA levels, Gleason Score, and clinical stage. The most common treatment approaches for high-risk nmPC include EBRT with androgen deprivation, radical prostatectomy, and ADT alone (for patients not eligible or not amenable to radiation and/or surgery). Therapies for curative intent are usually performed in patients with a life expectancy of greater than 10 years. Current standard treatments were reported to be associated with high failure rates (biochemical-free survival).Treatments that extend survival (metastasis-free survival and overall survival) in addition to maintaining or improving quality life are required.

Place in Therapy

Referring to the eligible patient population for the STAMPEDE trial, clinical experts noted that abiraterone plus prednisone would be a suitable addition to those undergoing local therapy of the prostate cancer (e.g., radiotherapy) at initial diagnosis, with no metastasis; and as first-line therapy in this patient population considered at high risk of distant failure.

Patient Population

Based on the STAMPEDE data, clinical experts noted that patients who fit the eligibility criteria for high-risk disease would be eligible for abiraterone 1,000 mg daily plus prednisone 5 mg daily. Abiraterone and prednisone would be an option for those with high-risk features without distant metastases, as determined by a negative bone scan and CT scan. The definition of "high-risk" used in the STAMPEDE trial was either: node positive; node negative, high risk (based on 2 of the following: tumour stage T3 or T4, Gleason sum score of 8 to 10, and PSA ≥ 40); or relapsing after previous treatment with high-risk features (≤ 12 months of total ADT with an interval of ≥ 12 months without treatment and a PSA concentration ≥ 4 ng/mL with a doubling time of < 6 months or a PSA concentration ≥ 20 ng/mL). However, it was noted that the study did not identify the "ideal" patient either in terms of efficacy or tolerability, or QoL metrics. Although the study protocol provided treatment of 2 years of combination treatment and 3 years of ADT, the optimal duration of treatment is not known.

The clinical experts provided the definition of high-risk nmPC, which varies depending on the classification system or guidelines used, such as the American Urologic Association or D'Amico classification, Radiation Therapy Oncology Group guidelines, and NCCN guidelines. They noted that the STAMPEDE trial's definition of "high risk" was different from the previously mentioned classification systems or guidelines. Further, the experts also noted that patients with castration-resistant prostate cancer have the highest risk of developing metastases. Of note, it was suggested that patients for whom conflict occurs in different imaging methods (e.g., prostate-specific membrane antigen [PSMA] PET positive but bone scan and CT scan negative) should still be treated as M0, as all current trial data are based on conventional non–PET scan-based imaging (i.e., bone scan or CT scan imaging).

Assessing Response to Treatment

The outcomes used in clinical practice include metastasis-free survival, overall survival, prostate cancer–specific survival, biochemical failure–free survival, and progression-free survival, which was noted to be aligned with the primary and secondary end points of the STAMPEDE trial. Further, all of these end points, except for biochemical failure–free survival, were noted to be associated with improved life expectancy.

Notable side effects of abiraterone plus prednisone include fatigue, elevated liver functioning tests (LFTs), hypertension, and hypokalemia. Therefore, regular physical exams are required, including blood pressure monitoring and blood work every 2 weeks in the first few months, then also including electrolytes and LFTs every 3 months thereafter.

Discontinuing Treatment

The most likely reason for treatment discontinuation was development of castration resistance (i.e., disease progression) that was referred as development of distant metastases, rising PSA, and developing clinical symptoms.

Prescribing Conditions

It was noted that treatment would take place in a specialist's clinic, with the specialist having expertise in the management of patients with prostate cancer and the ability to manage toxicities from treatment. However, a specific "specialized" infrastructure is not required.

Additional Considerations

The clinical experts did not prefer specific LHRH or GnRH agonists or antagonists based on their safety or efficacy and access or funding status. Further, they noted that androgen receptor-axis inhibitors (apalutamide, darolutamide, and enzalutamide) are used in high-risk nonmetastatic castration-resistant prostate cancer (nmCRPC), but there is a lack of evidence of clinical benefit in nmCSPC.

Clinician Group Input

This section was prepared by CADTH based on the input provided by a clinician group. The full clinician group input is included in the Stakeholder Input section at the end of this report.

The clinician input was submitted by OH-CCO. Four clinicians from OH-CCO provided input for the review.

Unmet Needs

The clinician group noted that the key treatment goals for patients with high-risk nmPC are to delay disease recurrence and prolong life. Given that there are no systemic therapies approved in high-risk nmPC, the group emphasized the need for better treatment options beyond ADT alone.

Place in Therapy

The clinician group suggested that abiraterone with prednisone would be a first systemic therapy option, in addition to ADT, in patients with high-risk nmPC.

Patient Population

The clinician group noted that the drug regimen would benefit patients with high-risk nmPC who are clinically suitable for abiraterone or prednisone, in addition to ADT.

Assessing Response to Treatment

The clinician group referred to "standard care assessment including clinical assessment and/or lab tests" as the outcome used to determine whether a patient is responding to treatment in clinical practice.

Discontinuing Treatment

Clinical progression or intolerability to abiraterone or prednisone were noted as reasons to discontinue treatment with abiraterone with prednisone.

Prescribing Conditions

Appropriate treatment setting for the drug is in hospital (outpatient clinic) under the supervision of a specialist with expertise in prostate cancer.

Additional Considerations

In terms of radiation to the primary tumour, the clinician group emphasized that while in qualifying cases, abiraterone and prednisone with ADT would be optimally combined with radiation therapy to the prostate, exceptions are allowed for qualifying patients who have a medical contraindication to prostate radiation therapy or refuse radiation therapy.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 6.

Drug plans noted that ADT is an appropriate comparator for the review of abiraterone and prednisolone. They also noted that patients with confirmed clinically significant cardiovascular disease (e.g., severe angina, recent myocardial infarction, or a history of cardiac failure) were excluded from the STAMPEDE trial. Drug plans also emphasized that currently, the use of abiraterone and prednisone is in metastatic settings only. Therefore, new use in nmPC may require additional pharmacy resources to dispense the drug and monitor the drug-drug interactions. Additional resources will be required to monitor AEs from abiraterone and prednisone. Availability of generic versions of abiraterone and prednisone was also highlighted. Drug plans also noted that oral anticancer drugs are not fully reimbursed in all Canadian jurisdictions.

Table 6: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Is the definition of high-risk disease that was used in the clinical trial consistent with how high-risk nmPC is defined in the clinical setting?	No. The definition of "high-risk nmPC" in the STAMPEDE trial is different than that used in the Canadian clinical setting. The patient population (high-risk) in the STAMPEDE trial would be considered more advanced than that of traditional definition in the Canadian setting. The traditional definition of "high-risk" includes 1 of the following (as opposed to 2, as defined by the STAMPEDE trial): high PSA, Gleason score ≥ 8, clinical stage ≥ T3. Nodal status is generally not used in the definition of "high-risk" in the clinical setting N1 but nonmetastatic patients are considered to be in the grey area instead. The clinical experts advised to clarify that the outcomes are applicable to the specific patient population in the STAMPEDE trial. If abiraterone and prednisolone receive a "reimburse" recommendation, when

Drug program implementation questions	Clinical expert response
	defining the appropriate patient population, the reimbursement criteria should use the definition of "high-risk" used in the STAMPEDE trial.
If a patient completes 2 years of abiraterone and prednisone therapy and then subsequently relapses, what would be an appropriate time frame that must elapse between the last dose of abiraterone and the restart of abiraterone?	The clinical experts noted that general principles would state that as long as the patient has relapsed more than 6 to 12 months from the completion of abiraterone, there would be rationale for re-treatment if deemed appropriate at the time by the treating clinician. The clinical experts highlighted, however, that this is based on standard oncology practice rather than on actual data.
For patients who started on ADT: what would be an appropriate time frame for adding abiraterone and prednisone to ADT (within 3 months from starting)?	The clinical experts indicated that generally, most treatment intensification strategies in later stages of disease (i.e., mCSPC) call for addition of ARPi within 3 to 4 months of starting ADT.
How may the drug (abiraterone and prednisone) change place in therapy of drugs reimbursed in subsequent lines?	According to the clinical experts, the drug should have no impact on subsequent lines of therapy in patients who completed their planned treatment duration. For patients who would progress while being on the drug, or shortly after the end of planned treatment, most clinicians would then recommend a non-ARPi based best line of therapy.

ADT = androgen deprivation therapy; ARPi = androgen receptor pathway inhibition; nmPC = nonmetastatic prostate cancer.

Industry Input

This section was prepared by CADTH based on the input provided by industry stakeholders.

The industry input was submitted by Janssen Inc., 1 of the manufacturers of abiraterone acetate in Canada. Input was provided on the research protocol. Their input noted the need to further define the patient population, as the term "high-risk nonmetastatic prostate cancer" is not reflective of the entire STAMPEDE patient population as per inclusion criteria.[6] Rather, "very high-risk localized prostate cancer" was suggested to be an appropriate term. "Very high-risk localized prostate cancer" aligns with language used to describe most patients in the STAMPEDE trial per the NCCN guideline definition,[15] and this term is also used in the Canadian Urologic Association guideline, although its definition is not outlined.[20] Industry input referred to the STAMPEDE study as a relevant published study to be considered in the clinical review.

Industry input raised the need to thoroughly consider the following when making the reimbursement recommendation for this review: the proposed indication, STAMPEDE study design, and generalizability to the population in Canada. With regard to the indication, it was highlighted that the proposed indication is "off label" and hence there is a need for the reimbursement recommendation to be clearly supported by evidence. In addition, the broad nature of the term "high-risk nonmetastatic prostate cancer" is not entirely reflective of the entire STAMPEDE study. Rather, most of the patient population in the STAMPEDE study aligns with the NCCN prostate cancer guideline's definition of "very high-risk" disease.[15] It was also highlighted that the STAMPEDE protocol publication noted that "the conclusions of the study should be restricted to patients who meet the protocol's definition for disease at high risk of relapse."[6] Further, 81% of all study participants were receiving radiotherapy in the STAMPEDE[6] study, an additional treatment that should be taken into consideration when assessing benefit for all patients. In alignment with the STAMPEDE protocol, the industry input highlighted that the NCCN guideline recommends the use of abiraterone acetate plus prednisolone with ADT and EBRT only in patients with very high-risk localized prostate cancer.[15] Similarly, recent European

Association of Urology guidelines recommend abiraterone acetate plus prednisolone in the high-risk localized setting only when used in conjunction with radiotherapy.[15] Therefore, the industry input emphasized that there is insufficient evidence to make an informed recommendation on the use of abiraterone acetate plus prednisolone in patients with high-risk features other than those defined in the STAMPEDE protocol. Additionally, the uncertainty around the magnitude of benefit in specific high-risk subgroups may lead to difficulty in implementation of the recommendation, which may differ across high-risk subgroups such as nonmetastatic patients relapsing after previous local therapy, given that this group is underrepresented in the STAMPEDE study.[6] Finally, it was suggested that it would be important to consider ongoing studies in the prostate cancer therapeutic area when assessing the broadness of the indication, given that the new evidence may disrupt the proposed treatment algorithm. For example, the recent ATLAS study encompasses a broader group of high-risk patients with localized or locally advanced prostate cancer, and as such, the STAMPEDE population represents a subset of the ATLAS study.

