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CADTH Reimbursement Review

Abiraterone Acetate and Prednisone or Dexamethasone With Docetaxel

Nonsponsored Review

Therapeutic area: Metastatic castration-sensitive prostate cancer (mCSPC)

Clinical Review

Table of Contents

List of Tables

List of Figures

Abbreviations

ABI	abiraterone acetate
ADT	androgen deprivation therapy
AE	adverse event
APA	apalutamide
ARPI	androgen receptor pathway inhibitor
CI	confidence interval
CrI	credible interval
CRPC	castration-resistant prostate cancer
DAR	darolutamide
DOC	docetaxel
ECOG	Eastern Cooperative Oncology Group
ENZ	enzalutamide
G-CSF	granulocyte colony-stimulating factor
GnRH	gonadotropin-releasing hormone
HR	hazard ratio
HRQoL	health-related quality of life
ITC	indirect treatment comparison
ITT	intention to treat
mCSPC	metastatic castration-sensitive prostate cancer
mCRPC	metastatic castration-resistant prostate cancer
NMA	network meta-analysis
OR	odds ratio
OS	overall survival
PAG	Provincial Advisory Group
PEACE	Prostate Cancer Consortium in Europe
PSA	prostate-specific antigen
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	risk ratio
rPFS	radiographic progression-free survival
SOC	standard of care
WDAE	withdrawal due to adverse event

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1. This was a nonsponsored review initiated at the request of the Provincial Advisory Group (PAG).

Table 1: Submitted for Review

Item	Description
Drug products	• Abiraterone acetate (Zytiga and generics) tablets, 250 mg uncoated tablets or 500 mg film-coated tablets, oral; plus • Prednisone tablets, 1 mg, 5 mg, or 50 mg tablets, oral or dexamethasone tablets, 0.5 mg or 4 mg, oral; plus • Docetaxel (Taxotere or generics) for injection, 10 mg/mL or 20 mg/mL, for IV infusion; plus • ADT (GnRH agonists or antagonists, various products), various formulations, for SC or IM injection
Indications	Abiraterone acetate: • In combination with prednisone for the treatment of metastatic prostate cancer (castration-resistant prostate cancer, mCRPC) in patients who: ◦ are asymptomatic or mildly symptomatic after failure of ADT ◦ have received prior chemotherapy containing docetaxel after failure of ADT • In combination with prednisone and ADT for the treatment of patients with newly diagnosed hormone-sensitive high-risk metastatic prostate cancer who may have received up to 3 months of prior ADT Docetaxel: • In combination with prednisone or prednisolone is indicated for the treatment of patients with androgen-independent (hormone-refractory) metastatic prostate cancer. ADT: • Various indications for the treatment of hormone-sensitive prostate cancer
Population under consideration for reimbursement	Abiraterone acetate plus prednisone or dexamethasone plus docetaxel for the treatment of adults with mCSPC in combination with docetaxel and ADT
Health Canada approval status	NA
NOC dates	NA
Requestor	PAG

ADT = androgen deprivation therapy; GnRH = gonadotropin-releasing hormone; IM = intramuscular; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; NA = not applicable; NOC = notice of compliance; PAG = Provincial Advisory Group; SC = subcutaneous.

Note: This was a nonsponsored submission and thus the drug product has not been approved by Health Canada for this indication.

Source: Product monographs for abiraterone acetate (Zytiga)[1] and docetaxel (Taxotere).[2]

Introduction

Prostate cancer is the most common cancer (excluding non-melanoma skin cancers) and the third leading cause of cancer death among males in Canada.[3] In its early stages, the disease is generally asymptomatic, but as the tumour grows, symptoms may include urination problems, erectile dysfunction, bleeding, pain, and fatigue.[4] Both the disease and its treatment can negatively impact health-related quality of life (HRQoL).[5] At

diagnosis, disease is localized to the prostate in most patients (approximately 90%);[6] however, some patients (approximately 5% to 10%) are diagnosed with locally advanced or de novo metastatic disease,[7] and the disease will progress over a period of many years in a subset of patients initially diagnosed with localized disease. Metastatic prostate cancer that requires androgens (male hormones including testosterone) to sustain growth and can be controlled by reducing androgen levels to castrate levels is called metastatic castration-sensitive prostate cancer (mCSPC),[8] while cancer that does not require androgens to sustain growth is called metastatic castration-resistant prostate cancer (mCRPC).[9]

In 2021, approximately 24,600 males were diagnosed with prostate cancer,[3] and as of 2018, the 25-year prevalence of prostate cancer was approximately 302,000 males in Canada.[10] The prevalence and incidence of mCSPC in Canada are not known with certainty; however, in 2018, approximately 1,200 males were diagnosed with de novo metastatic prostate cancer in Canada.[11] The 5-year survival of de novo metastatic prostate cancer in Canada is approximately 29%,[12] and median survival is approximately 3 years to 7 years.[13] Diagnosis of prostate cancer (including mCSPC) is made by a urologist based on clinical examination, prostate-specific antigen (PSA) testing, histological and pathological findings on prostate biopsy, and in some cases imaging (CT, MRI, and/or bone scan). Patients are subsequently followed by a urologist and medical oncologist for treatment.

According to the clinical expert consulted by CADTH, the mainstay of treatment in patients with mCSPC is androgen deprivation therapy (ADT). This is achieved either by surgery (orchiectomy) or by administration of gonadotropin-releasing hormone (GnRH) agonists or antagonists. ADT "intensification" via combination with androgen receptor pathway inhibitors (ARPIs) (androgen receptor antagonists [e.g., enzalutamide, apalutamide, darolutamide] and/or androgen synthesis inhibitors [abiraterone]) and/or chemotherapy (docetaxel) is supported by current guidelines.[14] Combinations of ADT plus either an ARPI or docetaxel are generically referred to as doublet therapies, while combinations of ADT plus an ARPI plus docetaxel are generically referred to as triplet therapies. The clinical expert relayed that docetaxel may be effective in the subset of patients whose tumours have androgen receptor–independent biology and are thus unresponsive to ARPIs, but that toxicity is a potential concern especially among patients with mCSPC. According to the clinical expert, mCSPC is incurable, and the goals of treatment are to palliate symptoms, maintain or improve HRQoL, delay progression, and prolong survival. Since most patients with mCSPC will achieve tumour shrinkage, decreased PSA levels, and symptomatic improvement with ADT alone, the goal of additional therapy is to delay progression and prolong survival without substantially increasing treatment toxicity.

Abiraterone acetate is an androgen synthesis inhibitor that is administered at a dose of 1,000 mg orally once per day with prednisone (5 mg twice per day or 10 mg once per day orally) or sometimes dexamethasone (0.5 mg to 1.5 mg per day orally).[1] Abiraterone has the following Health Canada–approved indications:

- in combination with prednisone for the treatment of metastatic cancer (castration-resistant prostate cancer, mCRPC) in patients who are symptomatic or mildly symptomatic after failure of androgen deprivation therapy, or who have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy[1]

- in combination with prednisone and androgen deprivation therapy for the treatment of patients with newly diagnosed hormone-sensitive high-risk metastatic prostate cancer who may have received up to 3 months of prior ADT.[1]

Abiraterone was previously reviewed by CADTH "for asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC) patients after failure of ADT (have not received prior chemotherapy)" and received a recommendation for reimbursement with conditions on October 22, 2013.[15] Reviews of abiraterone for other indications were initiated but either withdrawn or placed on hold. Docetaxel is a taxane antineoplastic drug that is administered at a dose of 75 mg/m^2 (maximum dose 150 mg per cycle) by IV infusion once every 3 weeks.[2] The relevant Health Canada indication for docetaxel is: "in combination with prednisone or prednisolone for the treatment of patients with androgen-independent (hormone-refractory) metastatic prostate cancer." ADT refers to a group of antihormone therapies that reduce androgen levels to castrate levels and are thus used to treat prostate cancer; options include surgery (orchiectomy) or chemical castration by systemic administration of GnRH agonists or antagonists via subcutaneous or intramuscular injection using various doses and administration schedules. ADTs have a variety of Health Canada indications for the treatment of hormone-sensitive prostate cancer.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of abiraterone (1,000 mg once per day orally) with prednisone (5 mg twice per day or 10 mg once per day orally) or dexamethasone (0.5 mg to 1.5 mg orally daily) plus docetaxel (75 mg/m^2 IV every 3 weeks; maximum dose 150 mg per cycle) for the treatment of adults with mCSPC in combination with ADT.

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 a clinical expert consulted by CADTH for the purpose of this review.

Patient Input

One patient group, the Canadian Cancer Society, provided input for this review. The Canadian Cancer Society is a national nonprofit organization committed to improving the lives of people living with cancer through research, advocacy, and compassionate support. Information was gathered through interviews of 4 individuals living with mCSPC. The interviewees described the negative impacts of their mCSPC diagnosis on mental health (e.g., anxiety, depression, lack of support), the inconvenience of treatment (e.g., long travel time, out-of-pocket expenses), and the effects of the disease and its treatment, including prostatectomy and ADT, on daily activities and HRQoL (e.g., diminished sexual function, hot flashes, reduced muscle mass, reduced capacity for physical activities, constipation, and incontinence). Three interviewees had experience with abiraterone (through a special access program) plus ADT; none had experience with the triplet therapy under review. The interviewees who received abiraterone plus ADT noted a generally good HRQoL and felt their disease was well controlled, but reported side effects including fatigue and loss of sexual function, muscle mass, bone density, body hair, and stamina. Some interviewees noted the convenience of once daily oral administration of abiraterone at home. The interviewees emphasized the need for additional treatment options that more effectively prolong survival, have less severe side effects, and are affordable.

Clinician Input

Input From a Clinical Expert Consulted by CADTH

According to a clinical specialist with expertise in the diagnosis and management of prostate cancer including mCSPC, despite improvements in survival observed with ADT intensification, treatment is not curative and a subset of patients have relatively short survival. New treatment options with acceptable toxicity profiles are needed to delay progression to mCRPC and prolong survival. The clinical expert indicated that triplet therapy with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT would be used as a first-line treatment for patients with mCSPC and that this therapy is not expected to cause a shift in the current treatment paradigm. Since this triplet therapy is more rigorous than the current standard of care (ARPI plus ADT in most patients), a patient's ability to tolerate treatment would be the most frequent practical basis for selection for treatment. The clinical expert highlighted that triplet therapy with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT may be considered for younger patients who are both well-informed and in better health, but have higher-risk disease features (e.g., critical organ involvement, high-volume disease, high-risk disease) and/or who may prefer more aggressive therapy; the patient would need to understand and accept the uncertainty of benefit and the increased adverse events (AEs) of the triplet compared with the current standard of care (ARPI plus ADT doublet). Patients who are not chemo-fit (e.g., due to comorbidities) or have contraindications to abiraterone would be least suitable for this triplet regimen. The clinical expert stated that although the Prostate Cancer Consortium in Europe (PEACE)-1 trial recruited patients with de novo metastatic mCSPC, there is no reason to expect that some patients with metachronous mCSPC could not benefit from this triplet therapy.

According to the clinical expert, treatment response in mCSPC is assessed in 3 domains: patient symptoms, PSA levels, and imaging (CT, MRI, and/or bone scan). However, all 3 domains will improve with ADT alone in more than 90% of patients with mCSPC, so these tools are not helpful in assessing the response specifically attributable to intensified treatment (doublet or triplet therapy). The clinical expert emphasized that abiraterone and docetaxel may contribute to additional AEs that require treatment modification, so patients should be carefully monitored. Treatment with this triplet therapy would be discontinued in the presence of unequivocal disease progression, or there are severe or persistent intolerable AEs that do not respond to dose modifications, or if long treatment breaks occur, or by patient preference. The triplet would be prescribed by a medical oncologist in an outpatient setting.

Clinician Group Input

No input from clinician groups was received for this review.

Industry Input

One industry stakeholder, Janssen Inc. (a manufacturer of abiraterone acetate in Canada), provided input for this review. According to Janssen, the target population of patients with mCSPC eligible for reimbursement of triplet therapy with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT should be evidence-based and reflect the PEACE-1 study eligibility criteria and main results. Specifically, based on the trial eligibility criteria (de novo mCSPC, chemo-fit), the fact that more than 90% of patients had either bone and/or visceral metastases, and the fact that point estimates of survival benefit were highest among

patients with high-volume disease, Janssen suggested that reimbursement should be limited to chemo-fit patients with high-volume mCSPC with bone and/or visceral metastases. The industry input noted that ADT with or without docetaxel is not the current standard of care for most patients with mCSPC according to treatment guidelines; Canadian Urological Association guidelines[11] recommend use of docetaxel in selected patients with good performance status and high-volume or high-risk disease. Janssen noted that several currently available treatment options for patients with mCSPC provide significant and clinically meaningful improvement in survival, suggesting that medical needs in this population are being met.

Janssen emphasized that the PEACE-1 study was not designed to assess the efficacy of addition of docetaxel to abiraterone plus ADT; rather, the study was intended to evaluate the efficacy of abiraterone to ADT compared to ADT alone (both with or without radiotherapy). The standard of care for mCSPC changed over the course of the PEACE-1 trial: docetaxel was initially forbidden, then optional, then mandatory in combination with ADT. Therefore, the contribution of docetaxel to the benefit seen in patients with mCSPC is unclear and needs to be further evaluated, and the subgroup of patients who would specifically benefit from triplet therapy remains unclear. Janssen noted that the PEACE-1 study was not designed with regulatory rigour for filing, and that the triplet therapy has not yet been reviewed nor approved by Health Canada; as such, the certainty in the evidence is limited.

According to Janssen, indirect treatment comparisons (ITCs) comparing triplet therapy with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT with doublet therapies (ARPIs plus ADT) have documented uncertain survival benefits of the triplet therapy, and perhaps in defined patient subsets (refer to the Indirect Evidence section). Therefore, the additional toxicities of the triplet therapy (e.g., febrile neutropenia, gastrointestinal disorders), its additional costs (e.g., docetaxel itself, chair time at infusion clinics, management of additional AEs), and its potential impact on sequencing of later-line treatment options (both abiraterone and docetaxel are options in patients with mCRPC) must be balanced with the uncertainty in clinical benefit.

