CADTH

CADTH Reimbursement Review

ABIRATERONE ACETATE AND PREDNISONE

(Non-Sponsored Review)

Therapeutic area: high-risk non-metastatic prostate cancer

CADTH

Table of Contents

List of Tables

List of Figures

Abbreviations

ADT	androgen deprivation therapy
AE	adverse event
CI	confidence interval
FDA	Food and Drug Administration
HR	hazard ratio
ITT	intention-to-treat population
LHRH	luteinizing hormone-releasing hormone
OL	open label
PSA	prostate-specific antigen
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
WDAE	withdrawal due to adverse event
WHO	World Health Organization

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 non-metastatic prostate cancer who are starting long-term ADT.
Health Canada Approval Status	Not approved
NOC date	N/A
Requester	Provincial Advisory Group

ADT = androgen deprivation therapy; N/A = not applicable

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 five-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 after failure of ADT, as well as an indication for the treatment of patients with newly diagnosed hormone-sensitive high-risk metastatic prostate cancer, 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 in order to reduce the adverse events 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 non-metastatic prostate cancer, 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 non-metastatic prostate cancer (nmPC).

The clinical and pharmacoeconomic evidence for the review were provided through the CADTH Non-sponsored Reimbursement Review process. The review includes an appraisal of the clinical evidence and a comparison between the treatment costs associated with abiraterone and prednisolone ± 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 clinical expert(s) 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, Canadian Cancer Society, submitted patient input for this review. Canadian Cancer society is a national non-profit 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 – August 2, 2022. 11 patients responded to the survey. Two of the survey respondents who had direct experience with abiraterone acetate also participated in an interview.

Respondents indicated nmPC impacts various aspects of their lives, ranging from 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 treatment were also reported.

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

Patients who had experience with abiraterone and prednisone credited their treatment for controlling their cancer and PSA levels; appreciated the ability to take abiraterone at home and do 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 (that is, permanent suppression of PSA), or long-term suppression of PSA or prevention of metastatic disease and maximizing quality of life. The most common treatment approaches for high-risk nmPC include external beam radiation with androgen deprivation, radical prostatectomy, and androgen deprivation therapy. 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 quality life.

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 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 quality of life (QoL) metrics. Although the study protocol provided treatment of two 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 / hormone "naïve" patients varies depending on the classification system or guidelines used such as the AUA / D'Amico classification, RTOG and National Comprehensive Cancer Network (NCCN) guidelines. They noted that the STAMPEDE trial's definition for 'high-risk' was different from the above-mentioned classification systems or 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

endpoints of the STAMPEDE trial. The most likely reason for treatment discontinuation were development of castration resistance (that is, disease progression) which 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 (CCO) Genitourinary Cancer Drug Advisory Committee (the OH-CCO). OH-CCO's Drug Advisory Committees (DAC) 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 (PDRP) 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 to retreatment, appropriate time to initiate therapy, treatment algorithm, as well as raised concerns with additional resource requirements.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

One published OL RCT was included in the systematic review: STAMPEDE (n = 1,974)[6] was a multiarm multistage platform RCT comparing various treatment options to standard of care in patients starting long-term ADT for high-risk non-metastatic prostate cancer. Among the treatment comparisons assessed in the trial, two were included in this review: the first evaluated the impact of adding the combination of abiraterone and prednisone to ADT and standard of care 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, ± 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; standard of care 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; or a node negative cancer with ≥ 2 risks 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 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 hazard ratios (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-, relapse-, and progression-free survival benefits in patients starting long-term ADT for high-risk non-metastatic prostate cancer. 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 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 hazard ratios 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 (i.e., restricted mean survival time) would be used in the case of non-proportional hazards; but presumably based on the Schoenfeld test results that indicated no evidence of non-proportional 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%] vs. 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 STAMPEDE as a high-risk population. In Canada, these patients would not be considered within the high-risk non-metastatic 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 STAMPEDE 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 two risk factors to meet the trial's high-risk definition; in Canada, the high-risk definition would include only one of the following risk factors: tumour stage T3 or T4; Gleason sum score 8 – 10; or PSA ≥ 40 ng/ml. Therefore, in terms of Canadian risk definition, patients from STAMPEDE 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.

STAMPEDE 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 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 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 with the addition of enzalutamide. The observed types of AEs were consistent with what is expected with these three 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.

Table 2: Summary of Key Results from STAMPEDE – Treatment Comparisons Presented Separately (Preplanned Subgroup Analysis)

Outcome	Abiraterone and prednisolone/prednisone comparison		Abiraterone, prednisolone/prednisone and enzalutamide comparison	
	Abiraterone / pred n = 459 (efficacy) n = 451 (safety)	Control n = 455	Abiraterone / pred 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 – 0.82)		0.54 (0.39 – 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 – 0.75)		0.44 (0.28 – 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 – 0.68)		0.53 (0.39 – 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 – 0.56)		0.45 (0.32 – 0.63)	
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)

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

Definitions:
- 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

STAMPEDE 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 details regarding standard-of-care received during 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 adverse events.