With regard to the study design, it was noted that the STAMPEDE study was not designed with regulatory rigour for filing and has not yet been reviewed or approved by Health Canada, and as such, the certainty in the evidence is limited. The industry input highlighted a previous assessment of the study design by CADTH,[20] where CADTH has noted the limitations regarding the introduction of detection bias and AE outcome reporting. Such limitations, especially the less-than-robust AE outcome reporting, including evaluation and extensive details of patient deaths, may not adequately capture the potential harms versus benefits, particularly for the use of abiraterone acetate plus prednisolone in a new disease stage where patients are generally younger and healthier. Caution in interpretation of the study findings was suggested, given that the strength of the recommendation and broadness of the indication should be tied to the certainty in the evidence.

With regards to the generalizability of the STAMPEDE study, it was noted that these were conducted only at sites in the UK and Switzerland, requiring clarity as to the relevance to the intended population in Canada, and the generalizability of treatment patterns to the Canadian clinical practice is needed.[6] It was also noted that the STAMPEDE study only allowed patients to ever receive 1 novel hormonal therapy (NHT) in their treatment pathway. Moreover, many of these patients would have progressed within the study before NHTs were reimbursed in the UK for nmCRPC, mCSPC and even mCRPC. An assessment on whether the subsequent treatments received by patients in the study represent the current Canadian SoC should be undertaken, taking jurisdictional differences in implementation into account. The industry input highlighted that CADTH's clinical assessment of a recent mCRPC treatment included the remark that "there is a limited number of available therapies for prostate cancer and sequencing of prior agents is variable in Canadian clinical practice,"[21] which will need to be taken into consideration when generalizing the STAMPEDE results to a Canadian setting.

Clinical Evidence

The clinical evidence included in the review of abiraterone acetate and prednisone (or prednisolone) is presented in 3 sections. The first section, the systematic review, includes studies that were selected

according to an a priori protocol. The second section would include indirect evidence selected from the literature that met the selection criteria specified in the review; however, no indirect evidence was considered relevant for inclusion in the review. The third section would include long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review; however, none were considered relevant for inclusion in the review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

Perform a systematic review of the beneficial and harmful effects of abiraterone acetate and prednisone (or prednisolone) oral tablets, with or without enzalutamide, for high-risk nmPC.

Methods

Studies selected for inclusion in the systematic review include those meeting the selection criteria presented in Table 7. Outcomes included in the CADTH review protocol reflect outcomes considered important to patients, clinicians, and drug plans.

Table 7: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Newly diagnosed patients with high-risk nmPC who are starting long-term ADT for the first time
Intervention	ADT, abiraterone acetate (1,000 mg daily) with prednisone (or prednisolone) tablets (5 mg daily) ± enzalutamide (160 mg daily)
Comparators	ADT with or without radiation • LHRH or GnRH antagonist • LHRH or GnRH agonists
Outcomes	OS Prostate cancer–specific survival Metastasis-free survival Relapse-free survival PFS: • Disease progression after ADT (castration-resistant, PSA levels) • Development of metastases HRQoL harms: • AEs, SAEs, WDAEs, death • Potential abiraterone-related harms (i.e., fatigue, hypertension, hypokalemia, cardio-renal) • Corticosteroid-related AEs
Study design	Published and unpublished phase III and IV RCTs

ADT = androgen deprivation therapy; AE = adverse event; DOR = duration of response; GnRH = gonadotropin-releasing hormone; LHRH = luteinizing hormone releasing hormone; nmPC = nonmetastatic prostate cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist.[22]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed 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. The main search concepts were abiraterone acetate and prednisolone. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, indirect treatment comparisons (ITCs), randomized controlled trials, or controlled clinical trials. Retrieval was not limited by publication date or 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 June 20, 2022, and regular alerts updated the search until May 24, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist.[23] 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.

Two CADTH 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 ITCs dealing with high-risk nmPC was run in MEDLINE All (1946–) on June 14, 2022. No search limits were applied.

Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 8. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

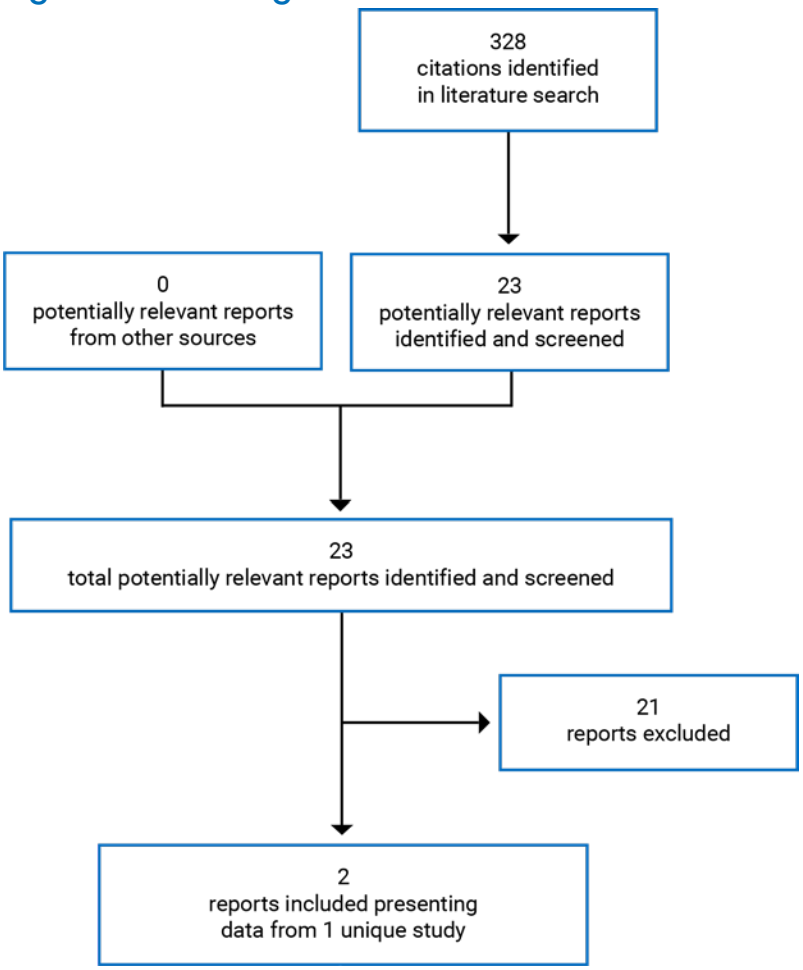

Table 8: Details of Included Study

Detail	STAMPEDE	
	Abiraterone and prednisolone or prednisone comparison (arm G vs. control)	Abiraterone, prednisolone or prednisone, and enzalutamide comparison (arm J vs. control)
Designs and populations		
Study design	OL, multi-arm, multi-stage, platform RCT in patients starting long-term hormone therapy for metastatic or high-risk nmPC	
Locations	Multicentre: 113 sites in the UK and Switzerland	
Patient enrolment dates	First patient assigned: November 15, 2011 Last patient assigned: January 17, 2014	First patient assigned: July 29, 2014 Last patient assigned: March 31, 2016
Randomized (N)	N = 914	N = 1,060

Detail	STAMPEDE	
	Abiraterone and prednisolone or prednisone comparison (arm G vs. control)	Abiraterone, prednisolone or prednisone, and enzalutamide comparison (arm J vs. control)

Inclusion criteria	Patients of any age with:
	• histologically confirmed prostate adenocarcinoma
	• intent to use long-term ADT for the first time
	• WHO performance status 0 to 2
	• no evidence of distant metastases in conventional imaging
	• a high-risk cancer presentation, defined as one of the following:
	  ◦ node-positive, or
	  ◦ node-negative cancer meeting the high-risk definition (i.e., having ≥ 2 of the following risk factors):
	  ▪ clinical tumour stage T3 or T4
	  ▪ Gleason sum score 8 to 10
	  ▪ PSA ≥ 40 /mL, or
	  ◦ node negative relapsing cancer with the following high-risk features:
	  ▪ total ADT ≤ 12 months, with no treatment in the previous 12 months, and
	  ▪ PSA ≥ 4 ng/mL with doubling time < 6 months, or PSA ≥ 20 ng/mL or nodal relapse	

Exclusion criteria	• Prior systemic treatment for locally advanced prostate cancer • Clinically significant cardiovascular disease • Abnormal hematological, renal, or liver function • Significant prior or current malignancy other than prostate cancer	
Drugs		
Intervention	Abiraterone acetate 1,000 mg + prednisolone or prednisone 5 mg Combination therapy administered orally once daily for 2 years (or until disease progression) + Standard of care	Abiraterone acetate 1,000 mg + prednisolone or prednisone 5 mg; and enzalutamide 160 mg Combination therapy administered orally once daily for 2 years (or until disease progression) + Standard of care
Comparator(s)	OL standard of care	
Concomitant medications and treatments	• Standard-of-care ADT for 3 years mandatory for all patients (including surgery or LHRH agonists and antagonists) • Radiotherapy mandatory for N0M0 patients with no nodal or metastatic spread; recommended for patients with node-positive, nonmetastatic disease	
Duration		
Follow-up	9 years (108 months)	
Outcomes		
Primary end point	Metastasis-free survival (Time from randomization to death from any cause or to distant metastases confirmed by imaging)	
Secondary and exploratory end points	• Overall survival (time from randomization to death) • Prostate cancer–specific survival (time from randomization to death from prostate cancer) • Progression-free survival (time from randomization to local progression, distant metastases, or death from prostate cancer)	

Detail	STAMPEDE	
	Abiraterone and prednisolone or prednisone comparison (arm G vs. control)	Abiraterone, prednisolone or prednisone, and enzalutamide comparison (arm J vs. control)
	• Failure-free survival (time from randomization to biochemical failure, local progression, distant metastases, or death from prostate cancer) • Toxicity and AEs	
Notes		
Publications	Attard et al. 2022[6] James et al. 2017[24]	

ADT = androgen deprivation therapy; AE = adverse event; LHRH = luteinizing hormone-releasing hormone; nmPC = nonmetastatic prostate cancer; OL = open-label; PSA = prostate-specific antigen; RCT = randomized controlled trial; SAE = serious adverse event.