Drug Program Input

The PAG identified the following jurisdictional implementation issues that may impact their ability to implement a recommendation: relevant comparators, considerations for initiation of therapy, considerations for discontinuation of therapy, considerations for prescribing of therapy, generalizability, and funding algorithm. The clinical expert consulted by CADTH for this review weighed evidence from the included study and other clinical considerations to provide responses to drug program implementation questions.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The PEACE-1 study (N = 1,173)[16] was a multicentre, open-label, randomized, phase III study with a 2 × 2 factorial design. The primary objective of the study was to evaluate the efficacy and safety of abiraterone plus prednisone, with or without radiotherapy, in addition to standard of care (ADT with or without docetaxel) in patients with de novo mCSPC. Adult males with de novo mCSPC and Eastern Cooperative Oncology Group

(ECOG) performance status of 0 or 1 (or 2 due to bone pain) who were receiving ADT and were willing and clinically fit to receive docetaxel were randomized 1:1:1:1 to receive standard of care (ADT with or without docetaxel), standard of care plus radiotherapy, standard of care plus abiraterone, or standard of care plus radiotherapy plus abiraterone. Randomization was stratified by study site, ECOG performance status, type of ADT, planned administration of docetaxel, and disease extent or burden based on metastatic status (lymph node metastases only versus bone metastases with or without lymph node metastases versus visceral metastases). Note that randomization was stratified by metastatic sites while subgroup analyses were conducted for high versus low metastatic burden (i.e., disease volume, which was not a stratification factor). Treatment with docetaxel was for 6 cycles whereas treatment with ADT (with or without abiraterone) was until disease progression to CRPC, withdrawal of consent, unacceptable toxicity, or death. Patients must have received ADT for a maximum of 3 months before randomization, and there had to be a minimum of 6 weeks between the start of ADT and the start of docetaxel. The coprimary efficacy outcomes were overall survival (OS) and radiographic progression-free survival (rPFS, evaluated using Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1).[17]

Most participants in the PEACE-1 study (78% to 79%) were from France. The median age of participants in the docetaxel plus ADT population was 66 years (range, 44 years to 84 years). Approximately two-thirds (69% to 70%) of the participants in the docetaxel plus ADT arm had ECOG performance status of 0 or 1, approximately four-fifths (79% to 81%) had bone metastases without visceral metastases, approximately one-eighth (12% to 13%) had visceral metastases with or without bone and/or lymph node metastases, approximately two-thirds (63% to 65%) had high-volume disease, and more than three-quarters (77% to 80%) had Gleason scores of 8 to 10.

Efficacy Results

Key efficacy results of the PEACE-1 study are summarized in Table 2.

Overall Survival

In the docetaxel plus ADT population, 121 of 355 patients (34.1%) in the abiraterone plus docetaxel plus ADT arm and 151 of 355 patients (42.5%) in the docetaxel plus ADT arm died; OS was censored for the remaining patients. In the docetaxel plus ADT population, median OS was not reached in the abiraterone plus docetaxel plus ADT arm and was 4.4 years (confidence interval [CI] not reported) in the docetaxel plus ADT arm. The median OS difference was 0.9 years (95.1% CI, 0.0 years to 2.0 years) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT. The hazard ratio (HR) for OS was 0.75 (95.1% CI, 0.59 to 0.95, P = 0.017) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT.

Subgroup analyses of OS in the docetaxel plus ADT population by ECOG performance status and metastatic burden were consistent with the main analysis. Among patients with high-volume disease in the docetaxel plus ADT population, median OS was 5.1 years in the abiraterone plus docetaxel plus ADT arm and 3.5 years (CI not reported) in the docetaxel plus ADT arm. The median OS difference was 1.1 years (95.1% CI, 0.2 years to 1.9 years) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT. Among patients with low-volume disease in the docetaxel plus ADT population, median OS was not reached in either the abiraterone plus docetaxel plus ADT arm or the docetaxel plus ADT arm, and thus the median OS difference

could not be calculated. Point estimates of the HR for OS were consistent with the main analysis among the approximately one-third (35.8%) of patients with low-volume disease (HR for OS = 0.83; 95.1% CI, 0.50 to 1.39) and the approximately two-thirds (64.2%) of patients with high-volume disease (HR for OS = 0.72; 95.1% CI, 0.55 to 0.95).

Table 2: Summary of Key Efficacy Results From the PEACE-1 Study

Outcome	Abiraterone + docetaxel + ADT N = 355	Docetaxel + ADT N = 355
OS, ADT plus docetaxel population		
Median, years[a]	NR	4.4
Median difference, years (95.1% CI)[b]	NA	
HR (95.1% CI)[c]	0.75 (0.59 to 0.95)	
P value[c]	0.017	
rPFS, ADT plus docetaxel population		
Median, years[a]	4.5	2.0
Median difference, years (99.9% CI)[b]	2.2 (0.6 to 2.8)	
HR (99.9% CI)[c]	0.50 (0.34 to 0.71)	
P value[c]	< 0.0001	

ADT = androgen deprivation therapy; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NA = not applicable; NR = not reached; OS = overall survival; rPFS = radiological progression-free survival.

[a]From Kaplan-Meier analysis.

[b]Nonparametric CIs for median survival differences calculated using the bootkm function of the R Hmisc package.

[c]P value from Cox proportional hazards model adjusted for radiotherapy and randomization stratification factors (ECOG performance status, ADT type, metastatic burden, and planned administration of docetaxel). P values were adjusted for multiplicity using a sequential testing strategy.

Source: Fizazi et al. (2022).[16]

Radiographic Progression-Free Survival

In the docetaxel plus ADT population, 139 of 355 patients (39.2%) in the abiraterone plus docetaxel plus ADT arm and 211 of 355 patients (59.4%) in the docetaxel plus ADT arm had rPFS events, while rPFS was censored for the remaining patients. In the docetaxel plus ADT population, median rPFS was 4.5 years (CI not reported) in the abiraterone plus docetaxel plus ADT arm and 2.0 years (CI not reported) in the docetaxel plus ADT arm. The median rPFS difference was 2.2 years (99.9% CI, 0.6 years to 2.7 years) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT. The HR for rPFS was 0.50 (99.9% CI, 0.34 to 0.71, P < 0.0001) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT.

Subgroup analyses of rPFS in the docetaxel plus ADT population by ECOG performance status and metastatic burden were consistent with the main analysis. Among patients with high-volume disease in the docetaxel plus ADT population, median rPFS was 4.1 years (CI not reported) in the abiraterone plus docetaxel plus ADT arm and 1.6 years (CI not reported) in the docetaxel plus ADT arm. The median rPFS difference was 2.2 years (99.9% CI, 0.6 years to 3.2 years) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT. Among patients with low-volume disease in the docetaxel plus ADT population, median

rPFS was not reached in the abiraterone plus docetaxel plus ADT arm and was 2.7 years (CI not reported) in the docetaxel plus ADT arm; thus, the median rPFS difference could not be calculated. Point estimates of the HR for rPFS were closer to the null with wider CIs among the approximately one-third (35.8%) of patients with low-volume disease (HR for rPFS = 0.58; 99.9% CI, 0.29 to 1.15) compared with the approximately two-thirds (64.2%) of patients with high-volume disease (HR for rPFS = 0.47; 99.9% CI, 0.30 to 0.72).

Harms Results

Key harms results of the PEACE-1 study are summarized in Table 3. Nearly all patients experienced at least 1 AE. Information on serious AEs was not provided.

In the docetaxel plus ADT population, 32 of 347 patients (9.2%) in the abiraterone plus docetaxel plus ADT arm and 1 of 350 patients (0.3%) in the docetaxel plus ADT arm had withdrawals due to adverse events (WDAEs). In the ADT population, 29 of 226 patients (12.8%) in the abiraterone plus ADT arm and 1 of 237 patients (0.4%) in the ADT arm had WDAEs.

In the docetaxel plus ADT population, 7 of 347 patients (2.0%) in the abiraterone plus docetaxel plus ADT arm and 3 of 350 patients (0.9%) in the docetaxel plus ADT arm had fatal AEs. In the ADT population, 8 of 226 patients (3.5%) in the abiraterone plus ADT arm and 5 of 237 patients (2.1%) in the ADT arm had fatal AEs.

In the docetaxel plus ADT population, 217 of 347 patients (62.5%) in the abiraterone plus docetaxel plus ADT arm and 181 of 350 patients (51.7%) in the docetaxel plus ADT arm had severe (grade 3 or higher) AEs. In the ADT population, 149 of 226 patients (65.9%) in the abiraterone plus ADT arm and 97 of 237 patients (40.9%) in the ADT arm had severe AEs.

The most common severe toxicities associated with abiraterone were hypertension (21.9% to 29.2% of abiraterone-treated patients versus 12.9% to 16.5% of non-abiraterone-treated patients) and hepatotoxicity (5.8% to 6.2% of abiraterone-treated patients versus 0.6% to 1.3% of non-abiraterone-treated patients), while the most common severe toxicities associated with docetaxel were neutropenia (approximately 10% of docetaxel-treated patients versus no events in non-docetaxel-treated patients), febrile neutropenia (approximately 5% of docetaxel-treated patients versus less than 1% of non-docetaxel-treated patients), and peripheral neuropathy (1% to 2% of docetaxel-treated patients versus less than 1% of non-docetaxel-treated patients). Grade 1 or 2 peripheral neuropathy was more common in patients receiving docetaxel (34% to 39.2% of docetaxel-treated patients versus 21.7% to 3.1% of non-docetaxel-treated patients).

Critical Appraisal

The PEACE-1 trial was not designed or reported with regulatory rigour for filing, and the triplet regimen of abiraterone with prednisone or dexamethasone plus docetaxel plus ADT has not been reviewed by Health Canada. Therefore, the primary internal validity concern is uncertainty in the evidence due to limited ability for critical appraisal. In addition, assignment of rPFS events (based on imaging results using RECIST version 1.1)[17] was performed by investigators who were not blinded to study drug group assignment; thus, observer bias and information bias may have affected the study results. Rules and reasons for rPFS censoring were not provided and potential imbalances in these factors could not be assessed. The primary objective, interventions, and statistical analysis plan changed over the course of the study: the original

design was meant to evaluate the efficacy of abiraterone plus ADT versus ADT alone; docetaxel use was initially forbidden, then optional, then required; and the analysis populations, statistical hierarchy and split of alpha were finalized at a very late stage in the study. For the subgroup analysis by metastatic burden, randomization was stratified by metastatic sites while data were presented for high versus low metastatic burden (not the stratification factor).

Table 3: Summary of Key Harms Results From the PEACE-1 Study

Outcome	Docetaxel + ADT population		ADT population	
	Abiraterone + docetaxel + ADT N = 347	Docetaxel + ADT N = 350	Abiraterone + ADT N = 226	ADT N = 237
Harms, n (%), safety population				
Any AEs	346 (100.0)	349 (100.0)	226 (100.0)	233 (98.3)
Severe (grade ≥ 3) AEs	217 (62.5)	181 (51.7)	149 (65.9)	97 (40.9)
Fatal (grade 5) AEs	7 (2.0)	3 (0.9)	8 (3.5)	5 (2.1)
Notable harms, n (%), safety population				
Hypertension, grade ≥ 3	76 (21.9)	45 (12.9)	66 (29.2)	38 (16.5)
Neutropenia, grade ≥ 3	34 (9.7)	32 (9.1)	0	0
Hepatotoxicity, grade ≥ 3	20 (5.8)	2 (0.6)	14 (6.2)	3 (1.3)
Febrile neutropenia, grade ≥ 3	18 (5.2)	19 (5.4)	2 (0.9)	1 (0.4)
Gamma-glutamyl transferase increase, grade ≥ 3	17 (4.9)	14 (4.0)	6 (2.7)	4 (1.7)
Blood alkaline phosphatase increase, grade ≥ 3	15 (4.3)	12 (3.4)	6 (2.7)	13 (5.5)
Peripheral neuropathy, grade ≥ 3	4 (1.2)	6 (1.7)	1 (0.4)	0
Peripheral neuropathy, grade 1 or 2	136 (39.2)	119 (34.0)	7 (3.1)	4 (1.7)

ADT = androgen deprivation therapy; AE = adverse event.

Source: Fizazi et al. (2022).[16]

Most patients in the PEACE-1 trial were from France, which the clinical expert consulted by CADTH for this review did not consider to be an external validity concern; however, industry input indicated that generalizability to patients in Canada may require further investigation, without giving specific generalizability concerns. The study enrolled males with de novo mCSPC; the clinical expert considered that those who had previously received local therapy and subsequently had metastases at recurrence could benefit from treatment. Generalizability according to potentially clinically relevant subgroups of metastatic sites (bone and/or visceral metastasis), high-volume disease, and high-risk disease could not be evaluated based on the available data. The requirement for docetaxel use via protocol amendment may have resulted in recruitment of some patients who, while fit to receive docetaxel, would not be expected to benefit from treatment according to current guidelines (e.g., low-volume and/or low-risk disease). The clinical expert did not consider the only comparator in the PEACE-1 trial (docetaxel plus ADT) as reflecting the current standard

of care for most patients with mCSPC (this would be doublet therapy with an ARPI plus ADT). Triplet therapies with other ARPIs (apalutamide, enzalutamide, darolutamide) plus docetaxel plus ADT are under study, with the darolutamide triplet recently conditionally recommended for funding in Canada. The clinical expert agreed with industry input for this review that the PEACE-1 study did not evaluate the contribution of docetaxel to the efficacy of the triplet therapy (versus abiraterone plus ADT doublet therapy).

Indirect Evidence

Indirect evidence was considered given the lack of trials directly comparing abiraterone plus docetaxel plus ADT to relevant comparators in patients with mCSPC (aside from docetaxel plus ADT).

Description of Network Meta-Analyses and Their Included Studies

A total of 6 ITCs, published in 2022 and 2023, were included.[18-23] The network meta-analyses (NMAs) overlapped substantially in their included randomized controlled trials (RCTs). The included trials were reported to be at low risk of bias for objective outcomes, whereas there was some concern for bias in subjective outcomes (e.g., progression-free survival [PFS], AEs) because several of the RCTs were open-label. In general, the networks formed by the RCTs in each NMA were sparse, with individual comparisons informed by 1 or 2 RCTs. Most evidence was indirect and the RCTs were most commonly connected by docetaxel plus ADT and/or ADT alone, as these were the most frequently occurring comparators. Some methodological and clinical heterogeneity was apparent, particularly in disease volume, metastatic presentation, outcome definitions, and length of follow-up when this was reported.

Efficacy Results

Overall Survival

All 6 NMAs reported on the effect of abiraterone plus docetaxel plus ADT versus 1 or more comparators of interest on OS.[18-23] Across 5 NMAs,[18,19,21-23] abiraterone plus docetaxel plus ADT was consistently superior to docetaxel plus ADT (point estimates for the HR ranged from 0.70 to 0.75), although in most cases the CIs or credible intervals (CrIs) also included the potential of little-to-no difference between the treatments. Results for the comparisons of abiraterone plus docetaxel plus ADT triplet to ARPI doublets (abiraterone plus ADT [3 NMAs[18,21,23]], apalutamide plus ADT [2 NMAs[18,21]], enzalutamide plus ADT [2 NMAs[18,21]], ARPIs as a group plus ADT [1 NMA[20]]) and to darolutamide plus docetaxel plus ADT (3 NMAs[18,19,21]) were affected by imprecision with CIs or CrIs that included the null, such that either group could be favoured.

Progression-Free Survival

Four NMAs[19,21-23] reported on the effect of abiraterone plus docetaxel plus ADT versus 1 or more comparators of interest on PFS. Across 4 NMAs,[19,21-23] abiraterone plus docetaxel plus ADT was consistently superior to docetaxel plus ADT (HR from 0.43 to 0.50). Across 2 NMAs,[21,23] abiraterone plus docetaxel plus ADT was superior to abiraterone plus ADT (HR from 0.61 to 0.70). For the comparisons with abiraterone plus ADT, in both cases the CIs or CrIs also included the potential of little-to-no difference between the treatments. Results for the comparisons to apalutamide plus ADT (1 NMA[21]) and enzalutamide plus ADT (1 NMA[21]) were affected by imprecision with CIs or CrIs that included the null, such that either group could be favoured. No NMAs compared abiraterone plus docetaxel plus ADT to darolutamide plus docetaxel plus ADT.