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 ± 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 and 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 STAMPEDE 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 non-metastatic prostate cancer. 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 non-metastatic prostate cancer 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 compared with ADT alone. Abiraterone with prednisone and enzalutamide is $6,186 more costly per 28-day cycle compared with ADT alone. As both regimens would be used as add-on therapy to ADTs, the reimbursement of abiraterone with prednisone for high-risk non-metastatic prostate cancer 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 healthcare 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, a 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 men died from the disease in 2021.[2] Common risk factors for prostate cancer include age > 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] Prostate-specific antigen (PSA) testing and digital rectal exam are routine tests for early prostate cancer detection.[9] A PSA elevation > 0.75 ng/mL/year or above the range for 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 prostate cancer patients are diagnosed with localized disease, for which the five-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 one, 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 will help to determine how quickly the cancer is likely to grow and spread. The second one is the TNM staging system; it is commonly used to classify disease extent. Staging can be clinical, if based on results of 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	Tumor 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

Other terms are also used to describe the growth and spread of cancer, such as 'localized' (limited to only in 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 attempt to eliminate the cancer completely.[14]

According to the clinical experts consulted for this review, treatment of non-metastatic prostate cancer 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	0-10 ng/mL	10-20 ng/mL	> 20 ng/mL
Gleason Score	≤ 6	7	8 to 10
Clinical T Stage	cT1 to T2a	cT2b	≥ cT2c

PSA = prostate-specific antigen

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, 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 includes active surveillance, radiation therapy with or without androgen deprivation therapy (ADT), radical prostatectomy, or high-intensity focused ultrasound (HIFU).

Approaches for high-risk non-metastatic 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 prostate cancer.[15]

The clinical experts indicated that the current goal of treatment for non-metastatic prostate cancer is cure; treatments aim to provide permanent or long-term suppression of PSA, prevent metastatic disease and maximize quality of life. 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 non-metastatic prostate cancer should include those that extend survival in addition to maintaining or improving health-related quality life.

Drug

Abiraterone and enzalutamide are anti-androgen 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 (Table 5).

The Provincial Advisory Group (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 non-metastatic prostate cancer, 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 non-metastatic prostate cancer and provide a reimbursement recommendation.

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

	Abiraterone	Enzalutamide	LHRH Agonists (for ADT) (Example: goserelin)	LHRH Antagonists (for ADT) (Example: degarelix)
Mechanism of action	An androgen biosynthesis inhibitor that selectively inhibits the enzyme CYP17, required for androgen biosynthesis in testicular, adrenal, and prostatic tumor tissues.	An androgen receptor inhibitor that inhibits translocation of androgen receptors and interaction of androgen receptors with DNA.	A synthetic analog 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-naïve 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 non-steroidal 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-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 depot at 28 day intervals (2 depots preceding and 2 during radiotherapy until completion of the radiation therapy.	Starting Dose: 240 mg given as two doses every 28 days of 120 mg at a concentration of 40 mg/mL Maintenance Dose[g]: 80 mg as one dose at a concentration of 20 mg/mL, monthly.

	Abiraterone	Enzalutamide	LHRH Agonists (for ADT) (Example: goserelin)	LHRH Antagonists (for ADT) (Example: degarelix)
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 and injection site injuries and vascular injuries.	Risk of QT prolongation and osteoporosis.

ADT = Androgen deprivation therapy; AUA = American Urologic Association; CYP17 = 17α-hydroxylase /C17,20-lyase; FSH = follicle stimulating hormone; GnRH = Gonadotropin-releasing hormone; LH = luteinizing hormone; LHRH = luteinizing hormone-releasing hormone; mCSPC = metastatic castration-sensitive prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; nmCRPC = non-metastatic castration-resistant prostate cancer; NoC = notice of compliance; TNM = Tumour Node-Metastasis

[a]Health Canada–approved indication. Abiaterone is has not received a Health Canada NoC for non-metastatic prostrate cancer.

[b] Not studied in patients with NM-CRPC 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 prior to 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 two hours before the dose and for at least one hour after the dose.

[g] The first maintenance dose should be given one 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, Canadian Cancer Society, submitted input for this review. Input was based on perspectives gathered through survey and interview responses between July 19, 2022 – August 2, 2022. The survey and interview opportunity with patients and their caregivers was shared through Cancer Connection forums, social media, through various support groups and prostate cancer treating clinicians who agreed to share it with their patients. 11 patients responded to the survey (10 patients with high-risk non-metastatic prostate cancer (nmPC) and one 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 (one patient with nmPC, and one 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, concentrate, 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 healthcare team, lack of familiarity with navigating the healthcare 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 three or more lines of therapy including external beam radiation, surgery, LHRH agonists, corticosteroid and/or an anti-androgen drug. With regards to current treatment related side effects, respondents reported the following had significant negative impacts: changes in libido and sexual function, fatigue, hot flushes, appetite changes, anemia, loss of muscle mass, weight changes, body hair loss, and rash or skin irritation. Patients would like to see improvements in future prostate cancer treatments to reduce side effect profiles (e.g. sexual functioning and of hot flashes), improve take-home cancer drug affordability, achieve more holistic care, better communication among healthcare workers and patients, and better access to imaging.