Source: Attard et al. (2022)[6] (including supplementary appendix).[7]

Description of Study

One published, open-label RCT was included in the systematic review: the STAMPEDE trial (N = 1,974).[6] The STAMPEDE platform used a multiarm, multistage protocol and nonoverlapping control groups to compare various treatment options (only intervention arms G and J are relevant for this review) for patients with nmPC and mPC. Findings for patients with metastatic disease were analyzed separately; therefore, the publication included in this systematic review only reported findings for patients with a high-risk, nonmetastatic, castration-sensitive presentation; the population of interest to this review. Randomization was performed centrally (by telephone, using a computerized algorithm) using the method of minimization over the following stratification factors:

- randomizing centre
- nodal involvement (N0 [negative] versus NX [intermediate] versus N+ [positive])
- age at randomization (< 70 years versus ≥ 70yrs)
- WHO performance status (0 versus 1 to 2)
- method of ADT (orchidectomy versus LHRH agonist versus LHRH antagonist versus dual androgen blockade)
- regular Aspirin or other nonsteroidal anti-inflammatory drug (NSAID) use at baseline (yes versus no)
- radiotherapy planned (yes versus no).

An additional random element of 80% was applied.

The randomization ratio for all STAMPEDE study arms, A:B:C:D:E:F:G:H:J:K:L, was 2:1:1:1:1:1:2:2:2:2:2. Therefore, the comparisons between group A (control) and treatment groups G and J were planned to have equal weighting (i.e., allocation ratio 1:1).

Treatment assignment was not blinded because it was “deemed impracticable” by the investigators.

The STAMPEDE protocol was sponsored by the UK Medical Research Council and by the University College London.

Populations

Inclusion and Exclusion Criteria

Patients of any age were eligible for the trial if they had histologically confirmed prostate adenocarcinoma of high-risk presentation, no evidence of metastases in conventional imaging, and intended to use long-term ADT for the first time. In the trial, a high-risk presentation was defined as a node-positive cancer; or a node-negative cancer with at least 2 risk factors (clinical tumour stage T3 or T4, Gleason sum score 8 to 10, and/or PSA ≥ 40 ng/mL); or a node-negative relapsing cancer with high-risk features (ADT for a maximum of 12 months without treatment in the previous 12 months; and PSA ≥ 4 ng/mL with a doubling time less than 6 months, or PSA ≥ 20 ng/mL or nodal relapse). Key exclusion criteria included prior systemic treatment for locally advanced prostate cancer; clinically significant cardiovascular disease; abnormal hematological, renal, or liver function; and significant prior or current malignancy other than prostate cancer.

Baseline Characteristics

Baseline characteristics are presented in Table 9 and were balanced between treatment groups. Overall, patients enrolled in the trial had a median age of 68 years. Median PSA values ranged between 32 ng/mL and 40 ng/mL across treatment arms. In terms of disease characteristics, 97% of patients included in the trial had a newly diagnosed cancer, 61% had a node-negative presentation, 82% had a WHO performance status of 0, 79% had a Gleason sum score of 8 to 10, and 92% had a T stage of 3 to 4. Most patients opted for an LHRH agonist or antagonist as ADT treatment option, while a total of 85% of patients had local radiotherapy.

Table 9: Summary of Baseline Characteristics

Characteristic	Abiraterone and prednisolone or prednisone comparison		Abiraterone, prednisolone or prednisone, and enzalutamide comparison	
	Abiraterone and prednisolone or prednisone n = 459	Control n = 455	Abiraterone, prednisolone or prednisone, and enzalutamide n = 527	Control n = 533
Age, years				
Median (IQR)	68 (63 to 73)	67 (62 to 73)	68 (63 to 73)	69 (64 to 73)
Range	44 to 84	48 to 83	46 to 86	43 to 86
PSA, ng/mL				
Median (IQR)	34 (15 to 68)	40 (16 to 83)	32 (13 to 74)	34 (15 to 74)
Range	1 to 2,300	1 to 1,000	0 to 556	1 to 2,773
Disease history, n (%)				
Newly diagnosed	434 (95)	443 (97)	512 (97)	517 (97)
Relapse	25 (5)	12 (3)	15 (3)	16 (3)
Nodal status, n (%)				
N0	267 (58)	263 (58)	332 (63)	335 (63)

Characteristic	Abiraterone and prednisolone or prednisone comparison		Abiraterone, prednisolone or prednisone, and enzalutamide comparison	
	Abiraterone and prednisolone or prednisone n = 459	Control n = 455	Abiraterone, prednisolone or prednisone, and enzalutamide n = 527	Control n = 533
N1	191 (42)	192 (42)	194 (37)	197 (37)
NX	1 (< 1)	0	1 (< 1)	1 (< 1)
WHO performance status, n (%)				
0	370 (71)	375 (82)	429 (81)	435 (82)
1 to 2	89 (19)	80 (17)	98 (19)	98 (18)
Gleason sum score, n (%)				
< 8	107 (23)	105 (23)	98 (19)	95 (18)
8 to 10	351 (77)	348 (76)	427 (81)	437 (82)
Missing	1	2	2	1
T stage				
T0 – T2	30 (7)	39 (9)	26 (5)	30 (6)
T3 – T4	423 (92)	411 (90)	493 (94)	496 (93)
TX	6 (1)	5 (1)	8 (2)	7 (1)
ADT treatment option, n (%)				
LHRH agonist or antagonist	455 (99)	448 (98)	524 (99)	532 (99)
Local radiotherapy, n (%)				
Yes	372 (81)	372 (82)	469 (89)	471 (88)

ADT = androgen deprivation therapy; IQR = interquartile range; LHRH = luteinizing hormone-releasing hormone; PSA = prostate-specific antigen; T = tumour.
Source: Attard et al. (2022).[6] Creative Commons Attribution Licence 4.0 https://creativecommons.org/licenses/by/4.0/.

Interventions

There were 2 relevant STAMPEDE treatment comparisons: 1 evaluated the efficacy and safety of adding the combination of abiraterone and prednisone to ADT and SoC in patients starting long-term hormone therapy for high-risk nmPC. In the other treatment comparison, enzalutamide was added to the combination therapy, with the other aspects of treatment being identical to the aforementioned treatment comparison. Both of these treatment intensification strategies were compared to non-overlapping OL control groups who received ADT and SoC.

The intervention evaluated consisted of a combination therapy with abiraterone 1,000 mg and prednisone or prednisolone 5 mg, with or without enzalutamide 160 mg, administered orally once daily for 2 years, or

until disease progression. All patients in the active treatment groups and in the control groups received SoC therapy. ADT was mandatory for every patient enrolled in the trial, which included surgery and/or the use of LHRH agonists and antagonists for 3 years (started ≤ 12 weeks before randomization). Radiotherapy after randomization was mandatory for patients with no nodal or metastatic spread and recommended for patients with node-positive nonmetastatic disease.

Study treatment was discontinued in the active treatment arms in case of disease progression. Of note, data on subsequent therapies following progression were described by the investigators as being "unreliable given this often occurred several years after completion of trial treatment."[6] The exact nature of subsequent therapies received was not reported in the published article.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 10. These end points are further summarized below.

Table 10: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	Analysis in the STAMPEDE trial
Overall survival	Secondary
Prostate cancer–specific survival	Secondary
Metastasis-free survival	Primary
Relapse-free survival	Secondary
Progression-free survival	Secondary
HRQoL	NR
AEs	Secondary
SAEs	NR
WDAEs	NR
Mortality	Secondary
Potential abiraterone-related harms	Secondary
Corticosteroid-related AEs	Secondary

AE = adverse event; HRQoL = health-related quality of life; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The primary efficacy outcome in the trial was metastasis-free survival, defined as time from randomization to death from any cause, or to distant metastases confirmed by imaging. The use of metastasis-free survival has been extensively studied and is considered an appropriate outcome measure and valid surrogate end point for overall survival by several regulatory agencies,[25-28] especially at an early and localized stage of the disease. Progression to mPC is also considered a meaningful outcome by patients, as it is associated with decreased well-being for patients living with the condition.

Other outcomes assessed as secondary end points in the trial included: overall survival, defined as time from randomization to death; prostate cancer–specific survival, defined as time from randomization to death from prostate cancer; failure-free survival, defined as time from randomization to biochemical failure, local

progression, distant metastases, or death from prostate cancer; and progression-free survival, defined as time from randomization to local progression, distant metastases, or death from prostate cancer.

Prespecified procedures and rules were used for ascertaining whether death was from prostate cancer based on an algorithm or a chart review conducted by a blinded panel of clinicians. Safety was assessed through the outcome of AEs.

Statistical Analysis

The sample size calculation estimated that having approximately 315 metastasis-free survival events in the control groups would enable the study to achieve 90% power at a 1-sided level of significance of 1.25% to detect a 25% relative improvement between groups (HR = 0.75), assuming a metastasis-free survival of 70% at 5.5 years for patients in the control groups.

The study was designed to test for superiority. The statistical analyses performed were specified in the study protocol. An independent data monitoring committee was established to manage data cleaning and verification as well as interim and final analyses.

Initially, the primary end point was overall survival; however, it was changed to metastasis-free survival in patients with nonmetastatic disease during the study conduct. This was 1 of a series of decisions that were made after completion of accrual to both treatment comparisons, but before inspection of detailed efficacy outcomes, to accrue sufficient events in the nonmetastatic population and due to the difference in the anticipated efficacy of treatments in the patient populations. These prespecified changes were approved by the independent steering committee and included:

- separate analysis and report of patients with metastatic and nonmetastatic disease
- pooling of patients from both treatment comparisons (group G plus group J) for the primary efficacy analysis
- change primary efficacy outcome to metastasis-free survival in patients with nonmetastatic disease
- extend follow-up to reach a sufficient number of events in the nonmetastatic population.

For time-to-event outcomes, analyses between groups were performed using standard survival analysis methods. A Cox proportional hazards regression, adjusted for stratification factors used at randomization, was used to generate the primary analysis estimate of treatment effect. Differences between groups were assessed using the log-rank chi-square test and results were expressed using an HR. Findings were also presented using Kaplan-Meier curves. The median follow-up calculation used a reverse Kaplan-Meier method, censoring on death or withdrawal. The assumption of proportional hazards was tested using scaled Schoenfeld residuals for all efficacy outcomes. For prostate cancer–specific survival, analyses were performed using competing-risks models, with the competing risk being death from non–prostate cancer causes. Patients who did not experience an event during the follow-up period were censored at the time they were last known to be event-free. Any missing data were treated as missing completely at random (MCAR) in the ITT analyses.

The preplanned pooling of the primary efficacy results of both treatment groups was presented. Estimates for each individual treatment comparison were pooled using fixed-effects individual patient data meta-analyses. Heterogeneity between treatment comparisons was assessed based on Cochran's Q test (quantified by the I^2 value); it was not reported whether heterogeneity beyond statistical sources was assessed.