Harms Results

Any AEs

One NMA[19] reported on overall frequency of AEs, and the only comparison of interest was to docetaxel plus ADT. Findings of the analysis favoured docetaxel plus ADT (odds ratio [OR] = 1.91; 95% CrI, 1.27 to 2.86).

Grade 3 or Higher AEs

Three NMAs[18,19,21] reported on the effect of abiraterone plus docetaxel plus ADT versus 1 or more comparators of interest on grade 3 or higher AEs. Docetaxel plus ADT was favoured over abiraterone plus docetaxel plus ADT across the 3 NMAs (OR or risk ratio [RR] range, 1.22 to 1.60).[18,19,21] The remaining comparisons were in a single NMA,[21] where abiraterone plus ADT (RR = 1.23; 95% CI = 1.04 to 1.47), apalutamide plus ADT (RR = 1.45; 95% CI = 1.18 to 1.78), enzalutamide plus ADT (RR = 1.80; 95% CI = 1.39 to 2.34), and darolutamide plus docetaxel plus ADT (RR = 1.16; 95% CI = 1.00 to 1.35) were all favoured over abiraterone plus docetaxel plus ADT. The comparison to darolutamide plus docetaxel plus ADT also included the potential for no difference between treatments.

Notable Harms

One NMA[19] reported on the effect of abiraterone plus docetaxel plus ADT versus docetaxel plus ADT on hypertension, neutropenia, and febrile neutropenia. Docetaxel plus ADT was favoured for hypertension (OR = 1.91; 95% CI = 1.27 to 2.86), but the CIs were wide, which introduced uncertainty for neutropenia and febrile neutropenia. One NMA[23] reported on the effect of abiraterone plus docetaxel plus ADT versus abiraterone plus ADT for febrile neutropenia. In this analysis, abiraterone plus ADT was favoured (OR = 23.91; 95% CI, 6.05 to 94.52).

Critical Appraisal

Four[19,21-23] of the 6 systematic reviews with NMA were informed by an a priori protocol, and methods used to identify eligible RCTs were adequate. Analysis methods generally appeared appropriate; however, model parameters (i.e., selection of priors, assessment of model fit, convergence) and assessments of consistency and heterogeneity (when relevant) were not always presented. The included RCTs were reported to be at low risk of bias for objective outcomes, but there was some concern for bias in subjective outcomes (e.g., PFS, AEs) because several of the RCTs were open-label. Most of the contributing RCTs were industry-sponsored.

Clinical and methodological heterogeneity was apparent in patient characteristics (including prior and subsequent therapies) and methodology (e.g., outcome definitions and ascertainment methods, length of follow-up, design features), which challenged the plausibility of the transitivity assumption underlying the NMA. The networks were sparse and all evidence for the comparisons of interest was indirect (aside from the comparison to docetaxel plus ADT). As a result, there was often considerable imprecision, which reduced the certainty of the effect estimates.

Across the NMAs, clinically relevant outcomes were considered, including OS, PFS, and AEs. Several important efficacy outcomes which may be of particular relevance to patients (e.g., HRQoL, symptoms, time to skeletal-related event) were either not considered or could not be analyzed due to insufficient data.

Other Relevant Evidence

No other relevant evidence was identified for this review.

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 plus docetaxel in combination with ADT and those of comparators deemed to be appropriate based on clinical expert consultations and drug plan feedback.

Based on publicly available list prices, abiraterone with prednisone plus docetaxel in combination with ADT (ABI + DOC + ADT) is expected to have a 28-day cost of between $4,494 and $4,665 per patient depending on the ADT prescribed. The 28-day cost of ABI + DOC + ADT is higher than ADT monotherapy (incremental cost from $4,071 to $4,413 per patient), and doublet therapies (i.e., incremental costs for ABI + ADT = $1,154 to $1,496; APA + ADT = $583 to $925; and ENZ + ADT = $801 to $1,143 per patient). Recently, the triplet of darolutamide plus docetaxel in combination with ADT (DAR + DOC + ADT) received a positive recommendation from CADTH;[24] at the submitted price for darolutamide, DAR + DOC + ADT is expected to have a slightly greater 28-day cost than ABI + DOC + ADT (incremental cost ranging from $87 to $429 per patient). As the current standard of care for mCSPC patients is ADT monotherapy, or an ARPI in combination with ADT, the addition of docetaxel to the ABI + ADT doublet will be more expensive than current standard of care ($697 to $4,403). These incremental costs or savings are based on publicly available list prices from Ontario and may not reflect actual prices paid by public drug plans in Canada. These findings were observed to be sensitive to the price of abiraterone. In a scenario analysis that employed alternative abiraterone drug pricing from Nova Scotia, ABI + DOC + ADT became less expensive than the doublet therapies of APA + ADT and ENZ + ADT (i.e., incremental 28-day cost savings for APA + ADT = $1,132 to 1,474, and for ENZ + ADT = $914 to $1,256).

Conclusions

Evidence from the PEACE-1 study suggested that the triplet regimen of abiraterone with prednisone plus docetaxel plus ADT was associated with potentially clinically meaningful prolongation of OS and rPFS among patients with de novo mCSPC compared with a docetaxel plus ADT doublet. However, the study provided no evidence regarding the comparative efficacy of the triplet under review versus the current standard of care in most patients (ARPI plus ADT doublets) or versus other triplet regimens (e.g., darolutamide plus docetaxel plus ADT). Indirect evidence (6 ITCs) was consistent with the trial evidence for the comparison of the triplet under review versus docetaxel plus ADT doublet therapy. The indirect evidence also suggested a potential advantage of the triplet under review versus abiraterone plus ADT doublet for PFS and versus apalutamide plus ADT and enzalutamide plus ADT doublets for time to castration resistance. Overall, the indirect evidence regarding the comparative efficacy of the triplet under review versus ARPI plus ADT doublets or a darolutamide plus docetaxel plus ADT triplet was associated with uncertainty due to limited assessment of ITC assumptions, risk of bias issues, and a lack of head-to-head trials in patients with mCSPC. Evidence from the PEACE-1 study suggested that the main severe (grade 3 or higher) toxicities associated with abiraterone were hypertension and hepatotoxicity, while the main severe toxicities associated with docetaxel

were neutropenia, febrile neutropenia, and peripheral neuropathy. The indirect evidence regarding harms was consistent in suggesting greater risk of grade 3 or higher toxicities with the abiraterone plus docetaxel plus ADT triplet compared with either abiraterone plus ADT or docetaxel plus ADT doublets and other ARPI plus ADT doublets (e.g., apalutamide, enzalutamide). Together, these results partially aligned with some outcomes identified as important to patients with mCSPC (prolonged survival), but alignment with other outcomes (maintained HRQoL, convenient administration, limited side effects) was less clear.

As a cost-effectiveness analysis was not submitted, the cost-effectiveness of ABI + DOC + ADT in comparison with the appropriate comparators for the treatment of mCSPC, could not be determined. As the current standard of care is ADT monotherapy, or an ARPI or taxane as an add-on therapy to ADT (doublet therapy), results of the cost comparison demonstrate that the reimbursement of ABI + DOC + ADT is expected to increase overall treatment costs (incremental costs from $697 to $4,403 per patient per 28-day period) based on Ontario list prices. These findings were found to be sensitive to the price of abiraterone. In a scenario analysis using the list price of abiraterone from Nova Scotia, the results differed in that ABI + DOC + ADT was found to be less expensive than APA + ADT and ENZ + ADT. In both analyses, ABI + DOC + ADT was always more expensive than ADT monotherapy and ABI + ADT, but always less expensive than DAR + DOC + ADT. Other costs such as administration costs were not considered as part of the cost comparison. To adequately consider this alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of this treatment compared with all current standard-of-care treatments would be required.

Introduction

Disease Background

Prostate cancer is the most common cancer (excluding non-melanoma skin cancers) and the third leading cause of cancer death among males in Canada.[3] Risk factors include age (aged more than 50 years), race and ethnicity, family history, height and weight, and inherited gene mutations.[25] In its early stages, the disease is generally asymptomatic, but as the tumour grows symptoms may include urination problems, erectile dysfunction, bleeding, pain, and fatigue.[4] Both the disease and its treatment can negatively impact HRQoL.[5] PSA testing and digital rectal exam are routine screening tests for early detection; PSA elevation above 0.75 ng/mL/year or above the normal range for age, as well as abnormalities on digital rectal exam, may lead to a suspicion of cancer.[26] At diagnosis, disease is localized to the prostate in approximately 90% of patients,[6] for whom the goal of treatment is cure. However, approximately 5% to 10% of patients[7] are either diagnosed with locally advanced or de novo metastatic disease, or have disease that will progress over many years after being initially diagnosed with localized disease (metachronous). De novo metastatic disease is often more aggressive, with shorter time to progression and shorter median survival compared with metachronous metastasis.[27] The most common sites of metastasis in prostate cancer are the bones, distant lymph nodes, liver, and thorax.[28]

Metastatic prostate cancer that requires androgens (male hormones including testosterone) to sustain growth and can be controlled by reducing androgen levels to castrate levels is called metastatic castration-sensitive prostate cancer, or mCSPC,[8] while prostate cancer that progresses despite androgen deprivation by becoming hypersensitive to low levels of androgens or by developing androgen-independent mechanisms to sustain growth is called metastatic castration-resistant prostate cancer, or mCRPC.[9] Patients with mCSPC progress over time to mCRPC, which carries a worse prognosis. Early interventions for mCSPC may delay disease progression and prolong survival.[13] Prognosis and treatment of prostate cancer is evaluated based on multiple factors including tumour stage (according to the TNM staging system) and grade (Gleason score).[29] "High-volume disease" is typically defined as the presence of visceral metastases or 4 or more bone metastases, with at least 1 outside of the vertebral bodies and pelvis.[30] The definition of "high-risk disease" include: PSA above 20 ng/mL, Gleason score 8 or more, and clinical T stage cT2c or above; Gleason score 8 or more or Gleason score of 7 plus either clinical T stage cT3 or above or lymph node-positive; and at least 2 of Gleason score 8 to 10, visceral metastases, and 3 or more bone metastases.[31]

In 2021, approximately 24,600 males were diagnosed with prostate cancer and 4,600 died from the disease in Canada.[3] As of 2018, the 25-year prevalence of prostate cancer was approximately 302,000 males in Canada.[10] The prevalence and incidence of mCSPC in Canada are not known with certainty. However, in 2018, approximately 1,200 males were diagnosed with de novo metastatic prostate cancer in Canada,[11] with disease considered castrate-sensitive at the time of diagnosis. The 5-year survival of de novo metastatic prostate cancer in Canada is approximately 29%,[12] and median survival is approximately 3 to 7 years.[13]

According to the clinical expert CADTH consulted for this review, initial suspicion of prostate cancer may be based on patients' symptoms and risk factors, PSA level, and clinical examination. Prostate cancer (including mCSPC) is diagnosed by a urologist based on clinical examination, PSA testing, histological and pathological findings on prostate biopsy, and in some cases, imaging (CT, MRI, and/or bone scan). Patients are subsequently followed by a urologist and radiation and/or medical oncologist for treatment.

Standards of Therapy

For patients with localized prostate cancer, radiotherapy and surgery are administered with curative intent. However, according to the clinical expert CADTH consulted, in patients with mCSPC the mainstay of treatment is ADT, which is achieved either by surgery (orchiectomy) or by administration of GnRH agonists (e.g., leuprolide, goserelin) or antagonists (e.g., degarelix). Current guidelines support ADT intensification via combination with ARPIs (androgen receptor antagonists [e.g., enzalutamide, apalutamide, darolutamide] and/or androgen synthesis inhibitors [abiraterone]) and/or chemotherapy (docetaxel).[14] First generation ARPIs or antiandrogens (e.g., bicalutamide, nilutamide, or flutamide) may be used to cover the testosterone flare of GnRH agonists, but are otherwise generally no longer used in clinical practice. Combinations of ADT plus either an ARPI or docetaxel are generically referred to as doublet therapies, while combinations of ADT plus an ARPI plus docetaxel are generically referred to as triplet therapies. The clinical expert indicated that docetaxel may be effective in the subset of patients whose tumours have androgen receptor–independent biology and are thus unresponsive to ARPIs, but that toxicity is a potential concern, especially among

patients with mCSPC; paradoxically, docetaxel appears to be more toxic in patients with mCSPC than in those with mCRPC.

According to the clinical expert, metastatic prostate cancer, including mCSPC, is incurable and the goals of treatment are to palliate symptoms, maintain or improve HRQoL, delay progression, and prolong survival. Since most patients with mCSPC will achieve tumour shrinkage, decreased PSA levels, and symptomatic improvement with ADT alone, the goal of additional therapy is to delay progression and prolong survival without substantially increasing treatment toxicity.

Drugs

Key characteristics of drugs used for treatment of prostate cancer are shown in Table 4. Abiraterone acetate is an androgen synthesis inhibitor that is administered at a dose of 1,000 mg orally once per day with prednisone (5 mg twice per day or 10 mg once per day orally) or sometimes dexamethasone (0.5 mg to 1.5 mg per day orally).[1] The drug's mechanism of action is inhibition of cytochrome P450 17A1 (CYP17), an enzyme required for androgen biosynthesis, thereby inhibiting the production of testosterone.[10] Corticosteroids are coadministered to suppress adrenocorticotropic hormone drive, thereby reducing the incidence and severity of AEs associated with the increased mineralocorticoid levels that result from cytochrome P450 17A1 (CYP17) inhibition.

Docetaxel is a taxane antineoplastic drug that is administered at a dose of 75 mg/m^2 (maximum dose 150 mg per cycle) by IV infusion once every 3 weeks.[2] The drug's mechanism of action is inhibition of microtubule depolymerization, resulting in impairment of cellular mitosis.[2]

ADT refers to a group of antihormone therapies used to treat prostate cancer. The goal of ADT is to reduce androgen levels to castrate levels. Options include surgery (orchiectomy) or chemical castration by systemic administration of GnRH agonists or antagonists via subcutaneous or intramuscular injection. Doses and administration schedules vary by product (generally every 1 to 5 months). The mechanism of action of GnRH agonists involves binding to GnRH receptors, producing a spike in gonadotropin levels that results in feedback inhibition and subsequent downregulation of androgen levels. The mechanism of action of GnRH antagonists involves competitive binding to and blockade of GnRH receptors, thereby reducing secretion of androgens.