Both interview respondents credited their treatment - which included abiraterone acetate – for controlling their cancer and PSA levels. The patients appreciate the ability to take abiraterone at home and 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 to be tolerable and they identified that they would recommend abiraterone acetate to others. However, there were concerns about their ability to access abiraterone acetate in the future and advocated for government funding.

Clinician Input

Input from clinical experts consulted by CADTH

All CADTH review teams include at least one 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 three clinical specialists with expertise in the diagnosis and management of prostate cancer.

Unmet Needs

The clinical experts reported that the treatment goals for nmPC is cure (that is, permanent suppression of PSA), or long-term suppression of PSA or prevention of metastatic disease and maximizing quality of life. It was noted that treatment in healthy men 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 includes external beam radiation with androgen deprivation, radical prostatectomy, and androgen deprivation therapy alone (for men not eligible or not amenable to radiation and/or surgery). Therapies for curative intent are usually performed in men 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 in this patient population considered at high risk of distant failure.

Patient population

Based on the STAMPEDE data, clinical experts noted that patients that fit the eligibility criteria for high-risk disease would be eligible for abiraterone 1000mg daily plus prednisone 5mg 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: node positive or if node negative were high risk (based on two of the following: tumor stage T3 or T4, Gleason sum score of 8–10, 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 two 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 non-metastatic prostate cancer, which varies depending on the classification system or guidelines used such as the AUA / D'Amico classification, RTOG and National Comprehensive Cancer Network (NCCN) guidelines. They noted that the STAMPEDE trial's definition for 'high-risk' was different from the above-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 if patients in which conflict occurs in different imaging (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 endpoints of the STAMPEDE trial. Further, all these endpoints, 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 LFTs, hypertension, and hypokalemia. Therefore, regular physical exams are required including blood pressure monitoring and blood work every two weeks in the first few months then every three months thereafter to include electrolytes and LFTs.

Discontinuing treatment

The most likely reason for treatment discontinuation were development of castration resistance (that is, disease progression) which 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 expertise in the management of men with prostate cancer and with 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/GnRH agonist or antagonists based on their safety or efficacy and access/funding status. Further, they noted that androgen receptor-axis inhibitors (apalutamide, darolutamide, and enzalutamide) are used in high-risk non-metastatic castration resistant prostate cancer, but there is lack of evidence of clinical benefit in non-metastatic castration sensitive prostate cancer.

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 Ontario Health (CCO) Genitourinary Cancer Drug Advisory Committee (the OH-CCO). Four clinicians from OH-CCO provided input for the review.

Unmet Needs

The clinician group noted that the key treatment goals for men with high-risk non-metastatic prostate cancer (nmPC) is 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 androgen deprivation therapy (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 men with high-risk nmPC.

Patient population

The clinician group noted that the drug regimen would benefit men with high-risk non metastatic prostate cancer who are clinically suitable for abiraterone/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 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 5.

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 (eg, severe angina, recent myocardial infarction, or a history of cardiac failure) were excluded in 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 adverse events from abiraterone and prednisone. Availability of generic version of abiraterone and prednisone was also highlighted. Drug plans also noted that oral anti-cancer drugs are not fully reimbursed in all Canadian jurisdictions.

Table 5: 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 clinical trial consistent with how high risk non-metastatic prostate cancer is defined in clinical setting?	No. The definition of 'high risk nmPC' in STAMPEDE is different than that used in Canadian clinical setting. Patient population (high-risk) in STAMPEDE trial would be considered more advanced than that of traditional definition in Canadian setting. The traditional definition of high-risk includes one of the following (as opposed to two 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 clinical setting. N1 but non-metastatic patients are rather considered to be in the grey area. Advise 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 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 last dose of abiraterone and the re-start of abiraterone?	The clinical experts noted that general principles would state that as long as the patient has relapsed more than 6-12 months from the completion of abiraterone, there would be rationale for retreatment 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 nest line of therapy.

ADT = androgen deprivation therapy; ARPi = androgen receptor pathway inhibition; nmPC = non-metastatic 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., one of the manufacturers of abiraterone acetate in Canada. Input was provided on the research protocol. Their input noted the need to further define the population, "high-risk non-metastatic prostate cancer" as the term 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 STAMPEDE patients per the National Comprehensive Cancer Network (NCCN) guideline definition,[15] and this term is

also used by 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 Canadian population. With regards to the indication, it was highlighted that the proposed indication is 'off label' and hence the need for the reimbursement recommendation to be clearly supported by evidence. Second, the broad nature of the term "high-risk non-metastatic prostate cancer" and is not entirely reflective of the entire STAMPEDE study. Rather, most of the patient population in the STAMPEDE study align with the NCCN prostate cancer guideline's definition of "very high-risk" disease.[15] It was also highlighted that STAMPEDE protocol publication has 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] Third, 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 guidelines recommend the use of abiraterone acetate plus prednisolone with ADT and external beam radiation therapy 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. Fourth, 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 non-metastatic patients relapsing after previous local therapy given this group is under-represented in the STAMPEDE study.[6] Finally, it was suggested it would be important to consider ongoing studies in the prostate cancer therapeutic area when assessing the broadness of the indication given 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 regards 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 nor 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 adverse event outcome reporting. Such limitations, especially the less than robust adverse event 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 United Kingdom 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 only 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 non-metastatic castration-resistant prostate cancer, metastatic castration-sensitive prostate cancer and even metastatic castration-resistant prostate cancer (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 a CADTH's clinical assessment of a recent mCRPC treatment made a following remark; "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 in 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 three 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

To perform a systematic review of the beneficial and harmful effects of abiraterone acetate and prednisone (or prednisolone) oral tablets ± enzalutamide for high-risk non-metastatic prostate cancer (nmPC).