Analysis Populations

Intention-to-treat (ITT) population: This population was used for all analyses and comprised all randomized patients. In the ITT analysis, patients were assigned to the treatment to which they were randomized.

Safety population: This population was used for analyses of AEs and comprised all patients who were included in the study and received at least 1 dose of their allocated study treatment. In the safety analysis, patients were analyzed according to the treatment they received.

Results

Patient Disposition

A total of 914 patients were randomized in the abiraterone and prednisone treatment comparison, and 1,060 patients were randomized in the combination therapy and enzalutamide treatment comparison. Discontinuation rates were reported for the active treatment groups. High proportions of patients discontinued treatment; however, most of these patients continued follow-up in the study. The most frequent reasons for discontinuation were AEs, followed by patient decision. Details regarding patient disposition are provided in Table 11.

Table 11: Patient Disposition

Patient disposition	Abiraterone and prednisolone or prednisone comparison		Abiraterone, prednisolone or prednisone, and enzalutamide comparison		
			Active treatment arm		
	Abiraterone and prednisolone or prednisone	Control arm	Abiraterone and prednisolone or prednisone	Enzalutamide	Control arm
Randomized	**459**	**455**	**527**		**533**
Treatment never started	8	NA	15	14	NA
Completed treatment	**266**	**NA**	**258**	**235**	**NA**
Treatment still ongoing	18	NA	25	20	NA
Discontinued from study, n (%)	**20 (4.4)**	**8 (1.8)**	**17 (3.2)**		**8 (1.5)**
Reason for discontinuation, n (%)	NR		NR		
Discontinued treatment intervention, n (%)	167 (36.4)	NA	229 (43.5)	258 (49.0)	NA
Reason for stopping treatment, n (%)					
Adverse events	60 (35.9)	NA	134 (58.5)	161 (62.4)	NA

Patient disposition	Abiraterone and prednisolone or prednisone comparison		Abiraterone, prednisolone or prednisone, and enzalutamide comparison		
			Active treatment arm		
	Abiraterone and prednisolone or prednisone	Control arm	Abiraterone and prednisolone or prednisone	Enzalutamide	Control arm
Disease progression	18 (10.8)		10 (4.4)	8 (3.1)	
Patient decision	19 (11.4)		36 (15.7)	38 (14.7)	
Clinician decision	3 (1.8)		4 (1.7)	3 (1.2)	
Death	3 (1.8)		1 (0.4)	1 (0.4)	
Other	64 (38.3)		44 (19.2)	47 (18.2)	
ITT, n	459	455	527		533
PP, n	NR	NR	NR		NR
Safety, n	451	455	513		533

ITT = intention to treat; NA = not applicable; NR = not reported; PP = per protocol.
Source: Attard et al. (2022)[6] (including supplementary appendix).[7]

Exposure to Study Treatments

The median follow-up time in the STAMPEDE trial was 85 months for the treatment comparison involving the combination of abiraterone and prednisone alone (interquartile range [IQR], 83 to 96); and 60 months when assigned with enzalutamide (IQR, 59 to 71). The median follow-up for both treatment groups combined was 72 months (IQR, 63 to 73).

Median exposure to the combination of abiraterone and prednisone, when assigned alone, was 23.7 months (IQR, 17.6 to 24.1). When assigned in combination with enzalutamide, median exposure to abiraterone and prednisone was 20.7 months (IQR, 4.4 to 24.0). Median exposure to enzalutamide 23.2 months (IQR, 6.3 to 24).

Most patients (data not reported) started ADT before randomization and the median time from initiation of ADT to the start of treatment with abiraterone combination regimens was 8.4 weeks (IQR, 5.1 to 11.3).

Efficacy

Only those efficacy outcomes identified in the review protocol are reported subsequently. Results are summarized in Table 12 (individual treatment comparisons) and Table 13 (pooled analysis).

Overall Survival

Overall survival was a secondary outcome in the trial, defined as time from randomization to death. In a preplanned subgroup analysis of individual treatment comparisons, the use of abiraterone and prednisone, when assigned alone, was associated with an HR of 0.63 (95% confidence interval [CI], 0.48 to 0.82) in favour of active treatment versus control. In the Kaplan-Meier plot, the curves appeared to separate at approximately 18 months, favouring the control. The curves then crossed at approximately 30 months. The curves remained separated throughout follow-up, in favour of the active treatment.

When assigned in combination with enzalutamide, the HR was 0.54 (95% CI, 0.39 to 0.76) in favour of combination treatment versus control. In the Kaplan-Meier plot, the curves appeared to separate between approximately 18 and 24 months, favouring the active treatment. The curves remained separated throughout follow-up.

Findings from a preplanned meta-analysis of the 2 treatment comparisons pooled together were consistent with those presented above for each individual treatment comparison. There was a total of 147 outcome events (14.9%) in the active treatment groups and 236 outcome events (23.9%) in the control groups; the 6-year overall survival was reported as 86% in the pooled combination groups and 77% in the control groups. The median for overall survival was not reached in any treatment group. The HR was 0.60 (95% CI, 0.48 to 0.73; P < 0.0001) in favour of the combination of abiraterone and prednisone with or without enzalutamide versus control. In the Kaplan-Meier plot for the pooled analysis, the curves appeared to separate between approximately 24 and 30 months, in favour of the active interventions. The curves remained separated throughout follow-up.

Prostate Cancer–Specific Survival

Prostate cancer–specific survival was also a secondary outcome in the trial, defined as time from randomization to death from prostate cancer. The preplanned analysis of individual treatment comparisons showed that the use of abiraterone and prednisone, when assigned alone, was associated with an HR of 0.52 (95% CI, 0.36 to 0.75) in favour of active treatment versus control. When assigned in combination with enzalutamide, the HR was 0.44 (95% CI, 0.28 to 0.71) in favour of combination treatment versus control.

When patients from the 2 treatment comparisons were pooled together, results were consistent with those presented above for each individual treatment comparison. There was a total of 73 outcome events (7.4%) in the active treatment groups and 142 outcome events (14.4%) in the control groups. The 6-year prostate cancer–specific survival was reported as 93% in the combination therapy groups compared with 85% in the control groups. The median for prostate cancer–specific survival was not reached in any treatment group. The HR was 0.49 (95% CI, 0.37 to 0.65; P < 0.0001) in favour of the combination of abiraterone and prednisone with or without enzalutamide versus control. In the Kaplan-Meier plot for the pooled treatment comparison, the curves appeared to separate between approximately 24 and 30 months, in favour of the active treatment. The curves remained separated throughout follow-up.

Metastasis-Free Survival

The primary efficacy outcome in the trial was metastasis-free survival, defined as time from randomization to death from any cause or to distant metastases confirmed by imaging. The use of abiraterone and prednisone, when assigned alone, was associated with an HR of 0.54 (95% CI, 0.43 to 0.68) in favour of active treatment versus control. When assigned in combination with enzalutamide, the HR was 0.53 (95% CI, 0.39 to 0.71) in favour of combination treatment versus control. These findings per treatment comparison were obtained from preplanned subgroup analyses. In the Kaplan-Meier plots for each treatment comparison, the curves appeared to separate between approximately 8 and 12 months, in favour of the active treatment. The curves remained separated throughout follow-up.

A preplanned meta-analysis of the 2 treatment comparisons was selected for primary outcome reporting. Findings obtained for the pooled populations were consistent with those presented above for each treatment comparison. There was a total of 180 primary outcome events (18.3%) in the active treatment groups and 306 primary outcome events (31.0%) in the control groups. The 6-year metastasis-free survival was reported as 82% in the abiraterone combination groups compared with 69% in the control groups. The breakdown of events included metastases and deaths; for both, the number of events was lower in patients receiving active treatment compared with control patients. The median for metastasis-free survival was not reached in any treatment group. The HR was 0.53 (95% CI, 0.44 to 0.64; P < 0.0001) in favour of the combination of abiraterone and prednisone with or without enzalutamide versus control. In the Kaplan-Meier plot for the pooled treatment comparison, the curves appeared to separate between approximately 8 and 12 months, in favour of the active treatment. The curves remained separated throughout follow-up.

Relapse-Free Survival

Data reported for the outcome of relapse-free survival were identified in the trial as failure-free survival, which was assessed as a secondary outcome and defined as time from randomization to biochemical failure, local progression, distant metastases, or death from prostate cancer. The preplanned subgroup analysis of individual treatment comparisons showed that the use of abiraterone and prednisone, when assigned alone, was associated with an HR of 0.39 (95% CI, 0.31 to 0.49) in favour of active treatment versus control. When assigned in combination with enzalutamide, the HR was 0.40 (95% CI, 0.31 to 0.53) in favour of combination treatment versus control.

When patients from the 2 treatment comparisons were pooled together, results were consistent with those presented above for each individual treatment comparison. There was a total of 204 outcome events (20.7%) in the active treatment groups and 402 outcome events (40.7%) in the control groups. The median for progression-free survival was not reached in the active treatment group and was 86 months in the control groups (IQR, 83 to not estimable). The HR was 0.39 (95% CI, 0.33 to 0.47; P < 0.0001) in favour of the combination of abiraterone and prednisone with or without enzalutamide versus control.

Progression-Free Survival

Progression-free survival, assessed as a secondary outcome in the trial, was defined as time from randomization to local progression, distant metastases, or death from prostate cancer. The preplanned subgroup analysis of individual treatment comparisons showed that the use of abiraterone and prednisone, when assigned alone, was associated with an HR of 0.43 (95% CI, 0.33 to 0.56) in favour of active treatment versus control. When assigned in combination with enzalutamide, the HR was 0.45 (95% CI, 0.32 to 0.63) in favour of combination treatment versus control.

When patients from the 2 treatment comparisons were pooled together, results were consistent with those presented above for each individual treatment comparison. There was a total of 73 outcome events (14.0%) in the active treatment groups and 142 outcome events (28.0%) in the control groups. The median for progression-free survival was not reached in any treatment group. The HR was 0.44 (95% CI, 0.36 to 0.54; P < 0.0001) in favour of the combination of abiraterone and prednisone with or without enzalutamide versus control. In the Kaplan-Meier plot for the pooled treatment comparison, the curves appeared to separate

after approximately 6 months, in favour of the active treatment. The curves remained separated throughout follow-up.

Health-Related Quality of Life

No data were reported for the outcome of HRQoL.