Abiraterone has the following Health Canada–approved indications:

- in combination with prednisone for the treatment of metastatic cancer (castration-resistant prostate cancer, mCRPC) in patients who are symptomatic or mildly symptomatic after failure of androgen deprivation therapy, or who have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy[1]
- in combination with prednisone and androgen deprivation therapy for the treatment of patients with newly diagnosed hormone-sensitive high-risk metastatic prostate cancer who may have received up to 3 months of prior ADT.[1]

Abiraterone was previously reviewed by CADTH (sponsor: Janssen Inc.) for the former part of the first indication listed above ("for asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer [mCRPC] patients after failure of ADT [have not received prior chemotherapy]") and received a recommendation for reimbursement with conditions, on October 22, 2013.[15] The drug was also previously under review by CADTH (sponsor: BC Cancer) for the second indication listed above; the submission was voluntarily withdrawn by the sponsor. CADTH also began a nonsponsored review of abiraterone plus prednisone for the treatment of high-risk nonmetastatic prostate cancer in 2022; that review is on hold until further notice.

Docetaxel has the following relevant Health Canada indication: "in combination with prednisone or prednisolone for the treatment of patients with androgen-independent (hormone-refractory) metastatic prostate cancer."

ADTs have a variety of Health Canada indications for the treatment of hormone-sensitive prostate cancer.

The PAG indicated an interest in clinical practice for treatment intensification strategies in patients with mCSPC. Specifically, the PAG requested that CADTH review triplet therapy with abiraterone (with prednisone or dexamethasone) plus docetaxel plus ADT for patients with mCSPC and provide a reimbursement recommendation.

Table 4: Key Characteristics of Systemic Therapies for mCSPC

Drug: Mechanism of action	Indications[a]	Dose and route of administration	Serious adverse events or safety issues
ARPIs			
Abiraterone: ARPI (androgen synthesis inhibitor via CYP17 inhibition)	With prednisone for the treatment of mCRPC in patients who: • are asymptomatic or mildly symptomatic after failure of ADT • have received prior chemotherapy containing docetaxel after failure of ADT In combination with prednisone and ADT for the treatment of patients with newly diagnosed hormone-sensitive high-risk metastatic prostate cancer who may have received up to 3 months of prior ADT	Abiraterone: 1,000 mg orally once daily Prednisone: 10 mg orally once daily (mCRPC) or 5 mg orally twice daily (newly diagnosed high-risk metastatic prostate cancer)	Abiraterone: hypertension, hypokalemia, and fluid retention; hepatotoxicity Prednisone: hyperglycemia
Apalutamide: ARPI	For the treatment of patients with nmCRPC[b] For the treatment of patients with mCSPC in combination with ADT	240 mg orally once daily	Cardiac disorders, QTc prolongation, hypertension, falls and fractures, seizures, rash, hypothyroidism

Drug: Mechanism of action	Indications[a]	Dose and route of administration	Serious adverse events or safety issues
Enzalutamide: ARPI	For the treatment of patients with nmCRPC[b] In the setting of medical or surgical castration for the treatment of mCRPC in patients who: • are chemotherapy-naive with asymptomatic or mildly symptomatic disease after failure of ADT • have received docetaxel therapy For the treatment of patients with mCSPC in combination with ADT	160 mg orally once daily	Seizures, posterior reversible encephalopathy syndrome, cardiac disorders, QTc prolongation, hypertension, fatigue, falls and fractures
Darolutamide: ARPI	For the treatment of patients with nmCRPC[b] For the treatment of patients with mCSPC in combination with docetaxel[c] and ADT	600 mg orally twice daily (total daily dose 1,200 mg)	Cardiac disorders, hepatotoxicity, seizures, rash, fatigue, falls and fractures, hypertension, seizures
Chemotherapy			
Docetaxel: microtubule depolymerization inhibitor	With prednisone or prednisolone for the treatment of patients with androgen-independent (hormone-refractory) metastatic prostate cancer	Docetaxel: 75 mg/m^2 as a 1-hour IV infusion every 3 weeks Prednisone or prednisolone: 5 mg orally twice daily	Enterocolitis, fluid retention, edema, neutropenia, hepatotoxicity, peripheral neuropathy, cystoid macular edema, ARDS, ILD, pneumonitis, cutaneous reactions, hypersensitivity reactions
ADT			
GnRH agonists: binding and stimulation of GnRH receptors resulting in feedback inhibition and downregulation of androgen levels	Various	Various doses; SC or IM	Tumour flare reaction, osteoporosis, injection site injuries and vascular injuries
GnRH antagonists: competitive binding and blockade of GnRH receptors	For the treatment of patients with advanced hormone-dependent prostate cancer in whom androgen deprivation is warranted	Various doses; SC or IM	QT prolongation, osteoporosis

ADT = androgen deprivation therapy; ARDS = acute respiratory distress syndrome; ARPI = androgen receptor pathway inhibitor; CYP17 = cytochrome P450 17A1; GnRH = gonadotropin-releasing hormone; ILD = interstitial lung disease; IM = intramuscular; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; SC = subcutaneous.

[a]Health Canada–approved indications relevant to prostate cancer are listed.

[b]The drug has not been studied in patients with nmCRPC at low risk of developing metastases. The benefit and risk profile in these patients is unknown.

[c]The first of 6 cycles of docetaxel should be administered within 6 weeks after the start of darolutamide treatment.

Source: Product monographs for abiraterone acetate (Zytiga),[1] docetaxel (Taxotere),[2] apalutamide (Erleada),[32] enzalutamide (Xtandi),[33] darolutamide (Nubeqa),[34] leuprolide acetate (Lupron),[35] goserelin (Zoladex),[36] and degarelix (Firmagon).[37]

Stakeholder Perspectives

Patient Group Input

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

One patient group, the Canadian Cancer Society, provided input for this review. The Canadian Cancer Society is a national nonprofit organization committed to improving the lives of people living with cancer through research, advocacy, and compassionate support. Information was gathered through interviews of 4 individuals living with mCSPC. The interviewees described the negative impacts of their mCSPC diagnosis on mental health (e.g., anxiety, depression, lack of support), the inconvenience of treatment (e.g., long travel time, out-of-pocket expenses), and the effects of the disease and its treatment, including prostatectomy and ADT, on daily activities and HRQoL (e.g., diminished sexual function, hot flashes, reduced muscle mass, reduced capacity for physical activities, constipation, and incontinence). Three interviewees had experience with abiraterone (through a special access program) plus ADT; none had experience with the triplet therapy under review. The interviewees who received abiraterone plus ADT noted a generally good HRQoL and felt their disease was well controlled, but reported side effects including fatigue and loss of sexual function, muscle mass, bone density, body hair, and stamina. Some interviewees noted the convenience of receiving once daily oral administration of abiraterone at home. The interviewees emphasized the need for additional treatment options that more effectively prolong survival, have less severe side effects, and are affordable.

Clinician Input

Input From a Clinical Expert Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise in 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 a clinical specialist with expertise in the diagnosis and management of prostate cancer including mCSPC.

Unmet Needs

According to the clinical expert consulted by CADTH for this review, despite improvements in survival observed with ADT intensification, treatment is not curative and most patients will eventually succumb to their prostate cancer. In addition, a subset of patients have relatively short survival. New treatment options with acceptable toxicity profiles are needed to delay progression to mCRPC and prolong survival. The clinical expert indicated that although the oral administration of ARPIs is convenient, their effectiveness requires adherence to long-term daily administration, which can be challenging for some patients.

Place in Therapy

The clinical expert CADTH consulted for this review stated that the mechanisms of action of abiraterone, docetaxel, and ADT are distinct and would be expected to complement one another. Because docetaxel

works through androgen receptor–independent mechanisms, it may complement the additive effects of abiraterone plus ADT. The clinical expert noted that triplet therapy with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT would not be the first regimen to address the underlying disease process rather than provide symptomatic management, as both docetaxel and ARPIs have demonstrated survival benefits when added to ADT. The clinical expert indicated that the triplet regimen under review would be used as a first-line treatment, would not be reserved for patients intolerant to other treatments or in whom other treatments are contraindicated, and is not expected to cause a shift in the current treatment paradigm.

Patient Population

According to the clinical expert consulted by CADTH for this review, no biomarkers are currently available to identify patients who would be more likely to benefit from treatment with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT. Although docetaxel may be effective in the subset of prostate cancers with androgen receptor–independent biology that are unresponsive to ARPIs, these cannot be identified before treatment. Since this triplet therapy is more rigorous than the current standard of care (ARPI plus ADT in most patients), a patient's ability to tolerate treatment would be the most likely practical basis for selection for treatment. The clinical expert highlighted that triplet therapy with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT may be considered for younger patients who are both well-informed and in better health, but have higher-risk disease features (e.g., critical organ involvement, high-volume disease, high-risk disease) and/or may prefer more aggressive therapy; the patient would need to understand and accept the uncertainty of benefit and the increased AEs of the triplet compared with the current standard of care (ARPI plus ADT doublet).

The clinical expert stated that while the PEACE-1 trial recruited patients with de novo metastatic mCSPC, it is not unreasonable to expect that some patients with metachronous mCSPC could also benefit from this triplet therapy. There are no challenges with diagnosis or misdiagnosis and no companion diagnostic tests are required. This triplet regimen would be least suitable for patients who are not chemo-fit (e.g., due to comorbidities) or who have contraindications to abiraterone.

Assessing Response to Treatment

The clinical expert stated that treatment response in mCSPC (including response to abiraterone with prednisone or dexamethasone plus docetaxel plus ADT) is assessed in 3 domains: patient symptoms, PSA level, and imaging (CT, MRI, and/or bone scan). Symptoms would be assessed and PSA levels measured at each clinic visit (approximately every 2 months to 3 months), and imaging would be performed approximately every 6 months, or sooner if progression is clinically suspected. However, all 3 domains will improve with ADT alone in more than 90% of patients with mCSPC, so these tools are not particularly helpful in assessing the response specifically attributable to intensified treatment (doublet or triplet therapy). Therefore, there is no minimum treatment response that would be required for continuation of intensified therapy, nor any accepted measure of a meaningful response to intensified therapy other than delayed progression to mCRPC and prolonged survival. The clinical expert emphasized that because abiraterone and docetaxel may contribute to additional AEs requiring treatment modification, patients should be carefully monitored.

Discontinuing Treatment

According to the clinical expert CADTH consulted for this review, mCSPC is incurable and progression to mCRPC is inevitable. Thus, treatment with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT would be discontinued in the presence of unequivocal disease progression; this includes the relatively small subset of patients who do not achieve improvement in the 3 domains of patient symptoms, PSA level, and imaging after initiating therapy. Discontinuation of treatment of 1 of the components may be necessary if severe or intolerable AEs that are persistent and not amenable to dose modifications occur, or if long treatment breaks occur. Treatment with 1 or more components could also be discontinued according to patient preference.

Prescribing Conditions

The clinical expert CADTH consulted for this review stated that abiraterone with prednisone or dexamethasone plus docetaxel plus ADT would be prescribed by a medical oncologist in an outpatient setting. Based on local practice, it may be possible for subsequent supervision of treatment to be delegated to trained clinicians, to allow for treatment closer to home in more remote locations.

Clinician Group Input

No input from clinician groups was received for this review.

Industry Input

This section was prepared by CADTH staff based on the input provided by an industry stakeholder. The full industry input is reproduced in the Stakeholder Input section at the end of this report.

One industry stakeholder, Janssen Inc. (a manufacturer of abiraterone acetate in Canada), provided input for this review. According to Janssen, the target population of patients with mCSPC eligible for reimbursement of triplet therapy with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT should be evidence-based and reflect the PEACE-1 study eligibility criteria and main results. Specifically, based on the trial eligibility criteria (de novo mCSPC, chemo-fit), the fact that more than 90% of patients had either bone and/or visceral metastases, and the fact that point estimates of survival benefit were highest among patients with high-volume disease, Janssen suggested that reimbursement should be limited to chemo-fit patients with high-volume mCSPC with bone and/or visceral metastases. The industry input noted that ADT with or without docetaxel is not the current standard of care for most patients with mCSPC according to treatment guidelines; Canadian Urological Association guidelines[11] recommend use of docetaxel in selected patients with good performance status and high-volume or high-risk disease. Janssen noted that several currently available treatment options for patients with mCSPC provide significant and clinically meaningful improvement in survival, suggesting that medical needs in this population are being met.

Janssen emphasized that the PEACE-1 study was not designed to assess the efficacy of addition of docetaxel to abiraterone plus ADT; rather, the study was intended to evaluate the efficacy of abiraterone to ADT compared to ADT alone (both with or without radiotherapy). The standard of care for mCSPC changed over the course of the PEACE-1 trial: docetaxel was initially forbidden, then optional, then mandatory in combination with ADT. Therefore, the contribution of docetaxel to the benefit seen in patients with mCSPC is

unclear and needs to be further evaluated, and the subgroup of patients who would specifically benefit from triplet therapy remains unclear. Janssen noted that the PEACE-1 study was not designed with regulatory rigour for filing and that the triplet therapy has not yet been reviewed or approved by Health Canada; as such, the certainty in the evidence is limited.

According to Janssen, ITCs comparing triplet therapy with abiraterone with prednisone or dexamethasone plus docetaxel plus ADT with doublet therapies (ARPIs plus ADT) have documented uncertain survival benefits of the triplet therapy and perhaps specifically in defined patient subsets (refer to the Indirect Evidence section). Therefore, the additional toxicities of the triplet therapy (e.g., febrile neutropenia, gastrointestinal disorders), its additional costs (e.g., docetaxel itself, chair time at infusion clinics, management of additional AEs), and the potential impact on sequencing of later-line treatment options (both abiraterone and docetaxel are options in patients with mCRPC) must be balanced with the uncertainty in clinical benefit.

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 expert consulted by CADTH are summarized in Table 5.