Methods

Studies selected for inclusion in the systematic review include those meeting the selection criteria presented in Table 6. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 6: Inclusion criteria for the systematic review

Patient Population	Newly diagnosed patients with high risk nmPC who are starting long-term androgen deprivation therapy (ADT) for the first time
Intervention	ADT, abiraterone acetate (1000mg/daily) with prednisone (or prednisolone) tablets (5mg/daily) ± enzalutamide (160mg/daily)
Comparators	ADT with or without radiation • luteinizing hormone-releasing hormone (LHRH)/gonadotropin-releasing hormone (GnRH) antagonist • LHRH/GnRH agonists

Outcomes	Overall survival (OS)
	Prostate cancer specific survival
	Metastasis-free survival
	Relapse free survival
	Progression free survival (PFS)
	    • Disease progression after ADT (castration resistant, PSA levels)
	    • Development of metastases
	Health-related quality of life
	Harms
	    • Adverse events, serious adverse events, withdrawal due to adverse events, death
	    • Potential abiraterone-related harms (i.e. fatigue, hypertension, hypokalemia, cardio-renal)
	    • Corticosteroid-related adverse events

Study Design	Published and unpublished Phase III and IV RCTs

ADT = androgen deprivation therapy; AE = adverse events; DOR = duration of response; nmPC = non metastatic prostate cancer; OS = overall survival; ORR = overall response rate; PFS = progression free survival; PSA = prostate-specific antigen; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

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 was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were abiraterone acetate and prednisolone. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization'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, 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. See 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, 2024.

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 Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials. See 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 one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

A focused literature search for indirect treatment comparisons (ITCs) dealing with high-risk non-metastatic prostate cancer 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 7. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

Alt text: 328 citations were identified, 326 were excluded, while no electronic literature and no grey literature potentially relevant full text reports were retrieved for scrutiny. In total 2 reports are included in the review.

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│ Potentially relevant    │   │ Potentially relevant      │
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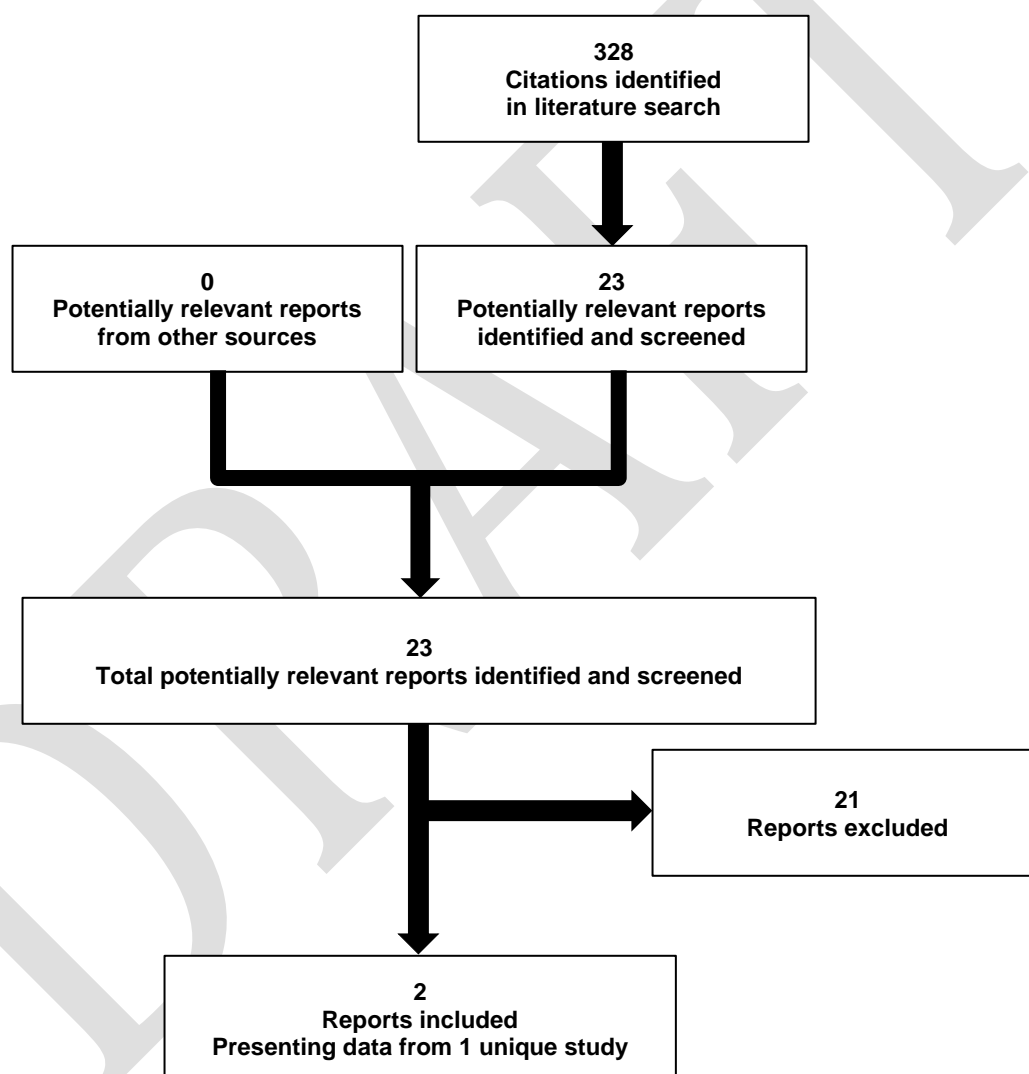
Table 7: Details of Included Study