Table 12: Summary of Efficacy Outcomes in the STAMPEDE Trial – Treatment Comparisons Presented Separately (Preplanned Analysis)

Outcome[a]	Abiraterone and prednisolone or prednisone comparison		Abiraterone, prednisolone or prednisone, and enzalutamide comparison	
	Abiraterone and prednisolone or prednisone	Control	Abiraterone, prednisolone or prednisone, and enzalutamide	Control
Number of patients contributing to the analysis	459	455	527	533
Overall survival				
Number of events, n (%)	95 (20.7)	142 (31.2)	52 (9.9)	94 (17.6)
HR (95% CI); P value[b]	0.63 (0.48 to 0.82); P = 0.0005		0.54 (0.39 to 0.76); P = 0.0004	
Prostate cancer–specific survival[c]				
Number of events, n (%)	48 (10.5)	86 (18.9)	25 (4.7)	56 (10.5)
HR (95% CI); P value	0.52 (0.36 to 0.75); P = NR		0.44 (0.28 to 0.71); P = NR	
Metastasis-free survival				
Number of events, n (%)	111 (24.2)	183 (40.2)	69 (13.1)	123 (23.1)
Breakdown of metastasis-free survival, number of events				
Deaths	60	73	33	44
Metastasis	51	110	36	79
HR (95% CI); P value[b]	0.54 (0.43 to 0.68); P < 0.0001		0.53 (0.39 to 0.71); P < 0.0001	
Progression-free survival				
Number of events, n (%)	84 (18.3)	166 (36.5)	54 (10.2)	111 (20.8)
HR (95% CI); P value	0.43 (0.33 to 0.56); P = NR		0.45 (0.32 to 0.63); P = NR	

CI = confidence interval; HR = hazard ratio; NR = not reported; NSAID = non-steroidal anti-inflammatory drug; vs. = versus.

Notes:

Metastasis-free survival was defined as time from randomization to death from any cause or to distant metastases confirmed by imaging.

Overall survival was defined as time from randomization to death.

Prostate cancer–specific survival was defined as time from randomization to death from prostate cancer.

Progression-free survival was defined as time from randomization to local progression, distant metastases, or death from prostate cancer.

Failure-free survival was defined as time from randomization to biochemical failure, local progression, distant metastases, or death from prostate cancer.

[a]Cox regression models adjusted for nodal involvement (N0 [negative] vs. NX [intermediate] vs. N+ [positive]), age at randomization (< 70 years vs. ≥ 70 years), WHO performance status (0 vs. 1 to 2), regular Aspirin or NSAID use at baseline (yes vs. no), and radiotherapy planned (yes vs. no).

[b]The authors did not report whether these P values were adjusted for multiple comparisons.

[c]Model used a competing-risks approach with death from non–prostate cancer causes as the competing risk.

Source: Attard et al. (2022)[6] (including supplementary appendix).[7]

Table 13: Summary of Efficacy Outcomes in the STAMPEDE Trial (Preplanned Meta-Analysis as Primary Outcome Reporting)

Outcome[a]	Abiraterone and prednisolone or prednisone ± enzalutamide treatment arms	Control arms
Number of patients contributing to the analyses	986	988
Overall survival		
Number of events, n (%)	147 (14.9)	236 (23.9)
Median (IQR)	Median not reached (IQR not estimable)	Median not reached (IQR, 103 to not estimable)
HR (95% CI); P value[b]	0.60 (0.48 to 0.73); P < 0.0001	
Prostate cancer–specific survival[c]		
Number of events, n (%)	73 (7.4)	142 (14.4)
Median (IQR)	Median not reached (IQR not estimable)	Median not reached (IQR not estimable)
HR (95% CI); P value[b]	0.49 (0.37 to 0.65); P < 0.0001	
Metastasis-free survival		
Number of events, n (%)	180 (18.3)	306 (31.0)
Breakdown of metastasis-free survival, number of events		
Deaths	93	117
Metastasis	87	189
Median (IQR)	Median not reached (IQR not estimable)	Median not reached (IQR, 97 to not estimable)
HR (95% CI); P value[b]	0.53 (0.44 to 0.64); P < 0.0001	
Progression-free survival		
Number of events, n (%)	138 (14.0)	277 (28.0)
Median (IQR)	Median not reached (IQR not estimable)	Median not reached (IQR, 103 to not estimable)
HR (95% CI); P value[b]	0.44 (0.36 to 0.54); P < 0.0001	

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NSAID = non-steroidal anti-inflammatory drug; vs. = versus.

Notes:

Metastasis-free survival was defined as time from randomization to death from any cause or to distant metastases confirmed by imaging.

Overall survival was defined as time from randomization to death.

Prostate cancer–specific survival was defined as time from randomization to death from prostate cancer.

Progression-free survival was defined as time from randomization to local progression, distant metastases, or death from prostate cancer.

Failure-free survival was defined as time from randomization to biochemical failure, local progression, distant metastases, or death from prostate cancer.

[a]Cox regression models adjusted for nodal involvement (N0 [negative] vs. NX [intermediate] vs. N+ [positive]), age at randomization (< 70 years vs. ≥ 70 years), WHO performance status (0 vs. 1 to 2), regular Aspirin or NSAID use at baseline (yes vs. no), and radiotherapy planned (yes vs. no).

[b]The authors did not report whether these P values were adjusted for multiple comparisons.

[c]Model used a competing-risks approach with death from non–prostate cancer causes as the competing risk.
Source: Attard et al. (2022)[6] (including supplementary appendix).[7]

Harms

Only those harms identified in the review protocol are reported below. Refer to Table 14 for detailed harms data.

Adverse Events

The total percentages of patients per group who experienced AEs through 2 years were not reported. The percentages of patients who experienced at least 1 grade 3 or worse AE were as follows: when abiraterone and prednisone were assigned alone, 37% of patients versus 29% of control patients; when abiraterone and prednisone were assigned in combination with enzalutamide, these proportions were 57% with active treatment versus 32% of control patients. The most frequently reported grade 3 or worse AEs were erectile dysfunction, hypertension, alanine transaminase and aspartate transaminase increase, fatigue, and hot flashes (additional details in Table 14). Grade 5 AEs were not reported in patients in the control groups, but 3 patients in the abiraterone and prednisone group and 4 patients in the abiraterone, prednisone, and enzalutamide group experienced a grade 5 AE, including 2 deaths (refer to the Mortality section).

Serious Adverse Events

No data were reported for the outcome of SAEs.

Withdrawals Due to Adverse Events

No data were reported for WDAEs as a harms outcome.

Mortality

Two patients in the abiraterone, prednisone, and enzalutamide group died, noted as “sudden death.” No additional information regarding these events was reported in the published article.

Notable Harms

When abiraterone and prednisone were assigned alone, fatigue was reported numerically more frequently in patients receiving active treatment versus control (n = 10 patients or 2% of the population, versus n = 4 patients or 1% of the population, respectively), as was the case for hypertension (n = 23 or 5%, versus n = 6 or 1%, respectively), hypokalemia (n = 5 or 1%, versus n = 1 or < 1%, respectively), insomnia (n = 8 or 2%, versus n = 1 or < 1%, respectively), cognitive disturbance (n = 2 or < 1%, versus n = 0, respectively) and dyspepsia (n = 1 or < 1%, versus n = 0, respectively).

When abiraterone and prednisone were assigned in combination with enzalutamide, these AEs were also reported numerically more frequently in patients receiving active treatment versus control, including fatigue (n = 49 patients or 10% of the population, versus n = 12 patients or 2% of the population, respectively), hypertension (n = 73 or 14%, versus n = 8 or 2%, respectively), hypokalemia (n = 6 or 1%, versus n = 1 or < 1%, respectively), insomnia (n = 7 or 1%, versus n = 1 or < 1%, respectively), cognitive disturbance (n = 2 or < 1%, versus n = 0, respectively) and dyspepsia (n = 2 or < 1%, versus n = 0, respectively).

Table 14: Summary of Key Harms Outcomes in the STAMPEDE Trial — Treatment Comparisons Presented Separately (Safety Population)

Outcome	Abiraterone and prednisolone or prednisone comparison		Abiraterone, prednisolone or prednisone, and enzalutamide comparison	
	Abiraterone and prednisolone or prednisone	Control	Abiraterone, prednisolone or prednisone, and enzalutamide	Control
Number of patients in safety population	451	455	513	533
Patients with ≥ 1 grade 3 or worse AEs over the first 24 months (planned duration of combination therapy)				
n (%)	169 (37)	130 (29)	298 (57)	172 (32)
Most common events, n (%)				
Erectile dysfunction	41 (9)	48 (11)	71 (14)	55 (10)
Hypertension	23 (5)	6 (1)	73 (14)	8 (2)
ALT increase	25 (6)	0 (0)	64 (12)	4 (1)
Fatigue	10 (2)	4 (1)	49 (10)	12 (2)
Hot flashes	18 (4)	16 (4)	39 (8)	32 (6)
AST increase	2 (< 1)	1 (< 1)	19 (4)	0 (0)
Other events of special interest in the trial, n (%)				
Insomnia	8 (2)	1 (< 1)	7 (1)	1 (< 1)
Hypokalemia	5 (1)	1 (< 1)	6 (1)	1 (< 1)
Acute coronary syndrome	5 (1)	3 (1)	4 (1)	7 (1)
Dizziness	1 (< 1)	0 (0)	4 (1)	1 (< 1)
Cardiac dysrhythmia	3 (1)	2 (< 1)	2 (< 1)	0 (0)
Anemia	2 (< 1)	5 (1)	2 (< 1)	2 (< 1)
Nausea	0 (0)	1 (< 1)	3 (1)	0 (0)
Cognitive disturbance	2 (< 1)	0 (0)	2 (< 1)	0 (0)
Dyspepsia	1 (< 1)	0 (0)	2 (< 1)	0 (0)
Anorexia	0 (0)	0 (0)	2 (< 1)	1 (< 1)
Headache	0 (0)	0 (0)	2 (< 1)	0 (0)
Anxiety	nr	nr	1 (< 1)	0 (0)
Depression	nr	nr	1 (< 1)	0 (0)
Constipation	1 (< 1)	3 (1)	1 (< 1)	0 (0)
Cough	5 (1)	0 (0)	0 (0)	0 (0)

Outcome	Abiraterone and prednisolone or prednisone comparison		Abiraterone, prednisolone or prednisone, and enzalutamide comparison	
	Abiraterone and prednisolone or prednisone	Control	Abiraterone, prednisolone or prednisone, and enzalutamide	Control
Patients with ≥ 1 grade 5 AEs over the first 24 months (planned duration of combination therapy)				
n (%)	3 (1)	0 (0)	4 (1)	0 (0)
Most common events, n (%)				
Rectal adenocarcinoma	1 (< 1)	0 (0)	0 (0)	0 (0)
Pulmonary hemorrhage	1 (< 1)	0 (0)	0 (0)	0 (0)
Respiratory disorder	1 (< 1)	0 (0)	0 (0)	0 (0)
Septic shock	0 (0)	0 (0)	2 (< 1)	0 (0)
Sudden death	0 (0)	0 (0)	2 (< 1)	0 (0)

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase.
Source: Attard et al. (2022)[6] (including supplementary appendix).[7]

Critical Appraisal

Internal Validity

Study Design, Intervention, and Comparators

The STAMPEDE trial was designed to evaluate the superiority of adding abiraterone and prednisone with or without enzalutamide to ADT and SoC, over ADT and SoC alone (control groups) in patients newly starting ADT for prostate cancer. The trial was randomized but was not blinded. Being an OL study, the STAMPEDE trial was susceptible to assessment and reporting biases, as knowledge of treatment assignment could influence investigators' assessment of certain efficacy outcomes and patient reporting of AEs. Ideally, anticancer drug trials should be blinded, when possible, with centralized review of tumour-based outcomes.[29] Without a comparison between investigator and central assessment of tumours, it is not possible to determine the impact or direction of a potential bias that knowledge of treatment assignment may have had.