Table 5: Summary of Drug Plan Input and Clinical Expert Response

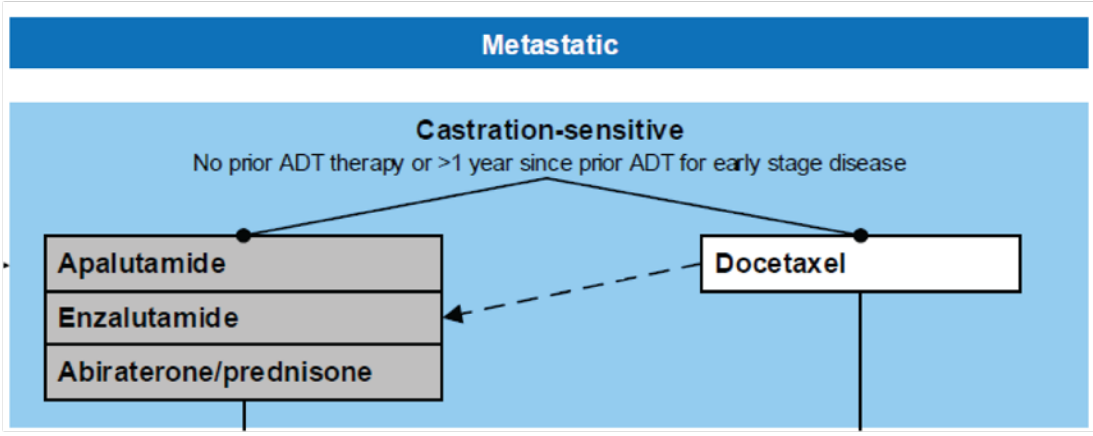
Implementation issues	Clinical expert response
Relevant comparators	
The PAG noted that the comparators in the PEACE-1 study were ADT (GnRH agonist or antagonist, or bilateral orchiectomy) + docetaxel (SOC) ± RT. Other publicly funded comparators for patients with mCSPC include 1 of the ARPIs (apalutamide/enzalutamide/abiraterone-prednisone) plus ADT. Patients receiving ARPI + ADT may have had prior treatment with docetaxel. Refer to Figure 1. 1. How does abiraterone + ADT + docetaxel compare with other publicly funded alternatives?	There is currently no direct clinical evidence evaluating the triplet of abiraterone plus docetaxel plus ADT vs. publicly funded doublet therapies other than docetaxel plus ADT (the standard-of-care arm in the PEACE-1 trial). Compared with docetaxel plus ADT, there appears to be a modest survival benefit of the triplet therapy but toxicity is increased. ITCs do not suggest an OS benefit of triplet therapy with abiraterone plus docetaxel plus ADT over ARPI doublet therapies including abiraterone plus ADT. PFS appears to be improved compared to abiraterone plus ADT (with associated uncertainty; refer to Indirect Evidence section). There is currently a gap in both the direct and indirect evidence regarding the efficacy of triplet therapy with abiraterone plus docetaxel plus ADT vs. doublet therapy with apalutamide plus ADT or enzalutamide plus ADT.
The PAG noted that there is a concurrent CADTH sponsored reimbursement review (PC0294 to 000) for darolutamide in combination with docetaxel and ADT for the treatment of mCSPC in patients who are eligible for chemotherapy (i.e., the same patient population) based on the ARASENS study.[38] 1. How does abiraterone-prednisone + ADT + docetaxel compare with darolutamide + ADT + docetaxel?	There is currently no direct clinical evidence evaluating these 2 triplets (abiraterone plus docetaxel plus ADT vs. darolutamide plus docetaxel plus ADT). However, ITCs have suggested that these regimens are potentially similar in efficacy and toxicity (refer to Indirect Evidence section).

Implementation issues	Clinical expert response
Considerations for initiation of therapy	
The PAG noted that the PEACE-1 study enrolled patients with de novo mCSPC and excluded patients with previous prostate cancer treated by a definitive local treatment. 1. Should the results from the PEACE-1 study be generalized to include patients who were diagnosed with localized disease and treated with curative surgery or radiotherapy who remained hormone-sensitive when their disease progressed to mCSPC?	While it remains unclear if the results of the PEACE-1 study can be generalized to patients previously treated with definitive local therapy who progressed to mCSPC (as they were excluded from the trial), there is no reason to think some of these patients could not potentially benefit from triplet therapy. However, triplet therapy would likely be administered in a selected patients with metachronous metastases (e.g., high-volume and/or high-risk disease, chemo-fit, understand the uncertain benefit of triplet therapy as well as the potentially increased toxicity).
The PAG noted that patients with ECOG performance status of 0 to 1 or 2 if due to bone pain were eligible for enrolment in the PEACE-1 study. 1. Are the results of the trial generalizable to patients with worse performance status than those enrolled in the PEACE-1 trial?	No, the results of the study cannot be generalized to patients with worse performance status than the trial population. Indirect comparisons confirm that triplet therapy is associated with greater severe toxicity than ARPI doublet therapy. Cautious use of ARPI plus ADT is preferred for patients with worse performance status than those eligible for the PEACE-1 trial.
The PAG noted that there may be subgroups of patients to consider separately for eligibility. 1. Would patients with low-volume disease equally benefit from the abiraterone/prednisone-ADT-docetaxel triplet therapy compared to patients with high-volume disease? 2. If there is a difference, what is the definition for low- vs. high-volume disease?	The PEACE-1 trial was not powered to assess differences in efficacy of this triplet in patients with high- and low-volume disease, so this is currently unknown. Disease volume is an imprecise surrogate for cancer biology. Patients with low-volume disease may be at lower risk, and treatment with a triplet regimen vs. the current standard of care (ARPI plus ADT doublet) should be considered clinically on an individual basis. As defined in the CHAARTED trial, high-volume disease is presence of visceral metastases or 4 or more bone metastasis with at least 1 outside the spine and pelvis.
The PAG noted that consistent initiation criteria should be used for drugs in the same therapeutic space. In the PEACE-1 study, docetaxel had to be administered at least 6 weeks after ADT initiation. Abiraterone was started within 6 weeks after ADT initiation (refer to Figure 2 for treatment flow chart). In the ARASENS study,[38] patients begin ADT (± first generation antiandrogen) not longer than 12 weeks before randomization, and the first cycle of docetaxel was administered within 6 weeks after the start of darolutamide, 1. Should there be alignment with other triplet therapy being considered in mCSPC?	Note that this figure describing treatment flow in the PEACE-1 study is not accurate. The figure shows that docetaxel and abiraterone had to be started simultaneously, but in the trial, docetaxel had to be started at least 6 weeks after ADT. However, randomization to abiraterone or standard of care was up to 3 months post-ADT initiation. Therefore, for example, one could have started docetaxel 8 weeks post-ADT initiation, and then been randomized at 12 weeks post-ADT initiation (i.e., abiraterone would have started after docetaxel in a subset of patients). In clinical practice, abiraterone would likely be started before docetaxel. Based on the PEACE-1 and ARASENS[38] trials, docetaxel should start not sooner than 6 weeks and not later than 3 months after ADT initiation. Docetaxel and ARPIs should not be started simultaneously (to make accurate assessments of drug-related toxicity). ARPIs should be started within 6 weeks before or after docetaxel.
Considerations for discontinuation of therapy	
The PAG noted that treatment interruptions may occur for 1 or more components of the abiraterone + docetaxel + ADT triplet. 1. For patients who were unable to complete 6 cycles	Patients who are unable to tolerate 6 cycles of docetaxel should still be continued on abiraterone plus ADT, which is 1 of the current standard-of-care treatment options.

Implementation issues	Clinical expert response
of docetaxel, should they be eligible to continue with abiraterone-prednisone and ADT? 2. For patients who are unable to tolerate abiraterone-prednisone, should they be eligible to switch to an alternative ARPI (such as darolutamide) provided all other criteria are met? 3. For patients who discontinued therapy (due to toxicities or the patient's choice), is there any evidence to re-treat with any component of the regimen when a patient progresses to mCRPC?	Patients who are unable to tolerate abiraterone should be eligible to switch to another ARPI, but there should be established criteria for this (e.g., heart failure). This question should also be referred to pERC for input. Patients with mCSPC who cannot tolerate abiraterone or docetaxel and discontinue treatment may or may not be eligible for re-treatment once they progress to mCRPC. The available data on re-treatment with docetaxel in mCRPC after it has been used in mCSPC are not encouraging. If re-treatment with docetaxel is to be considered, it should be administered after a reasonable time has passed from previous treatment (e.g., 1 year to 2 years). Re-treatment with abiraterone could also be considered if treatment was discontinued due to patient preference and not due to toxicity. Re-treatment decisions should be based on patient preference and clinician discretion.
Considerations for prescribing of therapy	
The PAG noted that the protocol for the PEACE-1 study was amended (January 22, 2018) to make G-CSF prophylaxis mandatory for patients who received docetaxel. Funding for prophylactic G-CSF may need to be considered as some jurisdictions fund G-CSF with restricted eligibility.	For pERC consideration.
Generalizability	
The PAG noted that patients on active treatment may have a time-limited opportunity to switch to the abiraterone + docetaxel + ADT triplet. 1. Should patients who recently initiated docetaxel + ADT for mCSPC be eligible to add on abiraterone-prednisone? What would be an appropriate time frame to allow this addition? 2. For mCSPC patients currently receiving ARPIs (apalutamide or enzalutamide or abiraterone-prednisone) + ADT, should they be allowed to switch to abiraterone-prednisone + ADT + docetaxel when funding is implemented?	Patients who recently initiated docetaxel plus ADT should be eligible to add on abiraterone within approximately 6 months following treatment initiation to allow overlap with the policy change (i.e., if the triplet therapy is funded). However, after a reasonable time has elapsed from policy implementation, this time frame should align with the clinical trial (i.e., abiraterone should be initiated within 3 months of starting treatment with docetaxel plus ADT). Patients who are currently receiving 1 of apalutamide or enzalutamide or abiraterone plus ADT should be allowed to switch to the triplet if funding is implemented. This decision would be based on patient preference and clinician discretion but should be made within a restricted time frame (e.g., approximately 4 months to 6 months).
Funding algorithm	
The PAG noted that this is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products. Therefore, development of a provisional funding algorithm may be required.	For pERC consideration.

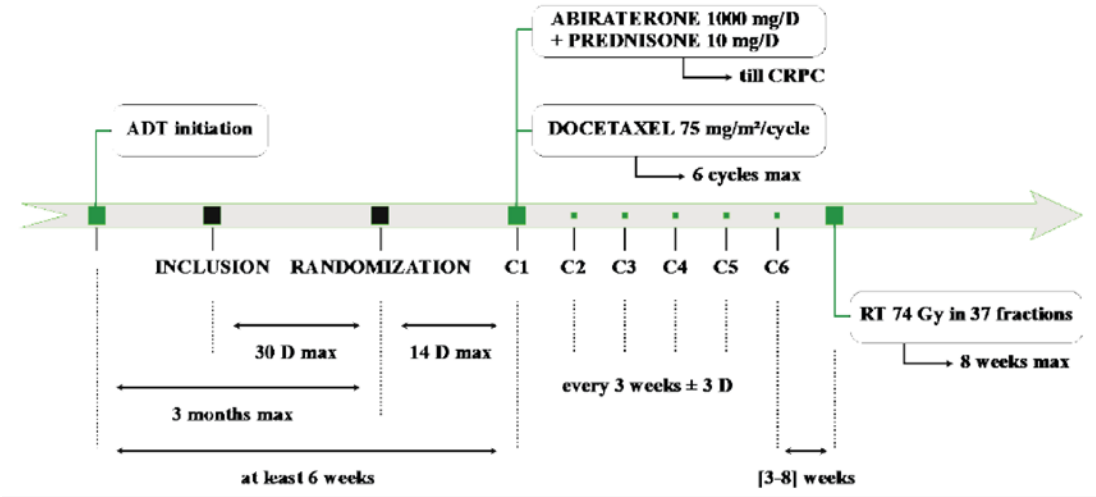
ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte colony-stimulating factor; GnRH = gonadotropin-releasing hormone; ITC = indirect treatment comparison; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; OS = overall survival; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PFS = progression-free survival; RT = radiotherapy; SOC = standard of care; vs. = versus.

Figure 1: June 2021 CADTH Provisional Funding Algorithm – Prostate Cancer



ADT = androgen deprivation therapy.

Figure 2: Treatment Flow Chart for PEACE-1 Clinical Trial



ADT = androgen deprivation therapy; C = cycle; CRPC = castration resistant prostate cancer; D = day.
Source: Fizazi et al. (2022).[16]

Clinical Evidence

The clinical evidence included in the review of abiraterone with prednisone or dexamethasone plus docetaxel plus ADT is presented in 2 sections. The first, the Systematic Review section, includes those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the literature that met the selection criteria specified in the review. No additional relevant studies were identified that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of abiraterone (1,000 mg once per day orally) with prednisone (5 mg twice per day or 10 mg once per day orally) or dexamethasone (0.5 mg to 1.5 mg orally daily) plus docetaxel (75 mg/m^2 IV every 3 weeks; maximum dose 150 mg per cycle) for the treatment of adults with mCSPC in combination with ADT.

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

Criteria	Description
Patient population	Adults aged 18 years or older with mCSPC Subgroups: • De novo vs. recurrent mCSPC • Metastatic burden/disease volume • Risk group • Performance status
Intervention	Abiraterone (1,000 mg orally once per day) with prednisone (5 mg twice per day or 10 mg once per day orally) or dexamethasone (0.5 mg to 1.5 mg orally daily) plus docetaxel (75 mg/m^2 IV every 3 weeks; maximum dose 150 mg per cycle) plus ADT
Comparators[a]	• Docetaxel plus ADT • Androgen receptor targeting agents (e.g., enzalutamide, apalutamide) plus ADT • Abiraterone with prednisone or dexamethasone plus ADT
Outcomes	Efficacy outcomes: • OS • HRQoL • PFS • Time to CRPC • Time to chemotherapy of CRPC • Cancer symptoms (e.g., time to pain progression) • CRPC-free survival • Prostate cancer–specific survival • Serious genitourinary event-free survival • Objective response rate • Time to next skeletal-related event • Time to PSA progression • PSA response rate • PSA nadir level

Criteria	Description

	Harms outcomes:
	• AEs
	• Serious AEs
	• Withdrawal due to AEs
	• Mortality
	• Notable harms/harms of special interest
	  ◦ Abiraterone: hypertension, hypokalemia, and fluid retention; hepatotoxicity
	  ◦ Prednisone or dexamethasone: hyperglycemia
	  ◦ Docetaxel: enterocolitis, fluid retention, edema, neutropenia, hepatotoxicity, peripheral neuropathy, cystoid macular edema, ARDS, ILD, pneumonitis, cutaneous reactions, hypersensitivity reactions

Study design	Published and unpublished phase III and IV RCTs

ADT = androgen deprivation therapy; AE = adverse event; ARDS = acute respiratory distress syndrome; CRPC = castration-resistant prostate cancer; HRQoL = health-related quality of life; ILD = interstitial lung disease; mCSPC = metastatic castration-sensitive prostate cancer; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RCT = randomized controlled trial; vs. = versus.

[a]Note that darolutamide plus docetaxel plus ADT was not an available treatment option for patients with mCSPC at the time this protocol was prepared but was under review by CADTH and was subsequent conditionally recommended for funding.

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[39]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the Population, Intervention, Comparison, Outcomes and Study (PICOS) framework and research questions. The main search concepts were abiraterone acetate, prednisone, dexamethasone, docetaxel, and chemotherapy. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on September 19, 2022. Regular alerts updated the search until the meeting of the CADTH Formulary Management Expert Committee on June 29, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (the US Food and Drug Administration and the European

Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Findings From the Literature

A single study was identified from the literature for inclusion in the systematic review (Figure 3). The included study is summarized in Table 7.