Detail	STAMPEDE	
	Abiraterone and prednisolone/prednisone comparison (arm G vs control)	**Abiraterone, prednisolone/prednisone and enzalutamide comparison (arm J vs control)**
Designs & Populations		
Study Design	Open-label multi-arm multi-stage platform RCT in patients starting long-term hormone therapy for metastatic or high-risk non-metastatic prostate cancer	
Locations	Multi-center: 113 sites in the United Kingdom and Switzerland	
Patient enrolment dates	First patient assigned: Nov 15, 2011 Last patient assigned: Jan 17, 2014	First patient assigned: July 29, 2014 Last patient assigned: March 31, 2016
Randomized (N)	N = 914	N = 1060

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 – 2
	• no evidence of distant metastases in conventional imaging
	• a high-risk cancer presentation, defined as one of the following:
	  o node positive; or
	  o 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 – 10
	    ▪ PSA ≥ 40 ng/ml; or
	  o 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)	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)

Detail	STAMPEDE	
	Abiraterone and prednisolone/prednisone comparison (arm G vs control)	**Abiraterone, prednisolone/prednisone and enzalutamide comparison (arm J vs control)**
	+ *standard of care*	+ *standard of care*
Comparator(s)	Open-label 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 non-metastatic 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) • Failure-free survival (time from randomization to biochemical failure, local progression, distant metastases or death from prostate cancer) • Toxicity and adverse events	
Notes		
Publications	• Attard et al. 2022[6] • James et al. 2017[24]	

ADT = androgen-deprivation therapy; AEs = adverse events; LHRH = luteinizing hormone-releasing hormone; PSA = prostate-specific antigen; RCT = randomized controlled trial; SAEs = serious adverse events; WHO = World Health Organization.

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

Description of study

One published open-label (OL) randomized controlled trial (RCT) was included in the systematic review: the Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) trial (n = 1,974).[6] The STAMPEDE platform used a multiarm multistage protocol and non-overlapping control groups to compare various treatment options (only intervention arms G and J are relevant for this review) for patients with non-metastatic and metastatic prostate cancer. 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 non-metastatic 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] vs NX [intermediate] vs N+ [positive])

- Age at randomization (<70 years vs ≥ 70yrs)

- WHO performance status (0 vs 1 to 2)

- Method of ADT (orchidectomy vs LHRH agonist vs LHRH antagonist vs dual androgen blockade)

- Regular aspirin or NSAID use at baseline (yes vs no)

- Radiotherapy planned (yes vs 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 two risks 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 8 and were balanced between treatment groups. Patients enrolled in the trial had a median age of 68 years overall. Median PSA values ranged between 32 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 – 10 and 92% had a T stage of 3 – 4. Almost all patients opted for an LHRH agonist or antagonist as ADT treatment option, while a total of 85 of patients had local radiotherapy.

Table 8: Summary of Baseline Characteristics

Characteristic	Abiraterone and prednisolone/prednisone comparison		Abiraterone, prednisolone/prednisone and enzalutamide comparison	
	Abiraterone / pred N = 459	Control N = 455	Abiraterone / pred and enzalutamide N = 527	Control N = 533
Age, years				
Median (IQR)	68 (63 – 73)	67 (62 – 73)	68 (63 – 73)	69 (64 – 73)
Range	44 – 84	48 – 83	46 – 86	43 – 86
PSA, ng/ml				
Median (IQR)	34 (15 – 68)	40 (16 – 83)	32 (13 – 74)	34 (15 – 74)
Range	1 – 2 300	1 – 1 000	0 – 556	1 – 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)
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 – 2	89 (19)	80 (17)	98 (19)	98 (18)
Gleason sum score, n (%)				
< 8	107 (23)	105 (23)	98 (19)	95 (18)
8 – 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)

Interventions

There were two relevant STAMPEDE treatment comparisons: one evaluated the efficacy and safety of adding the combination of abiraterone and prednisone to ADT and standard of care in patients starting long-term hormone therapy for high-risk non-metastatic prostate cancer. 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 these treatment intensification strategies were compared to non-overlapping OL control groups who received ADT and standard of care.

The intervention evaluated consisted of a combination therapy with abiraterone 1,000 mg and prednisone or prednisolone 5 mg, ± 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 standard of care 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 non-metastatic 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 endpoints identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 9. These endpoints are further summarized below.