The STAMPEDE trial was conducted in the UK and Switzerland at multiple centres in both countries. No detail was reported regarding local SoC used to treat patients in all treatment groups, both during the treatment period as well as after treatment was stopped, which could be due to treatment completion or disease progression. Therefore, it is not possible to assess whether there were differences between treatment groups in the use of background treatments that may have biased the results in favour of 1 treatment arm over the other. More specifically, this issue brings uncertainty to the overall survival analyses results, as changes to therapy upon disease progression may have an impact on patients' survival, which would not be related to the treatment they were randomized to in the STAMPEDE trial. Of note, the STAMPEDE protocol provided study sites with broad guidelines for treatments but the exact intervention was to be "per local practice."[7] Although information regarding the intervention (type, dosage, dose modifications, and so on) was to be provided, the published article does not report these details. Patient randomization in the STAMPEDE

trial was stratified by study centre, which may have helped to ensure variations in local practices were similarly distributed in the groups; however, outcome analyses were not adjusted for this stratification factor and therefore may not be adequately accounted for.[7]

Selection, Allocation, and Disposition of Patients

Patients were randomized at a ratio of 1:1 using appropriate randomization methods. Baseline characteristics were balanced between treatment groups within treatment comparison.

High proportions of patients in active treatment groups discontinued treatment but remained in the study. When abiraterone and prednisone were assigned alone, 36% of patients discontinued treatment. When the combination was assigned with enzalutamide, 44% of patients discontinued abiraterone and prednisone. The use of enzalutamide was discontinued by 49% of patients. These high treatment discontinuation rates are perhaps not unexpected, given the AE profiles of the drugs. The discontinuations could not be compared to those of the control arms because details were not reported, likely given the adaptive platform design of the trial. It was reported in the protocol that sensitivity analyses would be conducted if the MCAR assumption in the ITT analysis was uncertain; however, the sensitivity analyses based on missing at random (MAR) and missing not at random (MNAR) data were not reported in the article. Therefore, any potential impacts of patient disposition and discontinuation could not be fully appraised.

Outcome Measures

The primary efficacy outcome in the STAMPEDE trial was metastasis-free survival, defined as time from randomization to death from any cause or to distant metastases confirmed by imaging. Metastasis-free survival has been validated as a primary clinical end point for clinical study designs and the clinical experts consulted by CADTH considered it a relevant outcome, particularly in the context of early stage, localized but high-risk prostate cancer. The choice of secondary outcome measures was considered appropriate according to the experts' opinion, the most relevant being overall survival. No data were reported for the outcome of HRQoL.

However, it was not reported whether outcomes were assessed by the investigators or by central blinded assessors, which would be preferable to minimize the risk of bias in an OL setting. Outcome assessment by investigators in a multicentre trial like the STAMPEDE trial may also lead to greater inter-rater variation. In the absence of details about potential differences in outcome assessment between treatment groups, any potential biases could not be fully appraised.

Statistical Analysis

Changes were made to the study conduct while the study was ongoing (after completion of accrual to both treatment comparisons and before inspection of detailed efficacy outcomes), which is typical of the adaptive study design used for the STAMPEDE trial. They were nevertheless considered preplanned by the authors. Detailed information was provided in the publication to explain the changes and the impact that they would have on the presentation of the findings (i.e., on the patient population, data analysis, primary outcome measure, and extent of follow-up). The rationale and timing of these changes were not a threat to

internal validity and were deemed appropriate to inform treatment decisions per the adaptive design. It is not expected that they would result in significant bias in favour of any treatment group.

The STAMPEDE trial had sufficient power for the analysis of the primary outcome, and statistical significance was also reached for most of the secondary outcomes. However, no methods were described for accounting for multiplicity of comparisons. The methods used for the analysis were appropriate for time-to-event outcomes (Cox proportional hazards regression adjusted for certain randomization stratification factors). The clinical experts consulted acknowledged that nodal involvement, age, WHO performance status, method of ADT, and radiotherapy are clinically relevant covariates; however, the clinical experts agreed that randomization centre and regular Aspirin or NSAIDs are not clinically relevant. While the proportional hazards assumption appeared to be met for the primary analysis of metastasis-free survival, it is unclear whether the assumption was met for the overall survival analyses or for the prostate cancer–specific survival analyses. It was reported that the Schoenfeld residuals were inspected to assess the proportional hazards assumption for all of the time-to-event Cox survival analyses. For the pooled treatment analyses of overall survival and prostate cancer–specific survival, the article states that the assumption was met based on the test (P = 0.10 for overall survival and P = 0.44 for prostate cancer–specific survival, indicating no evidence of nonproportional hazards); the graphical representation of the Schoenfeld residuals was not provided. However, there is uncertainty in whether the assumption holds based on visual inspection of the Kaplan-Meier curves for unpooled overall survival analyses where the curves appear nearly identical at the beginning and only really start to diverge toward the end; the curves for the abiraterone and prednisone versus ADT alone appear to cross. Visual inspection of the Kaplan-Meier curve for prostate cancer–specific survival similarly showed the curves to be nearly identical at the beginning and possibly cross at a time point between 12 and 24 months of follow-up (note, only the pooled treatment Kaplan-Meier curves were presented for this analysis). Given the 6-year time frame for the analyses, it is unclear whether the proportional hazards assumptions would be reasonable, particularly in the population studied. With the lack of additional information to assess the tests and the assumptions, a definitive conclusion regarding the effects of abiraterone combinations on overall survival and prostate cancer–specific survival cannot be made.

Data from the 2 treatment groups were pooled. However, details on the methods for pooling and how heterogeneity beyond statistical sources was assessed were not reported in the article. Nonetheless, visual inspection of the baseline characteristics for the treatment groups by CADTH reviewers and the clinical experts consulted for the review did not identify clear sources of clinical heterogeneity; therefore, this is expected to have a small impact on the results, if any.

External Validity

Patient Selection

The inclusion and exclusion criteria appeared clinically relevant and reasonable. Patients included in the study were deemed representative of the population seen by experts in clinical practice; however, the definition used in the study for “high-risk” was not. The STAMPEDE definition differed from the definition used by clinicians in practice in Canada, which resulted in a population of patients whose risk was higher

than high-risk patients living in Canada. This should be taken into account when generalizing the findings from the study to real-life patients.

Treatment Regimen and Length of Follow-Up

The administration of abiraterone and prednisone in the trial were in line with the Health Canada recommended dosages in oncology and what would be used in the reimbursement population. The duration of treatment was consistent with experience from clinical practice based on input from clinical experts. While the median follow-up period was approximately 6 years, it may not have been long enough to adequately evaluate survival analyses given the median survivals were not reached in most of the analyses.

The lack of detail regarding co-interventions and local SoC received by patients during the trial precludes assessment of the generalizability of background treatment to the Canadian setting.

Outcome Measures

Primary and secondary outcome measures of survival were validated and considered relevant to clinical practice by the experts consulted by CADTH for this review. They were also identified as important for patients who provided input to this review.

Economic Evidence

As this review is part of the CADTH Nonsponsored Reimbursement Review program, in which an application filed by a sponsor is absent, CADTH does not have access to an economic model for abiraterone in this clinical condition. As a result, the economic review consisted only of a cost comparison for abiraterone with prednisone with or without enzalutamide as add-on to SoC (ADT) compared with ADT alone for the treatment of patients with high-risk nmPC.

CADTH Analyses

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on each product's respective product monographs and validated by clinical experts. If there were any discrepancies in dosing between what is indicated in the product monograph and what is done in Canadian clinical practice, the dose specified by clinical experts was used. As abiraterone does not have a Health Canada indication for high-risk nmPC, dosing was based on the STAMPEDE trial and validated by clinical experts consulted by CADTH for this review.[24] The price of each abiraterone 250 mg tablet is $26.0313 and each 500 mg tablet is $52.0625, based on public list prices from the Ontario Drug Benefit Formulary/Comparative Drug Index, accessed June 2023.[30] Pricing for comparator products was based on publicly available list prices.

Results of the cost comparison demonstrate that, over a 28-day cycle, abiraterone with prednisone is $2,916 more costly than ADT alone (Table 15). Abiraterone with prednisone and enzalutamide is $6,186 more costly per 28-day cycle than ADT alone. 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 15.

Table 15: CADTH Cost Comparison Table for Abiraterone Acetate and Prednisone With or Without Enzalutamide Regimen Under Review (Added on to ADT)

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Daily cost ($)	Average 28-day drug cost ($)	Annual cost ($)
Abiraterone acetate with prednisone +/− enzalutamide							
Abiraterone acetate	250 mg 500 mg	Tablet	26.0313 52.0625	1,000 mg once daily[a]	104.13	2,916	38,006
Prednisone	1 mg 5 mg 50 mg	Tablet	0.1276 0.0220 0.1735	5 mg once daily[a]	0.02	0.62	8
Enzalutamide (Xtandi)	40 mg	Soft gelatin capsules	29.1954[b]	160 mg daily[31]	116.78	3,270	42,625
Abiraterone acetate with prednisone					**104.15**	**2,916**	**38,014**
Abiraterone acetate with prednisone + enzalutamide					**220.93**	**6,186**	**80,639**

ADT = androgen deprivation therapy.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2023), unless otherwise indicated, and do not include dispensing fees.[30]

[a]Source: STAMPEDE abiraterone clinical trial dosing, and confirmed to be appropriate by clinical experts consulted by CADTH for this review.[24]

[b]Source: Ontario Exceptional Access Program (accessed June 2023).[32]

Issues for Consideration

- Abiraterone (in combination with prednisone or dexamethasone with docetaxel) is undergoing a concurrent nonsponsored Reimbursement Review by CADTH for the treatment of mCSPC, in combination with ADT.[33]
- The list price for abiraterone varies across jurisdictions. Pricing in the cost table is based on the Ontario list price;[30] however, CADTH noted that lower list prices are present in some jurisdictions. For example, in Nova Scotia, abiraterone is priced as $7.6563 and $15.3125 per 250 mg and 500 mg tab, respectively, as of June 1, 2023.[34] As abiraterone with prednisone with or without enzalutamide is used as an add-on therapy to ADT, the reimbursement of abiraterone for high-risk nmPC will lead to increased treatment acquisition cost. However, the magnitude of incremental costs will be jurisdiction dependent. To highlight this uncertainty, CADTH conducted a scenario analysis exploring abiraterone costs from an alternative jurisdiction (Nova Scotia) (refer to Table 19 in Appendix 3).
- Abiraterone has previously been reviewed by pERC for mCRPC.[35] A recommendation of "reimburse with clinical criteria and/or conditions" was issued on October 22, 2013.[35] In the recommendation, pERC specified that at the submitted price, abiraterone could not be considered cost-effective.[35] The price submitted by the sponsor for abiraterone for mCRPC ($28.33 per 250 mg tablet) within this pCODR review[35] is higher than the current public list price of generic abiraterone ($26.03).[30]
- As abiraterone with prednisone with or without enzalutamide is used as an add-on therapy to ADT, in addition to treatment acquisition costs, there could be an increase in pharmacy dispensing fees,

should the regimen be reimbursed by drug plans. Drug plan input also noted that additional resources may be required to monitor AEs from abiraterone and prednisone.