Table 7: Details of the Included Study

Item	PEACE-1
Design and population	
Study design	Multicentre, open-label, randomized, phase III study with a 2 × 2 factorial design
Locations	77 hospitals in Belgium, France, Ireland, Italy, Romania, Spain, and Switzerland
Patient randomization dates	November 27, 2013, to December 20, 2018
Data cut-off	September 1, 2020
Randomized (N)	1,173

Inclusion criteria	• Males aged 18 years to 80 years
	• Histologically or cytologically confirmed adenocarcinoma of the prostate
	• Metastatic disease documented by a positive bone scan (any technique) or CT scan or an MRI; for patients with nodal metastases only, only patients with extrapelvic enlarged lymph nodes (lymph nodes located above the iliac bifurcation) can be included if they have either:
	  ◦ At least 1 extrapelvic lymph node ≥ 2 cm
	  ◦ Extrapelvic lymph node(s) ≥ 1 cm if the patient also has at least 1 pelvic lymph node ≥ 2 cm
	• ECOG performance status ≤ 1 (patients with ECOG performance status of 2 due to bone pain can be accrued in the trial)
	• Life expectancy of at least 6 months
	• Adequate hematological function (hemoglobin ≥ 10.0 g/dL, platelet count ≥ 100,000/μL, neutrophils ≥ 1,500/mm^3)
	• Adequate biochemistry values:
	  ◦ Renal function: serum creatinine < 1.5 × ULN or a calculated creatinine clearance ≥ 60 mL/min
	  ◦ Serum potassium ≥ 4 mmol/L
	  ◦ Liver function: serum bilirubin ≤ 1.5 × ULN (except for patients with documented Gilbert's syndrome); AST and ALT ≤ 1.5 × ULN (and ≤ 5 × ULN in case of liver metastases); ALP ≤ 2.5 × ULN (in case of bone metastasis, ALP < 1,000 U/L if bilirubin levels are normal)
	• Patients must have received ADT for a maximum of 3 months before randomization and there must be a minimum of 6 weeks between the start of ADT and the start of docetaxel
	• Patients willing and clinically fit to receive docetaxel, which is defined by the following:
	  ◦ Patients respecting all inclusion and exclusion criteria

Item	PEACE-1
	◦ Patients with no contraindication to docetaxel according to the SmPC of the drug ◦ Patients presenting all medical requirements to receive docetaxel according to the investigator's opinion • Patients might have received previous radiation therapy directed to bone lesions • Patients able to take oral medication • Patients who have received the information sheet and signed the informed consent form • Male patients who will receive docetaxel and/or abiraterone acetate and have partners of childbearing potential and/or pregnant partners must use a method of birth control in addition to an adequate barrier protection (condoms) as determined to be acceptable by the study doctor during the treatment period and for 4 weeks after the last dose of abiraterone acetate and/or for 6 months after the last dose of docetaxel • Patients must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures • Patients with a public or a private health insurance coverage, according to local laws for participation in clinical trials
Exclusion criteria	• Patients with previous definitive local treatment directed to the prostate primary cancer (radiotherapy, brachytherapy, radical prostatectomy, ultrasound, cryotherapy, or other); a previous TURP and previous local treatments of metastases was allowed • Prior cytotoxic chemotherapy or biologic therapy for the treatment of prostate cancer • Any chronic medical condition requiring a higher dose of corticosteroid than 5 mg prednisone/ prednisolone twice daily • Active infection or other medical condition for which prednisone/prednisolone (corticosteroid) use would be contraindicated • Previously treated with ketoconazole for prostate cancer for more than 7 days • Prior systemic treatment with an azole drug (e.g., fluconazole, itraconazole) within 4 weeks of randomization • Hypertension not controlled by an antihypertensive (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 95 mm Hg; 3 consecutive measures taken 5 minutes apart) • Severe or moderate hepatic impairment (Child-Pugh class C or B) • Active or symptomatic viral hepatitis or chronic liver disease (except Gilbert's disease) • History of pituitary or adrenal dysfunction • Clinically known significant heart disease as evidence by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class II-IV heart disease or cardiac ejection fraction measurement of < 50% at baseline • Atrial fibrillation, or other cardiac arrythmia requiring therapy • Patient with unstable pulmonary disease (e.g., pulmonary embolism) • Pathological finding consistent with small cell carcinoma of the prostate • History of malignancy, except non-melanoma skin cancer, with a ≥ 30% probability of recurrence within 24 months • Known allergies, hypersensitivity or intolerance to the study drugs or excipients or docetaxel • Administration of an investigational therapeutic within 30 days of randomization • Patients already included in another therapeutic trial involving an experimental drug (patient in a non-experimental trial with no modification of the patient's care can be included) • Patients with significantly altered mental status prohibiting the understanding of the study or with psychological, familial, sociological, or geographical condition potentially hampering compliance

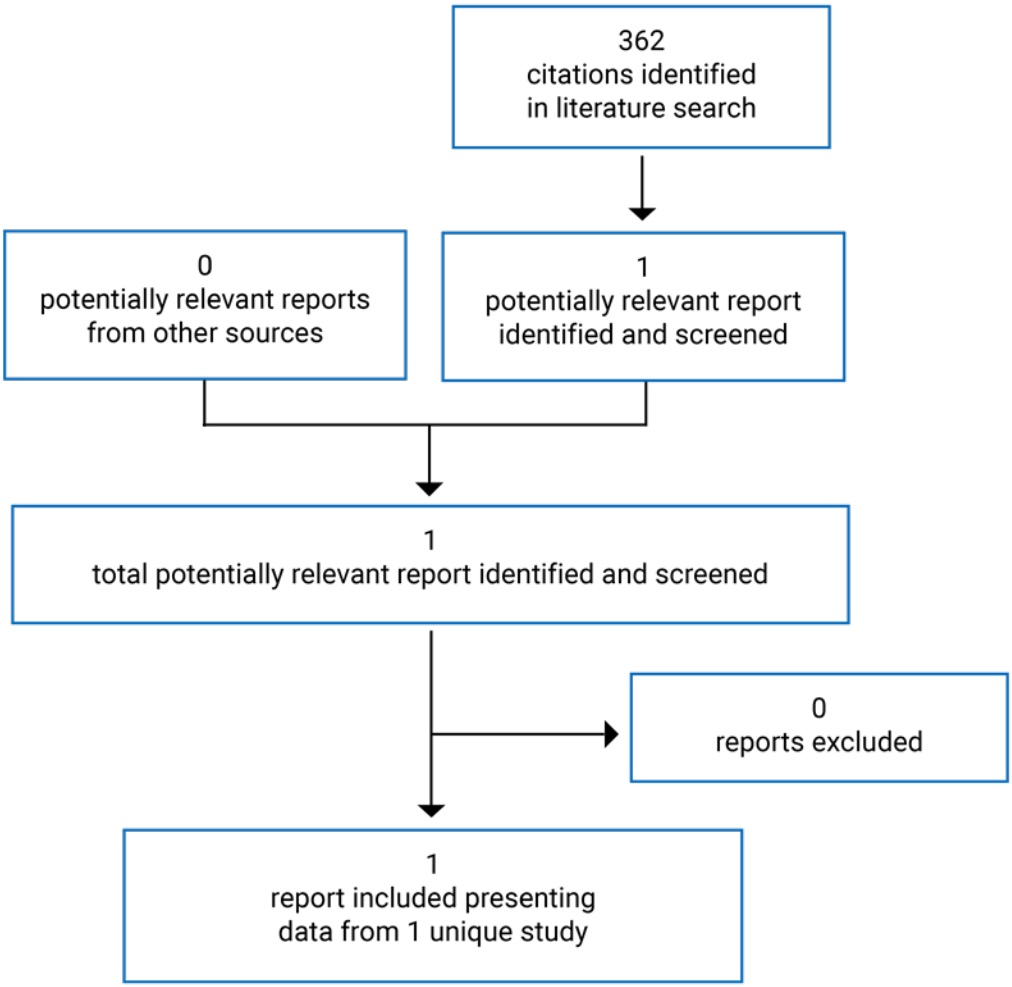
Item	PEACE-1
	with the study protocol and follow-up schedule or any condition which, in the opinion of the investigator, would preclude participation in the trial; those conditions should be discussed with the patient before registration in the trial • Individual deprived of liberty or placed under the authority of a tutor • Patients with impaired vision should undergo a prompt and complete ophthalmologic examination; patients with cystoid macular edema cannot be included due to potential risk of deterioration associated with docetaxel, and the patient should not receive docetaxel • Concomitant use of strong CYP3A4 inhibitors (clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin)
Drugs	
Intervention	• Abiraterone (1,000 mg orally once per day) with prednisone (5 mg twice per day) plus SOC [ADT (GnRH agonist or antagonist, or bilateral orchiectomy) with or without docetaxel (75 mg/m^2 IV every 3 weeks, 6 cycles; maximum dose 150 mg per cycle)] • Abiraterone (1,000 mg orally once per day) with prednisone (5 mg twice per day) plus SOC [ADT (GnRH agonist or antagonist, or bilateral orchiectomy) with or without docetaxel (75 mg/m^2 IV every 3 weeks, 6 cycles; maximum dose 150 mg per cycle)] plus radiotherapy (74 Gy in 37 fractions administered over 7 weeks to 8 weeks)
Comparator	• SOC [ADT (GnRH agonist or antagonist, or bilateral orchiectomy) with or without docetaxel (75 mg/m^2 IV every 3 weeks, 6 cycles; maximum dose 150 mg per cycle)] • SOC [ADT (GnRH agonist or antagonist, or bilateral orchiectomy) with or without docetaxel (75 mg/m^2 IV every 3 weeks, 6 cycles; maximum dose 150 mg per cycle)] plus radiotherapy (74 Gy in 37 fractions administered over 7 weeks to 8 weeks)
Duration	
Phase	
Screening	30 days
Open-label treatment	ADT with or without abiraterone and prednisone: until disease progression to CRPC, withdrawal of consent, unacceptable toxicity, or death Docetaxel: 6 cycles or until withdrawal of consent, unacceptable toxicity, or death
Follow-up	10 years
Outcomes	
Coprimary end points	• OS • rPFS
Secondary and exploratory end points	**Secondary:** • CRPC-free survival • Serious genitourinary event-free survival • Prostate cancer–specific survival • Time to next skeletal-related event • PSA response rate • Prognostic study of serum PSA measured 6 months to 8 months after initiation of systemic therapy • Time to pain progression • Time to chemotherapy of CRPC • Changes in HRQoL

Item	PEACE-1
	• Changes in bone mineral density • Correlation of biomarkers with outcome **Safety:** • Toxicity • Event rate per 100 person-years of treatment
Notes	
Publications	Fizazi et al. (2022)[16]

ADT = androgen deprivation therapy; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; CRPC = castration-resistant prostate cancer; CYP3A4 = cytochrome P450 3A4; ECOG = Eastern Cooperative Oncology Group; GnRH = gonadotropin-releasing hormone; HRQoL = health-related quality of life; NYHA = New York Heart Association; OS = overall survival; PSA = prostate-specific antigen; rPFS = radiographic progression-free survival; SmPC = summary of product characteristics; SOC = standard of care; ULN = upper limit of normal.

Source: Fizazi et al. (2022).[16]

Figure 3: Flow Diagram for Inclusion and Exclusion of Studies



Description of the Study

Key characteristics of the PEACE-1 study are shown in Table 7. The PEACE-1 study (N = 1,173) was a multicentre, open-label, randomized, phase III study with a 2 × 2 factorial design.[16] The primary objective of the study was to evaluate the efficacy and safety of abiraterone plus prednisone, with or without radiotherapy, in addition to standard of care (ADT with or without docetaxel) in patients with de novo mCSPC. The coprimary efficacy outcomes were OS and rPFS, while secondary efficacy outcomes included CRPC-free survival, serious genitourinary event-free survival, prostate cancer–specific survival, time to next skeletal-related event, PSA response rate, prognostic study of serum PSA measured 6 months to 8 months after initiation of systemic therapy, time to pain progression, time to chemotherapy of CRPC, changes in HRQoL, changes in bone mineral density, and correlation of biomarkers with outcome.

Following screening, adult males with mCSPC, ECOG performance status of 0 or 1 (or 2 due to bone pain), and adequate hematological and organ function who were receiving ADT and were willing and clinically fit to receive docetaxel were enrolled from 2013 to 2018 at 77 hospitals in Europe (predominantly France) and randomized 1:1:1:1 to receive standard of care (ADT with or without docetaxel), standard of care plus radiotherapy, standard of care plus abiraterone, or standard of care plus radiotherapy plus abiraterone. Treatment with docetaxel was for 6 cycles, whereas treatment with ADT (with or without abiraterone) continued until disease progression to CRPC, withdrawal of consent, unacceptable toxicity, or death. Patients must have received ADT for a maximum of 3 months before randomization, and there must have been a minimum of 6 weeks between the start of ADT and the start of docetaxel. Randomization was stratified by study site, ECOG performance status (0 versus 1 or 2), type of ADT (GnRH agonist versus GnRH antagonist versus orchiectomy), planned administration of docetaxel (yes versus no), and disease extent or burden based on metastatic status (lymph node metastases only versus bone metastases with or without lymph node metastases versus visceral metastases). The study is closed to recruitment and the data cut-off at the time of publication was September 1, 2020. The planned survival follow-up of up to 10 years for each patient is ongoing. The study was funded by Janssen-Cilag, Ipsen, Sanofi, and the French Government.

Note that the randomization stratification factor planned administration of docetaxel (yes versus no) was added to the randomization process via protocol amendment in October 2015, when 273 patients had already been randomized. Note also that after a further 593 patients had been randomized (total 866 patients accrued), the protocol was amended again in August 2017 to restrict accrual to patients who could be treated with docetaxel. Therefore, this randomization stratification factor only applied to 593 patients randomized between October 2015 and August 2017.

Populations

Inclusion and Exclusion Criteria

The eligibility criteria for the PEACE-1 study are shown in Table 7. Adult males (aged 18 years to 80 years) were eligible if they had histologically or cytologically confirmed adenocarcinoma of the prostate documented as de novo metastatic by CT, MRI, or bone scan according to RECIST version 1.1,[17] had ECOG performance status of 0 or 1 (or 2 due to bone pain), had adequate hematological and organ functions (liver and kidney), were willing and clinically fit to receive docetaxel, had received ADT for no more than 3 months

before randomization, and had received ADT for at least 6 weeks before the first docetaxel dose. Patients with small cell carcinoma of the prostate, patients who had previously received definitive local treatment for prostate cancer, and patients with hypertension, hepatic impairment, or clinically significant heart disease were excluded.

Note that the inclusion criterion of willingness and clinical fitness to receive docetaxel was added via protocol amendment in August 2017 when 866 patients had already been randomized.

Baseline Characteristics

The baseline demographic and disease characteristics of patients in the PEACE-1 study are shown in Table 8. Most patients (78% to 79%) were from France. The median age in the abiraterone plus docetaxel plus ADT arm was 66 years (range, 37 years to 85 years) and the median age in the docetaxel plus ADT arm was 66 years (range, 44 years to 84 years). Half (50%) of the study participants in each arm were assigned to receive radiotherapy.

In the ADT with docetaxel population, approximately two-thirds of participants (69% to 70%) had ECOG performance status of 0 or 1 while approximately one-third (29% to 30%) had ECOG performance status of 2 due to bone pain. Approximately four-fifths (79% to 81%) had bone metastases without visceral metastases, approximately one-eighth (12% to 13%) had visceral metastases with or without bone and/or lymph node metastases, and 8% had lymph node metastases only. Approximately two-thirds (63% to 65%) had high-volume (high-burden) disease, while approximately one-third (35% to 37%) had low-volume disease. More than three-quarters (77% to 80%) had Gleason scores of 8 to 10 and less than one-quarter (20% to 23%) had Gleason scores of 7 or lower. At randomization, the median PSA level was 12 ng/mL to 14 ng/mL.