Table 9: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome Measure	Analysis in STAMPEDE
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 endpoint for overall survival by several regulatory agencies,[25-28] especially at an early and localized stage of the disease. Progression to metastatic prostate cancer is also considered a meaningful outcome by patients, as it is associated with a decreased wellbeing for patients living with the condition.

Other outcomes assessed as a secondary endpoint 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 thought the outcome of adverse events.

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 endpoint was overall survival; however, it was changed to metastasis-free survival in patients with non-metastatic disease during the study conduct. This was one 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 non-metastatic 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 non-metastatic 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 non-metastatic disease;
- extend follow-up to reach a sufficient number of events in the non-metastatic population.

For time-to-event outcomes, analyses between groups were preformed 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 χ^2 test and results were expressed using a hazard ratio (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 preformed 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 intention-to-treat analyses.

The preplanned pooling of the primary efficacy results of both treatment groups were 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 I² value); it was not reported whether heterogeneity beyond statistical sources were assessed.

Analysis populations

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 adverse events and comprised all patients who were included in the study and received at least one 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 adverse events, followed by patient decision. Details regarding patient disposition are provided in Table 10.

Table 10: Patient Disposition

Patient disposition	Abiraterone and prednisolone/prednisone comparison		Abiraterone, prednisolone/prednisone and enzalutamide comparison		
	Abiraterone / pred	Control arm	Active treatment arm		Control arm
			Abiraterone / pred	Enzalutamide	
Randomized	**459**	**455**	**527**		**533**
Treatment never started	8	n/a	15	14	n/a
Completed treatment	**266**	**n/a**	**258**	**235**	**n/a**
Treatment still ongoing	18	n/a	25	20	n/a
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)	n/a	229 (43.5)	258 (49.0)	n/a
Reason for stopping treatment, n (%)					
Adverse events	60 (35.9)		134 (58.5)	161 (62.4)	
Disease progression	18 (10.8)		10 (4.4)	8 (3.1)	
Patient decision	19 (11.4)	n/a	36 (15.7)	38 (14.7)	n/a
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)	

Patient disposition	Abiraterone and prednisolone/prednisone comparison		Abiraterone, prednisolone/prednisone and enzalutamide comparison		
	Abiraterone / pred	Control arm	Active treatment arm		Control arm
			Abiraterone / pred	Enzalutamide	
ITT, N	459	455	527		533
PP, N	nr	nr	nr		nr
Safety, N	451	455	513		533

ITT = intention to treat; n/a = non-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 11 (individual treatment comparisons) and Table 12 (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 a hazard ratio (HR) of 0.63 (95% CI 0.48 – 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 – 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 two 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 – 0.73; p < 0.0001) in favour of the combination of abiraterone and prednisone ± enzalutamide versus control. In the Kaplain-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 a HR of 0.52 (95% CI 0.36 – 0.75) in favour of active treatment versus control. When assigned in combination with enzalutamide, the HR was 0.44 (95% CI 0.28 – 0.71) in favour of combination treatment versus control.

When patients from the two 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 – 0.65; p < 0.0001) in favour of the combination of abiraterone and prednisone ± 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 a HR of 0.54 (95% CI 0.43 – 0.68) in favour of active treatment versus control. When assigned in combination with enzalutamide, the HR was 0.53 (95% CI 0.39 – 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 two 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 – 0.64; p < 0.0001) in favour of the combination of abiraterone and prednisone ± enzalutamide versus control. In the Kapaln-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 a HR of 0.39 (95% CI 0.31 – 0.49) in favour of active treatment versus control. When assigned in combination with enzalutamide, the HR was 0.40 (95% CI 0.31 – 0.53) in favour of combination treatment versus control.

When patients from the two 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 – not estimable). The HR was 0.39 (95% CI 0.33 – 0.47; p < 0.0001) in favour of the combination of abiraterone and prednisone ± 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 a HR of 0.43 (95% CI 0.33 – 0.56) in favour of active treatment versus control. When assigned in combination with enzalutamide, the HR was 0.45 (95% CI 0.32 – 0.63) in favour of combination treatment versus control.

When patients from the two 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 – 0.54; p < 0.0001) in favour of the combination of abiraterone and prednisone ± 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 11: Summary of Efficacy Outcomes in the STAMPEDE trial – Treatment Comparisons Presented Separately (Preplanned Analysis)

Outcome[a]	Abiraterone and prednisolone/prednisone comparison		Abiraterone, prednisolone/prednisone and enzalutamide comparison	
	Abiraterone / pred	Control	Abiraterone / pred 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 – 0.82); p=0.0005		0.54 (0.39 – 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 – 0.75); p nr		0.44 (0.28 – 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 – 0.68); p<0.0001		0.53 (0.39 – 0.71); p<0.0001	
Progression-Free Survival				

Outcome[a]	Abiraterone and prednisolone/prednisone comparison		Abiraterone, prednisolone/prednisone and enzalutamide comparison	
	Abiraterone / pred	Control	Abiraterone / pred and enzalutamide	Control
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 – 0.56); p nr		0.45 (0.32 – 0.63); p nr	