- The funding algorithm for abiraterone remains unclear. If not reimbursed in patients with high-risk nmPC, abiraterone may be used in a different treatment line (e.g., metastatic cancer).
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on May 24, 2023.

Discussion

Summary of Available Evidence

One published, open-label RCT was reviewed; the STAMPEDE trial (N = 1,974)[6] evaluated the impact of adding the combination of abiraterone and prednisone with or without enzalutamide to ADT and SoC in patients starting long-term ADT for high-risk nmPC. In the trial, a high-risk presentation was defined as node-positive cancer; or node-negative cancer with at least 2 risk factors (clinical tumour stage T3 or T4, Gleason sum score 8 to 10, and/or PSA ≥ 40 ng/mL); or node-negative relapsing cancer with high-risk features. Abiraterone 1,000 mg and prednisone or prednisolone 5 mg, with or without enzalutamide 160 mg, were administered orally once daily for 2 years or until disease progression. These treatment intensification strategies were compared to non-overlapping control groups who received ADT and SoC; this allowed preplanned pooling of the results. ADT was mandatory for every patient enrolled in the trial; SoC also included radiotherapy.

Findings from the STAMPEDE trial are generalizable to a population with a higher level of risk than what is considered a high-risk patient according to the Canadian definition. The lack of detail regarding SoC received during the treatment period and upon disease progression precludes assessment of the impact of these co-interventions on survival findings. Being an OL study, STAMPEDE was susceptible to assessment and reporting biases, the impact or direction of which are uncertain. High proportions of patients discontinued active treatment, highlighting the importance of perceived balance between the impact of the drug on disease progression versus the numerous AEs.

Interpretation of Results

Efficacy

The use of abiraterone and prednisone, when assigned alone or in combination with enzalutamide, was consistently associated with HRs in favour of active treatment versus control (ADT alone) for analyses of metastasis-free survival, relapse-free survival, and progression-free survival. Although the median survivals were not yet reached, the magnitude of the absolute differences in events during the median 6-year follow-up time between groups was considered clinically meaningful by the clinical experts consulted by CADTH for this review. This suggests that intensifying ADT treatment with abiraterone and prednisone results in metastasis-free, relapse-free, and progression-free survival benefits in patients starting long-term ADT for high-risk nmPC. There were no direct comparisons between the abiraterone and prednisone combination and

the abiraterone, prednisone, and enzalutamide triple therapy groups. However, the magnitude of the benefit appeared only somewhat larger when enzalutamide was added to abiraterone and prednisone, and when combined with what appeared to be more AE events with the therapy, the data suggest that there was no added clinically important benefit with the triple therapy versus dual therapy. The authors of the study drew a similar conclusion, which also aligned with their previous research that also did not suggest added benefit with this triple therapy regimen.

Although the HRs for overall survival and prostate cancer–specific survival favoured the abiraterone combination treatments versus ADT alone, there is uncertainty about these results. It was unclear whether the proportional hazards assumption for the adjusted analyses was met. The STAMPEDE protocol indicated that other survival analysis methods (i.e., restricted mean survival time) would be used in the case of nonproportional hazards; but presumably based on the Schoenfeld test results that indicated no evidence of nonproportional hazards, other methods to validate these survival results were not reported. As well, the authors of the study acknowledged that it is unclear what impact treatment modifications may have had on these survival analyses. It was also noted that the number of deaths as a percentage of events contributing to the metastasis-free survival analyses was higher in the abiraterone combination groups than in the control groups (93 deaths out of 180 events [52%] versus 117 deaths out of 306 events [38%]). Therefore, although the overall survival and prostate cancer–specific survival results are promising, a concrete conclusion cannot be made based on the results of the STAMPEDE trial alone.

The STAMPEDE criteria for high-risk prostate cancer differed from the Canadian definition of high-risk disease. Patients with node-positive cancer were included in the STAMPEDE trial as a high-risk population. In Canada, these patients would not be considered within the high-risk nonmetastatic category; instead, they would be considered to have a level of risk that is higher than those patients included in the high-risk strata. Patients with node-positive disease were well represented in the STAMPEDE trial and efficacy in these patients was confirmed by a preplanned subgroup analysis for the outcome of metastasis-free survival. As for patients with node-negative disease, the inclusion criteria in the trial required them to have at least 2 risk factors to meet the trial's high-risk definition; in Canada, the high-risk definition would include only 1 of the following risk factors: tumour stage T3 or T4, Gleason sum score 8 to 10, or PSA greater than or equal to 40 ng/mL. Therefore, in terms of Canadian risk definition, patients from the STAMPEDE trial would be considered at highest risk or at very high risk. It is unknown if the magnitude of treatment effect would be similar if abiraterone and prednisone was administered in patients with a risk that is lower than that of patients included in the trial. The authors of the article emphasized that the results were only generalizable to the population enrolled in the trial, and the clinical experts consulted by CADTH agreed.

The STAMPEDE trial was not informative regarding the impact of abiraterone and prednisone on HRQoL or other patient-reported efficacy outcomes because data for these were not reported.

Harms

The proportions of patients who experienced AEs were low, especially considering the high treatment discontinuation rates due to AEs, and they were numerically higher in patients receiving active treatment versus control. The clinical experts consulted by CADTH indicated that it is common for patients to

experience numerous AEs. In the trial, however, patients and clinicians were aware of the treatment strategy received, which may have introduced bias in these subjectively measured outcomes. Potential abiraterone-related harms, as well as corticosteroid-related AEs, were reported in a small proportion of patients, but were also numerically higher in patients receiving active treatment versus control. The differences between treatment groups were more apparent when enzalutamide was added on. The observed types of AEs were consistent with what is expected with these 3 drugs. The patient input provided to CADTH for this review highlighted that AEs of abiraterone and prednisone may be tolerable considering the potential benefits of the drugs.

Other Considerations

Cost Information

Based on publicly available list prices, abiraterone with prednisone is expected to have a 28-day cost of $2,916, whereas abiraterone with prednisone and enzalutamide is expected to have a 28-day cost of $6,186. As both regimens would be used as add-on therapy to ADTs, all costs are expected to be incremental.

Conclusions

Findings from the STAMPEDE trial suggest that treatment intensification of ADT with abiraterone and prednisone may result in clinically meaningful prevention of metastasis and disease relapse versus ADT alone, in patients starting long-term ADT for high-risk nmPC. The overall survival and prostate cancer–specific survival benefits of abiraterone and prednisone added on to ADT could not be determined because of a lack of reporting of important methods and statistical analysis details. Median survival times were not estimable for any of the analyses. The trial definition for high-risk differed from the Canadian definition; these patients would instead be considered at very high risk or at highest risk in clinical practice. Enzalutamide, when added to abiraterone and prednisone, did not appear to add clinically meaningful benefit but seemed to increase toxicity. Despite small proportions of patients reporting AEs, high discontinuation rates due to AEs were observed in the trial. However, patient input suggests that AEs may be acceptable considering the potential benefits of the treatment regimen.

As a cost-effectiveness analysis was not submitted, the cost-effectiveness of treatment intensification of ADT with abiraterone and prednisone compared with ADT alone in patients with high-risk nmPC could not be determined. Results of the cost comparison of treatment costs demonstrate that, over a 28-day cycle, abiraterone and prednisone added on to ADT is $2,916 more costly than ADT alone. Abiraterone with prednisone and enzalutamide is $6,186 more costly per 28-day cycle than ADT alone. As both regimens would be used as add-on therapy to ADTs, the reimbursement of abiraterone with prednisone for high-risk nmPC is expected to increase overall treatment costs. Other costs such as administration costs were not considered as part of the cost comparison. To consider this alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of treatment intensification of ADT with abiraterone and prednisone compared with ADT alone would be required.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

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

Date of search: June 20, 2022

Alerts: Bi-weekly search updates until project completion

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; guidelines; overview of reviews; randomized controlled trials; controlled clinical trials.

Limits:

- Conference abstracts: excluded

Table 16: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical 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
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number

Syntax	Description
.nm	Name of substance word (MEDLINE)
.jw	Journal title word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

1. (abretone* or abiraterone* or cb-7630 or cb7630 or drgt-45 drgt45 or jnj-212082 or jnj212082 or sol-804 or sol804 or tavt-45 or tavt45 or yonsa* or zytiga*).ti,ab,kf,ot,hw,nm,rn.
2. (akpred or ak-pred or bubblipred or bubbli-pred or codelcorton* or cordrol* or cortalon* or cotogesic or cotolon* or decaprednil* or decortin* or delcortol* or deltacortef* or delta-cortef* or deltacortenol* or deltacortril* or delta-cortril* or deltastab* or delta-stab* or dicortol* or donisolon* or dydeltrone* or eazolin* or erbacort* or erbason* or estilson* or fernisolon* or hostacortin* or hydeltra* or hydeltrasol* or hydrodeltalon* or hydrodeltison* or hydroretrocort* or inflamase* or keypred or key-pred or klismacort* or lentoson* or metacortandralon* or meticortelone* or metiderm* or meti-derm* or millipred* or orapred* or panafcortelon* or paracortol* or pediapred* or precortilon* or precortisyl* or prednedome* or predne-dome* or prednelan* or prednicen* or predniliderm* or predniretard* or prednisolon* or prednison* or predonine* or prelone* or prenolon* or rolison* or scherisolon* or solone* or sterane or sterolone* or ulacort* or ultracorten*).ti,ab,kf,ot,hw,nm,rn.
3. 1 and 2
4. 3 use medall
5. *abiraterone acetate/
6. (abretone* or abiraterone* or cb-7630 or cb7630 or drgt-45 drgt45 or jnj-212082 or jnj212082 or sol-804 or sol804 or tavt-45 or tavt45 or yonsa* or zytiga*).ti,ab,kf,dq.
7. 5 or 6
8. *prednisolone/
9. (akpred or ak-pred or bubblipred or bubbli-pred or codelcorton* or cordrol* or cortalon* or cotogesic or cotolon* or decaprednil* or decortin* or delcortol* or deltacortef* or delta-cortef* or deltacortenol* or deltacortril* or delta-cortril* or deltastab* or delta-stab* or dicortol* or donisolon* or dydeltrone* or eazolin* or erbacort* or erbason* or estilson* or fernisolon* or hostacortin* or hydeltra* or hydeltrasol* or hydrodeltalon* or hydrodeltison* or hydroretrocort* or inflamase* or keypred or key-pred or klismacort* or lentoson* or metacortandralon* or meticortelone* or metiderm* or meti-derm* or millipred* or orapred* or panafcortelon* or paracortol* or pediapred* or precortilon* or precortisyl* or prednedome* or predne-dome* or prednelan* or prednicen* or predniliderm* or predniretard* or prednisolon* or prednison* or predonine* or prelone* or prenolon* or rolison* or scherisolon* or solone* or sterane or sterolone* or ulacort* or ultracorten*).ti,ab,kf,dq.
10. 8 or 9
11. 7 and 10