Table 8: Baseline Characteristics in the ITT Population

Characteristic, n (%)	Overall population (n = 1,172)		ADT with docetaxel population (n = 710)[a]	
	SOC plus abiraterone groups (with or without radiotherapy; n = 583)	SOC without abiraterone groups (with or without radiotherapy; n = 589)	SOC plus abiraterone groups (with or without radiotherapy; n = 355)	SOC without abiraterone groups (with or without radiotherapy; n = 355)
Assigned to receive radiotherapy	291 (50%)	293 (50%)	178 (50%)	177 (50%)
Country				
Belgium	29 (5%)	25 (4%)	16 (5%)	16 (5%)
France	458 (79%)	462 (78%)	278 (78%)	280 (79%)
Ireland	30 (5%)	30 (5%)	17 (5%)	13 (4%)
Italy	1 (< 1%)	3 (1%)	0	0
Romania	4 (1%)	5 (1%)	0	0
Spain	55 (9%)	56 (10%)	38 (11%)	39 (11%)
Switzerland	6 (1%)	8 (1%)	6 (2%)	7 (2%)

Characteristic, n (%)	Overall population (n = 1,172)		ADT with docetaxel population (n = 710)[a]	
	SOC plus abiraterone groups (with or without radiotherapy; n = 583)	SOC without abiraterone groups (with or without radiotherapy; n = 589)	SOC plus abiraterone groups (with or without radiotherapy; n = 355)	SOC without abiraterone groups (with or without radiotherapy; n = 355)
Age, years				
Median	67 (61 to 72)	66 (59 to 72)	66 (60 to 70)	66 (59 to 70)
Range	37 to 94	43 to 87	37 to 85	44 to 84
ECOG performance status				
0	412 (71%)	412 (70%)	250 (70%)	246 (69%)
1 to 2	171 (29%)	177 (30%)	105 (30%)	109 (31%)
T-stage				
T1	23 (4%)	23 (4%)	10 (3%)	13 (4%)
T2	109 (19%)	94 (16%)	64 (19%)	45 (13%)
T3	287 (51%)	310 (53%)	167 (49%)	189 (55%)
T4	98 (17%)	99 (17%)	68 (20%)	65 (19%)
Tx	45 (8%)	54 (9%)	32 (9%)	35 (10%)
Missing data	21 (4%)	9 (2%)	14 (4%)	8 (2%)
N-stage				
N1	307 (55%)	325 (57%)	198 (58%)	207 (60%)
N0	186 (33%)	174 (30%)	99 (29%)	97 (28%)
NX	69 (12%)	76 (13%)	43 (13%)	39 (11%)
Missing data	21 (4%)	14 (2%)	15 (4%)	12 (3%)
Time from diagnosis, months				
Median	2.3 (1.6 to 3.2)	2.3 (1.4 to 3.1)	2.2 (1.6 to 3.0)	2.2 (1.4 to 2.9)
Missing data	10 (2%)	10 (2%)	6 (2%)	7 (2%)
Metastatic localization				
Bone[b]	472 (81%)	475 (81%)	287 (81%)	279 (79%)
Lymph node only	47 (8%)	52 (9%)	27 (8%)	29 (8%)
Visceral[c]	64 (11%)	62 (11%)	41 (12%)	47 (13%)
Metastatic burden[d]				
High burden	331 (57%)	336 (57%)	224 (63%)	232 (65%)
Low burden	252 (43%)	253 (43%)	131 (37%)	123 (35%)
Gleason score				
≤ 7	145 (25%)	133 (23%)	79 (23%)	71 (20%)
8 to 10	429 (75%)	441 (77%)	270 (77%)	276 (80%)
Missing data	9 (2%)	15 (3%)	6 (2%)	8 (2%)

Characteristic, n (%)	Overall population (n = 1,172)		ADT with docetaxel population (n = 710)[a]	
	SOC plus abiraterone groups (with or without radiotherapy; n = 583)	SOC without abiraterone groups (with or without radiotherapy; n = 589)	SOC plus abiraterone groups (with or without radiotherapy; n = 355)	SOC without abiraterone groups (with or without radiotherapy; n = 355)
PSA at randomization, ng/mL				
Median	14 (3 to 62)	11 (3 to 55)	14 (2 to 59)	12 (3 to 60)
Missing data	2 (< 1%)	4 (1%)	0	2 (< 1%)
Medical history				
Hypertension	270 (47%); N = 574	241 (43%); N = 562	156 (44%); N = 352	148 (43%); N = 344
Type 2 diabetes	62 (11%); N = 566	80 (14%); N = 556	33 (9%); N = 351	56 (16%); N = 344
High cholesterol	229 (40%); N = 568	229 (41%); N = 556	136 (39%); N = 351	130 (38%); N = 343

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; ITT = intention to treat; PSA = prostate-specific antigen; SOC = standard of care.

Note: Data are n (%) or median (IQR) unless otherwise stated. All numbers are rounded to the nearest integer. Ethnicity-related information is not presented, as French laws forbid the collection of such data. SOC in the overall population was ADT with or without docetaxel. SOC in the ADT with docetaxel population was ADT with docetaxel.

[a]The median number of docetaxel cycles was 6 (IQR, 6 to 6) in both the SOC with abiraterone and SOC without abiraterone groups.

[b]Without visceral metastases.

[c]With or without lymph node and bone metastases.

[d]The metastatic burden was classified as reported by Sweeney and colleagues (2015),[30] with a high burden characterized by 4 or more bone metastases with 1 or more outside the vertebral bodies or pelvis, or visceral metastases, or both; all other assessable situations were classified as low burden.

Source: Fizazi et al. (2022).[16]

Interventions

In all patients participating in the PEACE-1 trial, ADT (GnRH agonist, GnRH antagonist, or orchiectomy) was continuously maintained until disease progression to mCRPC, withdrawal of consent, unacceptable toxicity, or death. Patients assigned to receive docetaxel received 6 cycles of IV docetaxel (75 mg/m^2 per cycle; maximum dose 150 mg per cycle) every 21 ± 3 days. Granulocyte colony-stimulating factor (G-CSF) injections after each docetaxel cycle were recommended until a protocol amendment (January 22, 2018; ethics committee approval March 22, 2018) made primary prophylaxis with G-CSF mandatory for patients receiving docetaxel. The first docetaxel cycle had to be administered within 14 days after randomization and at least 6 weeks after ADT initiation.

Patients assigned to receive abiraterone received 4 tablets of 250 mg orally once daily (total daily dose 1,000 mg) as well as 2 prednisone tablets of 5 mg orally twice daily (total daily dose 10 mg). The dose of prednisone was based on the approved dosing of abiraterone with prednisone in mCRPC. The first dose of abiraterone with prednisone had to be administered within 6 weeks after ADT initiation. Abiraterone with prednisone was continuously maintained until disease progression to mCRPC, withdrawal of consent, unacceptable toxicity, or death.

Patients assigned to receive radiotherapy (74 Gy in 37 fractions administered over 7 weeks to 8 weeks) were planned to start radiotherapy at least 3 weeks but no more than 8 weeks after docetaxel completion. The timing of radiotherapy in patients who did not receive docetaxel was not stated.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the PEACE-1 trial is provided in Table 9. These end points are further summarized in the text that follows. Note that only the coprimary outcomes (OS and rPFS), the secondary outcomes of CRPC-free survival and prostate-cancer–specific survival, and harms outcomes were reported; other outcomes were still under investigation at the time of publication.

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

Outcome measure	PEACE-1	Definition	Censoring rules
OS	Coprimary	Time between randomization and death from any cause	Patients without events were censored at the date of last follow-up
rPFS	Coprimary	Time between randomization and the occurrence of radiological progression or death from any cause. Radiological progression of soft-tissue lesions was evaluated by either CT or MRI on the basis of RECIST version 1.1.[17] Progression of bone lesions was assessed by bone scan according to the adapted version of Prostate Cancer Working Group 2 criteria, with no secondary bone scan required to confirm progression	Not reported
HRQoL	Secondary (not reported)	FACT-P,[40] BPI-SF,[41] and QLQ-C30[42] questionnaires	NA
Time to chemotherapy of CRPC	Secondary (not reported)	Not reported	Not reported
Time to pain progression	Secondary (not reported)	Not reported	NA
CRPC-free survival	Secondary	Time between randomization and CRPC or death from any cause. CRPC was defined as either radiographical progression or a confirmed PSA rise (based on 3 independent measurements: A, B, and C, with A < B < C, and C ≥ 0.50 ng/mL)	Not reported
Prostate cancer–specific survival	Secondary	Time from randomization to the occurrence of death from prostate cancer	Not reported
Serious genitourinary event-free survival	Secondary (not reported)	Not reported	Not reported

Outcome measure	PEACE-1	Definition	Censoring rules
Time to next skeletal-related event	Secondary (not reported)	Not reported	Not reported
PSA response rate	Secondary (not reported)	Not reported	NA

BPI-SF = Brief Pain Advisory – Short Form; CRPC = castration-resistant prostate cancer; FACT-P = Functional Assessment of Cancer Therapy –Prostate; HRQoL = health-related quality of life; NA = not applicable; OS = overall survival; PSA = prostate-specific antigen; QLQ-C30 = Quality of Life Questionnaire Core 30; RECIST = Response Evaluation Criteria in Solid Tumours; rPFS = radiographic progression-free survival.

Source: Fizazi et al. (2022).[16]

OS and rPFS were the primary outcomes in the PEACE-1 trial and are broadly accepted outcome measures in oncology trials for treatment of prostate cancer (outcome definitions are in Table 9). Radiographic progression of soft-tissue lesions was evaluated by CT or MRI based on RECIST version 1.1.[17] Progression of bone lesions was assessed by bone scan according to the adapted version of Prostate Cancer Working Group criteria with no secondary bone scan required to confirm progression. Radiological assessments (bone scan plus CT or MRI) were performed at baseline and at end of treatment; the same imaging modality was used for each patient throughout the study. Radiological assessments were also performed on day 1 of abiraterone treatment, on day 1 of each docetaxel cycle, and then at month 6 and every 6 months thereafter until the end of treatment if disease progression was biologically or clinically diagnosed or suspected. Note that rules for rPFS censoring were not provided. Although not explicitly stated in the study, rPFS was most likely investigator-assigned (not through blinded independent central review), according to the clinical expert CADTH consulted for this review.

CRPC-free survival and prostate cancer–specific survival were secondary outcomes in the PEACE-1 trial and are broadly accepted outcome measures in oncology trials for treatment of prostate cancer (outcome definitions are found in Table 9). Note that rules for censoring of CRPC-fee survival and prostate cancer–specific survival were not provided.

Changes in HRQoL, time to chemotherapy of CRPC, time to pain progression, serious genitourinary event-free survival, time to next skeletal-related event, and PSA response rate were secondary outcomes in the PEACE-1 trial. HRQoL was assessed using the Functional Assessment of Cancer Therapy – Prostate (FACT-P),[40] Brief Pain Advisory – Short Form (BPI-SF),[41] and Quality of Life Questionnaire Core 30 (QLQ-C30)[42] questionnaires; all 3 instruments are patient-reported outcomes. Because data for these outcomes were not available for this review, the measurement properties of these outcomes in patients with mCSPC were not considered relevant.

Harms outcomes included treatment-emergent AEs as well as AE rates per 100 person-years of treatment. The Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term classification was used for AE coding, and grading criteria were not stated.

Statistical Analysis

Statistical analyses in the PEACE-1 trial are summarized in Table 10. The analyses were affected by protocol changes over the course of the trial.

Table 10: Statistical Analysis of Efficacy End Points in the PEACE-1 Trial

End point	Position in statistical hierarchy	Statistical model	Adjustment factors	Sensitivity analyses
OS in the overall population	1 or 2 (2-sided alpha = 0.049)	• Kaplan-Meier analysis with median survival and nonparametric CIs calculated using the bootkm function of the R Hmisc package (5,000 repeats) • Cox proportional hazards model adjusted for radiotherapy and stratification factors provided P value and HR with CIs adjusted to match significance levels in the corresponding test (i.e., 99.9% for rPFS, 95.1% for OS, and 95% for secondary end points)	• Radiotherapy • Stratification factors: ECOG performance status (0 vs. 1 to 2), ADT type (GnRH agonist vs. antagonist vs. bilateral orchiectomy), metastatic burden (low vs. high), and docetaxel (no docetaxel before amendment vs. no docetaxel after amendment vs. with docetaxel after amendment)	Not reported
rPFS in the overall population	1 or 2 (2-sided alpha = 0.001)	As per coprimary OS analysis	As per coprimary OS analysis	Not reported
OS in the ADT with docetaxel population	3 or 4 (2-sided alpha = 0.049)	As per coprimary OS analysis	As per coprimary OS analysis	Not reported
rPFS in the ADT with docetaxel population	3 or 4 (2-sided alpha = 0.001)	As per coprimary OS analysis	As per coprimary OS analysis	Not reported
CRPC-free survival	Not included	As per coprimary OS analysis	As per coprimary OS analysis	Not reported
Prostate cancer–specific survival	Not included	As per coprimary OS analysis	As per coprimary OS analysis	Not reported

ADT = androgen deprivation therapy; CI = confidence interval; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; GnRH = gonadotropin-releasing hormone; HR = hazard ratio; OS = overall survival; rPFS = radiographic progression-free survival; vs. = versus.

Source : Fizazi et al. (2022).[16]

Protocol Amendments

Several changes in the study protocol over the course of the study (including the primary objective, randomization procedure, interventions and cointerventions, coprimary outcomes and timing of final analysis, splitting of alpha between coprimary outcomes, planned follow-up time, and planned sample size) are relevant in understanding the statistical analyses. These changes are summarized below.