CI = confidence interval; HR = hazard ratio; nr = not reported.
Definitions:
- 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 ≥ 70yrs), 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 12: Summary of Efficacy Outcomes in the STAMPEDE trial (Preplanned Meta-Analysis as Primary Outcome Reporting)

Outcome[a]	Abiraterone and prednisolone / 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 – not estimable)
HR (95% CI); p-value[b]	0.60 (0.48 – 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 – 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	Median not reached

Outcome[a]	Abiraterone and prednisolone / prednisone ± enzalutamide treatment arms	Control arms
	(IQR not estimable)	(IQR 97 – not estimable)
HR (95% CI); p-value[b]	0.53 (0.44 – 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 – not estimable)
HR (95% CI); p-value[b]	0.44 (0.36 – 0.54); p<0.0001	

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

Definitions:

- 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 ≥ 70yrs), 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. See Table 13Table 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 AE of Grade 3 or worse 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, ALT and AST increase, fatigue and hot flashes (additional details in Table 13). Grade 5 AEs were not reported in patients in the control groups, but three patients in the abiraterone and prednisone group and four patients in the abiraterone, prednisone, enzalutamide group experienced a Grade 5 AE, including two deaths (see Mortality).

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, enzalutamide group died, labelled 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 13: Summary of Key Harms Outcomes in the STAMPEDE trial – Treatment Comparisons Presented Separately (Safety Population)

Outcome	Abiraterone and prednisolone/prednisone comparison		Abiraterone, prednisolone/prednisone and enzalutamide comparison	
	Abiraterone / pred	Control	Abiraterone / pred 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)

Outcome	Abiraterone and prednisolone/prednisone comparison		Abiraterone, prednisolone/prednisone and enzalutamide comparison	
	Abiraterone / pred	Control	Abiraterone / pred and enzalutamide	Control
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)
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 ± enzalutamide to ADT and standard of care over ADT and standard of care alone (control groups) in patients newly starting ADT for prostate cancer. The trial was randomized, but was not blinded. Being an OL study, STAMPEDE 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.

STAMPEDE was conducted in the UK and Switzerland at multiple centres in each country. No detail was reported regarding local standard of care used to treat patients in all treatment groups, both during 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 one 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, etc.) were to be provided, the published article does not report these details. Patient randomization in STAMPEDE

was stratified by study centre, which may help 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 MAR and 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 STAMPEDE 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 was 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 was 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 multicenter trial such as STAMPEDE 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, that is, 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 non-steroidal anti-inflammatory drugs 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 non-proportional 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. 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 two 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 and 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 details regarding co-interventions and local standard of care 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 non-sponsored 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 of only a cost comparison for abiraterone with prednisone +/- enzalutamide as add-on to standard of care (androgen deprivation therapy [ADT]) compared with ADT alone for the treatment of patients with high-risk non-metastatic prostate cancer.

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 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 non-metastatic prostate cancer, dosing was based on the STAMPEDE trial and validated by clinical experts consulted by CADTH for this review.[24] The price of abiraterone 250 mg and 500 mg tablets is $26.0313 and $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 compared with ADT alone (Table 14). Abiraterone with prednisone and enzalutamide is $6,186 more costly per 28-day cycle compared with 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 14.

Table 14: CADTH Cost Comparison Table for abiraterone acetate with prednisone +/- enzalutamide regimen under review (added on to androgen deprivation therapy)

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily cost ($)	Average 28-day drug Cost ($)	Annual costs ($)
Abiraterone acetate with prednisone +/- enzalutamide							
Abiraterone acetate	250 mg 500 mg	Tablet	26.0313 52.0625	1000 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**

LHRH = luteinising hormone-releasing hormone

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/dexamethasone with docetaxel) is undergoing a concurrent non-sponsored reimbursement review by CADTH for the treatment of metastatic castration sensitive prostate cancer in combination with androgen deprivation therapy.[33]

- The list prices for abiraterone varies across jurisdictions. Pricing in the cost table is based on 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 ± enzalutamide is used as an add-on therapy to ADT, the reimbursement of abiraterone for high-risk non-metastatic prostate cancer 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 (i.e., Nova Scotia) (see Table 18 in Appendix 3).

- Abiraterone has previously been reviewed by pERC for metastatic castration resistant prostate cancer.[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 metastatic castration resistant prostate cancer ($28.33 per 250 mg tablet) within this pCODR review[35] is higher than the current public list prices of generic abiraterone ($26.03)[30].

- As abiraterone with prednisone ± 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 adverse events from abiraterone and prednisone.

- The funding algorithm for abiraterone remains unclear. If not reimbursed in patients with high-risk non-metastatic prostate cancer, 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 OL RCT was reviewed: STAMPEDE (n = 1,974)[6] evaluated the impact of adding the combination of abiraterone and prednisone ± enzalutamide to ADT and standard of care in patients starting long-term ADT for high-risk non-metastatic prostate cancer. In the trial, a high-risk presentation was defined as a node positive cancer; or a node negative cancer with ≥ 2 risks factors (clinical tumor 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. Abiraterone 1,000 mg and prednisone or prednisolone 5 mg, ± 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 standard of care; this allowed preplanned pooling of the results. ADT was mandatory for every patient enrolled in the trial; standard of care also included radiotherapy.

Findings from STAMPEDE 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 details regarding standard-of-care received during 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 adverse events.