12. 11 use oemezd
13. (conference review or conference abstract).pt.
14. 12 not 13
15. 4 or 14
16. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
17. Randomized Controlled Trial/
18. exp Randomized Controlled Trials as Topic/
19. "Randomized Controlled Trial (topic)"/
20. Controlled Clinical Trial/
21. exp Controlled Clinical Trials as Topic/
22. "Controlled Clinical Trial (topic)"/
23. Randomization/
24. Random Allocation/
25. Double-Blind Method/
26. Double Blind Procedure/
27. Double-Blind Studies/
28. Single-Blind Method/
29. Single Blind Procedure/
30. Single-Blind Studies/
31. Placebos/
32. Placebo/
33. Control Groups/
34. Control Group/
35. (random* or sham or placebo*).ti,ab,hw,kf.
36. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
37. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
38. (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
39. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
40. allocated.ti,ab,hw.
41. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
42. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
43. (pragmatic study or pragmatic studies).ti,ab,hw,kf.

44. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
45. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
46. (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
47. or/16-46
48. (systematic review or meta-analysis).pt.
49. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
50. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
51. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
52. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
53. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
54. (handsearch* or hand search*).ti,ab,kf.
55. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
56. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
57. (meta regression* or metaregression*).ti,ab,kf.
58. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
59. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
60. (cochrane or (health adj2 technology assessment) or evidence report).jw.
61. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
62. (outcomes research or relative effectiveness).ti,ab,kf.
63. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
64. [(meta-analysis or systematic review).md.]
65. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
66. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
67. umbrella review*.ti,ab,kf.
68. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
69. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
70. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
71. or/48-70

72. 47 or 71
73. 15 and 72
74. remove duplicates from 73

Clinical Trials Registries

ClinicalTrials.gov

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

[Search -- Studies with results | abiraterone acetate, zytiga]

WHO ICTRP

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

[Search terms -- abiraterone acetate, zytiga]

Health Canada's Clinical Trials Database

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

[Search terms -- abiraterone acetate, zytiga]

EU Clinical Trials Register

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

[Search terms -- abiraterone acetate, zytiga]

Grey Literature

Search dates: June 9, 2022, to June 13, 2022

Keywords: abiraterone acetate, zytiga, non-metastatic prostate cancers

Limits: none

Relevant websites from the following sections of the CADTH 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)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Excluded Studies

Note that this appendix has not been copy-edited.

Table 17: Excluded Studies

Reference	Reason for exclusion
AL-ASAAED, S., et al. Canadian Journal of Urology 2014 21(2 Supp 1):37 to 41	Other design (review article, clinical practice guideline, or expert opinion)
ANGULO, J., et al. Revista Colombiana de Cancerologia 2017 21(2):95 to 103	Language other than English
ATTARD, G., et al. European Urology 2014 66(5):799 to 802	Other design (review article, clinical practice guideline, or expert opinion)
CHENG, M. L., et al. Current Treatment Options in Oncology 2014 15(1):115 to 126	Other design (review article, clinical practice guideline, or expert opinion)
EFSTATHIOU, E., et al. European Urology 2019 76(4):418 to 424	Ineligible intervention or comparator
GRUNWALD, V., et al. European Urology 2022 81(6):621	Other design (review article, clinical practice guideline, or expert opinion)
HEIDENREICH, A., et al. European Urology 2014 65(2):467 to 79	Other design (review article, clinical practice guideline, or expert opinion)
MANCEAU, C., et al. Expert Review of Anticancer Therapy 2020 20(8):629 to 638	Other design (review article, clinical practice guideline, or expert opinion)
MATSUBARA, N., et al. Cancer Science 2014 105(10):1313 to 20	Ineligible population
MCKAY, R. R., et al. Journal of Clinical Oncology 2019 37(11):923 to 931	Ineligible intervention or comparator
MCKAY, R. R., et al. Journal of Urology 2021 206(1):80 to 87	Ineligible intervention or comparator
OHLMANN, C. H. Urologe (Ausg. A) 2017 56(11):1424 to 1429	Language other than English
OHLMANN, C. H., et al. Trials [Electronic Resource] 2017 18(1):457	Ineligible population
OMLIN, A., et al. Urologe (Ausg. A) 2012 51(1):8 to 14	Language other than English
RUSH, H. L., et al. Journal of Clinical Oncology 2022 40(8):825 to 836	Ineligible intervention or comparator
SPETSIERIS, N., et al. European Journal of Cancer 2021 157(259 to 267	Ineligible population
SYDES, M. R., et al. Annals of Oncology 2018 29(5):1235 to 1248	Ineligible intervention or comparator
VIRGO, K. S., et al. Journal of Clinical Oncology 2017 35(17):1952 to 1964	Other design (review article, clinical practice guideline, or expert opinion)
VIRGO, K. S., et al. Journal of Clinical Oncology 2021 39(11):1274 to 1305	Other design (review article, clinical practice guideline, or expert opinion)

Reference	Reason for exclusion
WALLIS, C. J. D., et al. European Urology 2018 73(6):834 to 844	Ineligible population
WU, Y., et al. Current Opinion in Oncology 2011 23(3):290 to 296	Other design (review article, clinical practice guideline, or expert opinion)

Appendix 3: Cost Comparison Table of ADT Therapies

Note that this appendix has not been copy-edited.

Table 18: CADTH Cost Comparison Table of ADT for High-Risk nmPC

Drug or comparator	Strength	Dosage form	Price ($)	Recommended Dose	Average 28-day Drug Cost ($)	Annual cost ($)
ADTs						
Leuprolide acetate						
Leuprolide acetate (Eligard)	7.5 mg 22.5 mg 30 mg 45 mg	Lyophilized powder for injection, Prefilled syringe	310.7200 891.0000 1,285.2000 1,645.0000	22.5 mg every 3 months[36,a]	273	3,564
Leuprolide acetate (Lupron depot)	3.75 mg 7.5 mg 11.25 mg 22.5 mg 30 mg	Prefilled syringe	389.1300 387.9700 1,159.5200 1,071.0000 1,428.0000	22.5 mg every 3 months[37,a]	329	4,284
Leuprolide acetate (Zeulide depot)	3.75 mg 22.5 mg	Lyophilized powder for injection	304.0000 873.0000	22.5 mg every 3 months[38,a]	268	3,492
Other LHRH agonists						
Goserelin depot (Zoladex)	3.6 mg 10.8 mg	Depot	422.6778 1,204.7322	10.8 mg every 3 months[39,b]	370[b]	4,819
Triptorelin (Trelstar)	3.75 mg 11.25 mg 22.5 mg	Sterile vial of powder for injectable suspension	346.3100 1,038.9700 1,659.9000	3.75 mg monthly[40]	319	4,156
LHRH antagonists						
Degarelix acetate (Firmagon)	80 mg 120 mg	Powder for injection	274.1760 370.9440	Starting dose: 240 mg once Maintenance dose: 80 mg monthly one month after starting dose[19]	Starting dose: 683[c] Maintenance dose: 252[d]	First year: 3,758 Subsequent year: 3,290

ADT = androgen deprivation therapy; LHRH = luteinizing hormone-releasing hormone.

Notes:

All prices are from the Ontario Drug Benefit Formulary (accessed June 2023), unless otherwise indicated, and do not include dispensing fees.[30]

All dosing is from respective product monographs, unless otherwise indicated.

For regimens with monthly doses, 28-day costs were calculated by converting monthly costs to daily costs (assuming 30.42 days in a month) and multiplying by 28.

[a]While product monograph dosing indicates a dose of 7.5 mg monthly, clinical experts consulted for this review indicated that the most commonly used dose was 22.5 mg every 3 months.

[b]While product monograph dosing indicates a dose of 3.6 mg monthly, clinical experts consulted for this review indicated that the most commonly used dose was 10.8 mg every 3 months.

[c]The cost for the first month was $741.89. The 28-day costs were calculated by converting monthly costs to daily costs (assuming 30.42 days in a month) and multiplying by 28.

[d]The cost per maintenance dose is $274.18. The 28-day costs were calculated by converting monthly costs to daily costs (assuming 30.42 days in a month) and multiplying by 28.

Table 19: CADTH Cost Comparison Table for Abiraterone Acetate and Prednisone With or Without Enzalutamide Regimen Under Review (Added on to ADT) Using Nova Scotia List Prices (Scenario Analysis)

Drug or comparator	Strength	Dosage form	Price ($)	Recommended dose	Daily cost ($)	Average 28-day drug cost ($)	Annual cost ($)
Abiraterone acetate with prednisone ± enzalutamide							
Abiraterone acetate	250 mg 500 mg	Tablet	7.6563 15.3125	1,000 mg once daily[a]	30.63	858	11,178
Prednisone	1 mg 5 mg 50 mg	Tablet	0.1276 0.0401 0.1735	5 mg once daily[a]	0.04	1.12	15
Enzalutamide (Xtandi)	40 mg	Soft gelatin capsules	29.1953	160 mg daily[31]	116.78	3,270	42,625
Abiraterone acetate with prednisone					30.67	859	**11,193**
Abiraterone acetate with prednisone + enzalutamide					147.45	4,129	**53,818**

ADT = androgen deprivation therapy; LHRH = luteinizing hormone-releasing hormone.

Note: All prices are from the Nova Scotia Formulary (accessed June 2023), unless otherwise indicated, and do not include dispensing fees.[34]

[a]Source: STAMPEDE abiraterone clinical trial dosing, and confirmed to be appropriate by clinical experts consulted by CADTH for this review.[24]