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-, relapse-, and progression-free survival benefits in patients starting long-term ADT for high-risk non-metastatic prostate cancer. 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 hazard ratios 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 non-proportional hazards; but presumably based on the Schoenfeld test results that indicated no evidence of non-proportional 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%] vs. 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 STAMPEDE as a high-risk population. In Canada, these patients would not be considered within the high-risk non-metastatic 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 STAMPEDE 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 two risk factors in order to meet the trial's high-risk definition; in Canada, the high-risk definition would include only one of the following risk factors: tumour stage T3 or T4; Gleason sum score 8 – 10; or PSA ≥ 40 ng/ml. Therefore, in terms of Canadian risk definition, patients from STAMPEDE 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.

STAMPEDE 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 three 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 STAMPEDE 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 non-metastatic prostate cancer. 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 non-metastatic prostate cancer 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 compared with ADT alone. Abiraterone with prednisone and enzalutamide is $6,186 more costly per 28-day cycle compared with ADT alone. As both regimens would be used as add-on therapy to ADTs, the reimbursement of abiraterone with prednisone for high-risk non-metastatic prostate cancer 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 healthcare 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

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 15: 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
.nm	Name of substance word (MEDLINE)
.jw	Journal title word (MEDLINE)

Syntax	Description
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 U.S. 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 the World Health Organization. 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 9-13, 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

Table 16: Excluded Studies

Reference	Reason for Exclusion
AL-ASAAED, S., et al. Canadian Journal of Urology 2014 21(2 Supp 1):37-41	Other design (review article, clinical practice guideline or expert opinion)
ANGULO, J., et al. Revista Colombiana de Cancerologia 2017 21(2)(95-103	Language other than English
ATTARD, G., et al. European Urology 2014 66(5):799-802	Other design (review article, clinical practice guideline or expert opinion)
CHENG, M. L., et al. Current Treatment Options in Oncology 2014 15(1)(115-126	Other design (review article, clinical practice guideline or expert opinion)
EFSTATHIOU, E., et al. European Urology 2019 76(4):418-424	Inelgible 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):467-79	Other design (review article, clinical practice guideline or expert opinion)
MANCEAU, C., et al. Expert Review of Anticancer Therapy 2020 20(8):629-638	Other design (review article, clinical practice guideline or expert opinion)
MATSUBARA, N., et al. Cancer Science 2014 105(10):1313-20	Inelgible population
MCKAY, R. R., et al. Journal of Clinical Oncology 2019 37(11):923-931	Inelgible intervention or comparator
MCKAY, R. R., et al. Journal of Urology 2021 206(1):80-87	Inelgible intervention or comparator
OHLMANN, C. H. Urologe (Ausg. A) 2017 56(11):1424-1429	Language other than English
OHLMANN, C. H., et al. Trials [Electronic Resource] 2017 18(1):457	Inelgible population
OMLIN, A., et al. Urologe (Ausg. A) 2012 51(1):8-14	Language other than English
RUSH, H. L., et al. Journal of Clinical Oncology 2022 40(8):825-836	Inelgible intervention or comparator
SPETSIERIS, N., et al. European Journal of Cancer 2021 157(259-267	Inelgible population
SYDES, M. R., et al. Annals of Oncology 2018 29(5):1235-1248	Inelgible intervention or comparator
VIRGO, K. S., et al. Journal of Clinical Oncology 2017 35(17):1952-1964	Other design (review article, clinical practice guideline or expert opinion)
VIRGO, K. S., et al. Journal of Clinical Oncology 2021 39(11):1274-1305	Other design (review article, clinical practice guideline or expert opinion)
WALLIS, C. J. D., et al. European Urology 2018 73(6):834-844	Inelgible population
WU, Y., et al. Current Opinion in Oncology 2011 23(3)(290-296	Other design (review article, clinical practice guideline or expert opinion)

Appendix 3: Cost Comparison Table of ADT Therapies

Table 17: CADTH Cost Comparison Table of androgen deprivation therapy for high-risk non-metastatic prostate cancer

Drug / 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, Pre-filled syringe	310.7200 891.0000 1,285.2000 1,645 0000	22.5 mg every 3 months[36a]	273	3,564
Leuprolide acetate (Lupron depot)	3.75 mg 7.5 mg 11.25 mg 22.5 mg 30 mg	Pre-filled syringe	389.1300 387.9700 1,159.5200 1,071.0000 1,428.0000	22.5 mg every 3 months[37a]	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[38a]	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[39b]	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 = luteinising hormone-releasing hormone

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

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

Note: 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. 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. 28-day costs were calculated by converting monthly costs to daily costs (assuming 30.42 days in a month) and multiplying by 28.

Table 18: CADTH Cost Comparison Table for abiraterone acetate with prednisone +/-enzalutamide regimen under review (added on to androgen deprivation therapy) using Nova Scotia list prices (Scenario Analysis)

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily cost ($)	Average 28-day drug Cost ($)	Annual costs ($)
Abiraterone acetate with prednisone +/- enzalutamide							
Abiraterone acetate	250 mg 500 mg	Tablet	7.6563 15.3125	1000 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**

LHRH = luteinising 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]