- Original protocol (July 13, 2013)

- Objective: evaluate efficacy of abiraterone plus ADT versus ADT (with or without radiotherapy according to the factorial design) in males with de novo mCSPC
- Randomization stratification factors: study site, ECOG performance status, type of ADT, metastatic burden
- Interventions and cointerventions: abiraterone plus ADT, ADT (both with or without radiotherapy)
- Coprimary outcomes and timing of final analysis: OS, PFS (based on rPFS and PSA progression) in the overall study population; interim analysis planned
- Splitting of alpha: OS (0.04), PFS (0.01)
- Follow-up time: median expected OS in standard-of-care arm = 4 years
- Planned sample size: 916 patients

- Amendment 14 (October 7, 2015; n = 273 patients already randomized)
  - Objective: no changes
  - Randomization stratification factors: study site, ECOG performance status, type of ADT, metastatic burden, **planned administration of docetaxel**
  - Interventions and cointerventions: abiraterone plus ADT with or without docetaxel, ADT **with or without docetaxel** (both with or without radiotherapy); **G-CSF injections after each docetaxel cycle recommended**
  - Coprimary outcomes and timing of final analysis: no changes
  - Splitting of alpha: no changes
  - Follow-up time: median OS expected in standard-of-care arm **5 years; estimated follow-up duration after last patient entry until data maturity increased by 1 year, bringing the expected study duration to 3 years of recruitment and 6.5 years of follow-up**
  - Planned sample size: no changes
  - **Rationale: a number of studies established the benefit of adding docetaxel to ADT in patients with de novo mCSPC; follow-up time extended to account for longer OS mediated by addition of docetaxel**
- Amendment 20 (August 10, 2017; n = 866 patients already randomized)
  - Objective: no changes
  - Interventions and cointerventions: abiraterone **plus docetaxel plus ADT**, **docetaxel plus ADT** (both with or without radiotherapy); G-CSF injections after each docetaxel cycle recommended
  - Coprimary outcomes and timing of final analysis: no changes
  - Splitting of alpha: no changes
  - Follow-up time: no changes
  - Planned sample size: **1,173 (or 1,168) patients as per main text of publication and supplementary appendix, respectively**

- **Rationale: because data from the LATITUDE[43] and STAMPEDE[44] trials suggested that addition of abiraterone to ADT increased OS in males with de novo mCSPC, for ethical reasons only patients who could be treated with docetaxel plus ADT were recruited; sample size increased due to potential interaction between abiraterone and docetaxel, with the efficacy of abiraterone hypothesized to be weaker in patients receiving docetaxel**

- Amendment 23 (January 22 or March 22, 2018)
  - Objective: no changes
  - Interventions and cointerventions: abiraterone plus docetaxel plus ADT, docetaxel plus ADT (both with or without radiotherapy); **G-CSF injections after each docetaxel cycle mandatory**
  - Coprimary outcomes and timing of final analysis: no changes
  - Splitting of alpha: no changes
  - Follow-up time: no changes
  - Planned sample size: no changes
  - **Rationale: 2 docetaxel-related deaths in 1 week at a single centre paused the study; the trial was restarted on the condition that G-CSF prophylaxis become mandatory and a blood test be conducted around day 6 of each docetaxel cycle for early neutropenia detection**
- Amendment 32 (January 13, 2021)
  - Objectives: **(i) evaluate efficacy of abiraterone plus docetaxel plus ADT versus docetaxel plus ADT (with or without radiotherapy according to the factorial design) in males with de novo mCSPC, and (ii) assess efficacy of radiotherapy in males with de novo mCSPC receiving ADT (with or without abiraterone and/or docetaxel, according to the factorial design) with low metastatic burden as defined in the Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial**
  - Interventions and cointerventions: no changes
  - Coprimary outcomes and timing of final analysis: **OS, rPFS in the docetaxel plus ADT population; interim analysis removed and focus shifted to final analysis**
  - Splitting of alpha: **OS (0.049), rPFS (0.001); sequential testing first in the overall population and then in the docetaxel plus ADT population**
  - Follow-up time: no changes
  - Planned sample size: no changes
  - **Rationale: the efficacy of abiraterone plus ADT versus ADT alone in patients with mCSPC had already been investigated by the LATITUDE[43] and STAMPEDE[44] studies, and the efficacy of radiotherapy plus ADT versus ADT alone in patients with mCSPC had already been investigated by the HORRAD[45] and STAMPEDE[44] studies; several studies demonstrated that PSA progression had poor prognostic value as a surrogate end point, whereas rPFS was a valid surrogate end point for OS in mCSPC; the OS analysis was "prioritized" by assigning a greater proportion of**

alpha; it was believed to be unethical to "discard" information provided by about 40% of the patients in the overall population (those receiving ADT alone as standard of care)

Timing of Analyses

At the time of publication, the results for coprimary outcomes (OS and rPFS) corresponded to the final planned analyses; no interim analyses were conducted. While the trigger for final analysis of OS and rPFS was reported to be a prespecified number of events in the ADT with docetaxel population, it was not explicitly stated whether the trigger was OS or rPFS events, nor the threshold triggering the analysis. There was no specific trigger identified in terms of event numbers for reporting of secondary outcomes, and the reasons why these were not reported in the publication were not given. The triggers for analysis of the effect of radiotherapy on OS and rPFS (preplanned number of events) were 213 OS events and 299 rPFS events among the subgroup of patients with low metastatic burden. These triggers were stated to have not been reached at the time of publication.

Power Calculations

Power for the coprimary outcomes (OS and rPFS) was grounded in the hypothesis that adding abiraterone to docetaxel plus ADT would prolong OS by 30% over a median of 53 months in the standard-of-care arm and rPFS by 40% over a median of 30 months in the docetaxel plus ADT arm. With 355 patients each randomized to the abiraterone plus docetaxel plus ADT and docetaxel plus ADT arms, 249 OS events would result in 80% power to detect an OS HR of 0.70 (2-sided alpha = 0.049) and 262 rPFS events would result in 80% power to detect an rPFS HR of 0.60 (at 2-sided alpha = 0.001).

Power calculations assumed that no significant interaction would take place between radiotherapy and abiraterone to allow for a 2 × 2 factorial analysis of abiraterone efficacy. Power calculations for secondary outcomes were not provided. The rationales for the assumptions regarding expected numbers of events and HRs for OS and rPFS were not provided (aside from "prioritizing" the OS analysis). The rationale for the splitting of alpha between coprimary outcomes was not provided.

Control of Type I Error

Type II error was controlled using a hierarchical testing strategy to limit the overall 2-sided type I error rate to alpha = 0.05 divided between the coprimary end points (alpha = 0.049 for OS and alpha = 0.001 for rPFS). For the coprimary efficacy outcomes, a sequential hypothesis testing procedure was used for multiplicity adjustment. Abiraterone efficacy was first evaluated in the overall population and then in the ADT with docetaxel population; in both populations, it was not explicitly stated if OS or rPFS was tested first. If statistical significance was not achieved for an end point within the hierarchy, subsequent end points in the prespecified order were not considered statistically significant and P values were considered nominal. The secondary end points, CRPC-free survival and prostate cancer–specific survival, were not included within the testing hierarchy (i.e., not controlled for type I error).

Analytical Techniques

The factorial design of the study assumed that there would be no interaction between abiraterone with prednisone and radiotherapy. Before conducting any statistical analyses of efficacy outcomes, the presence

of such an interaction for both coprimary end points was tested by calculating maximum likelihood estimates using a Cox model adjusted for stratification factors (ECOG performance status, ADT type, metastatic burden, and planned administration of docetaxel). In the absence of a qualitative interaction ($P > 0.05$) between abiraterone and radiotherapy, the groups (abiraterone, yes or no; radiotherapy, yes or no) were to be combined 2 by 2 on the basis of abiraterone administration before assessing abiraterone efficacy.

Potential heterogeneity in the effect of abiraterone on the strata of randomization stratification variables was evaluated using Cox proportional hazards models adjusted for radiotherapy, including an interaction term between abiraterone and each stratification variable in turn.

For time-to-event analyses, median survival and associated CIs (99.9% for rPFS; 95.1% for OS, CRPC-free survival, and prostate cancer–specific survival) were estimated using the Kaplan-Meier method. Missing data were not imputed and were accounted for by censoring, as defined in Table 9 (for most end points the censoring rules were not reported). HRs and associated CIs comparing treatment arms were calculated from Cox proportional hazards models adjusted for radiotherapy and randomization stratification factors; adjustment was made to the CIs in the corresponding test (99.9% for rPFS, 95.1% for OS, and 95% for secondary end points). The proportional hazards assumption was evaluated based on the weighted Schoenfeld residuals. Median follow-up time was estimated using the inverse Kaplan-Meier method. Methods used to calculate median survival differences between groups were not stated, but nonparametric CIs differences were calculated using the bootkm function of the R Hmisc package.

Sensitivity and Subgroup Analyses

No sensitivity analyses were conducted. Subgroup analyses of OS and rPFS were conducted by the following randomization stratification factors: ECOG performance status (0 versus 1 or 2), type of ADT (GnRH agonist versus GnRH antagonist versus orchiectomy), planned administration of docetaxel (yes versus no [not yet standard of care] versus no [physician decision]), and metastatic burden (high versus low). Of these, ECOG performance status and metastatic burden were identified as of interest in the CADTH review protocol. The study was not specifically powered to evaluate differences in outcomes among the individual strata.

Subgroup analyses were not reported for the randomization stratification factor study site. Note that the prespecified strata for the randomization stratification variable planned administration of docetaxel (yes versus no) differed in the reported subgroup analysis (yes versus no [not yet standard of care] versus no [physician decision]). Note also that the prespecified strata for the randomization stratification variable disease extent or burden based on metastatic status (lymph node metastases only versus bone metastases with or without lymph node metastases versus visceral metastases) differed in the reported subgroup analysis (high versus low metastatic burden).

Analysis Populations

The overall intention-to-treat (ITT) population consisted of all patients randomly assigned to a treatment group. The ADT with docetaxel population consisted of the subset of the overall ITT population who were assigned to received docetaxel, while the ADT population consisted of the subset of the overall population who were not assigned to receive docetaxel. The safety population consisted of all patients who received at

least 1 dose of study drug; patients were analyzed according to the treatment actually received and those who did not receive any investigational treatment were excluded from the safety analysis.

Results

Patient Disposition

In the PEACE-1 trial the number of patients screened, number of screen failures, and reasons for screen failure were not stated. Of the 1,173 patients enrolled and randomized, 1 withdrew consent and data for this patient were not presented. In the docetaxel plus ADT population (n = 710), 355 patients were assigned to receive abiraterone plus docetaxel plus ADT while 355 patients were assigned to receive docetaxel plus ADT. In the docetaxel plus ADT population, 347 patients (97.7%) received abiraterone plus docetaxel plus ADT while 350 patients (98.6%) received docetaxel plus ADT and were included in safety analyses.

In the overall population (n = 1,172), 18 patients (3.1%) assigned to receive abiraterone plus ADT with or without docetaxel and 15 patients (2.5%) assigned to received ADT with or without docetaxel were lost to follow-up or withdrew consent.

In the overall population, median follow-up time for rPFS was 3.5 years (interquartile range [IQR], 2.8 years to 4.6 years) and median follow-up time for OS was 4.4 years (IQR, 3.5 years to 5.4 years). Median rPFS follow-up times in the abiraterone plus ADT with or without docetaxel arm and the ADT with or without docetaxel arm were 3.56 years and 3.52 years, respectively. Median OS follow-up times in the abiraterone plus ADT with or without docetaxel arm and the ADT with or without docetaxel arm were 4.39 years and 4.44 years, respectively.

In the docetaxel plus ADT population, median follow-up time for rPFS was 3.0 years (IQR, 2.1 years to 3.8 years) and median follow-up time for OS was 3.8 years (IQR, 2.9 years to 4.5 years). Median rPFS follow-up times in the abiraterone plus ADT plus docetaxel arm and the docetaxel plus ADT arm were 2.97 years and 3.00 years, respectively. Median OS follow-up times in the abiraterone plus ADT plus docetaxel arm and the docetaxel plus ADT arm were 3.85 years and 3.75 years, respectively.

Exposure to Study Treatments

On-Study Treatment

In the docetaxel plus ADT population, the median number of docetaxel cycles administered was 6 (IQR, 6 to 6) in both the abiraterone plus docetaxel plus ADT arm and the docetaxel plus ADT arm. Information on exposure to ADT and radiotherapy in the PEACE-1 trial was not provided.

Reasons for treatment discontinuation in the PEACE-1 trial are summarized in Table 11. Among patients in the trial who received abiraterone, 183 (53%) of 347 in the ADT plus docetaxel population and 138 (61%) of 226 in the ADT population discontinued abiraterone treatment. The median abiraterone treatment duration before discontinuation was 34.1 months (95% CI, 30.0 to 43.5 months) in the docetaxel plus ADT population and 33.2 months (95% CI, 25.5 to 43.2 months) in the ADT population. In the docetaxel plus ADT population, reasons for treatment discontinuation were available for 183 patients (52.7%) who received abiraterone plus docetaxel plus ADT and for 252 (72.0%) who received docetaxel plus ADT. Among patients in the docetaxel

plus ADT population and in the abiraterone plus docetaxel plus ADT arm who discontinued treatment, the most common reasons were disease progression (n = 124; 67.8%), toxicity (n = 32; 17.5%), patient's decision (n = 11; 6.0%), and death (n = 13; 7.1%). Among patients in the docetaxel plus ADT population and in the docetaxel plus ADT arm who discontinued treatment, the most common reason was disease progression (n = 241; 95.6%).

Table 11: Reasons for Treatment Discontinuation in the PEACE-1 Trial – Safety Population

	Treatment allocation			
	ADT with docetaxel population (SOC = ADT + DXL ± RT)		ADT population (SOC = ADT ± RT)	
Safety population Available (nonavailable) Reason, n (%)	SOC + Abi Arm B+D (n = 347) 183 (164)	SOC Arm A+C (n = 350) 252 (98)	SOC + Abi Arm B+D (n = 226) 138 (88)	SOC Arm A+C (n = 237) 163 (74)
Second cancer	1 (< 1)	3 (1)	5 (4)	4 (3)
Disease progression	124 (68)	241 (95)	88 (64)	148 (89)
Patient's decision	11 (6)	4 (2)	4 (3)	5 (3)
Death	13 (7)	2 (< 1)	9 (7)	4 (3)
Toxicity/adverse event	32 (18)	1 (< 1)	29 (21)	1 (< 1)
Other	2 (1)	1 (< 1)	3 (2)	1 (< 1)

Abi = abiraterone; ADT = androgen deprivation therapy; DXL = docetaxel; RT = radiotherapy; SOC = standard of care.

Note: Data are n (%). As the patients were not randomly assigned according to docetaxel prescription, toxicities recorded in the ADT without docetaxel and ADT with docetaxel populations are not directly comparable. Percentages are rounded to the nearest integer. The safety population includes patients who actually received the assigned treatment. Severe adverse events (grade ≥ 3) are reported according to the Medical Dictionary for Regulatory Activities Preferred Term classification.

Source : Fizazi et al. (2022).[16]

Postprogression Treatment

Treatments administered after progression to mCRPC in the docetaxel plus ADT population are shown in Table 12. Post-progression therapy could be selected and altered as appropriate based on PSA level, clinical progression, and/or radiographic evidence. Overall, 141 patients (39.7%) assigned to receive abiraterone plus docetaxel plus ADT received post-progression therapy while 263 patients (74.1%) assigned to receive docetaxel plus ADT received post-progression therapy. Among patients assigned to receive abiraterone plus docetaxel plus ADT who received post-progression therapy, the most common therapies received were life-prolonging treatment (n = 104; 73.8%), cabazitaxel (n = 84; 59.6%), second-generation hormonal therapy (n = 65; 46.1%), and enzalutamide (n = 57; 40.4%). Among patients assigned to receive docetaxel plus ADT who received post-progression therapy, the most common therapies received were life-prolonging treatment (n = 221; 84.0%), second-generation hormonal therapy (n = 213; 81.0%), abiraterone (n = 153; 58.2%), enzalutamide (n = 119; 45.2%), and cabazitaxel (n = 114; 43.3%).

Table 12: Treatments Given Post-Progression in the ADT + Docetaxel Population in the PEACE-1 Trial – ITT Population

At least 1 treatment, n (%)	SOC + Abi CRPC (n = 141)	SOC CRPC (n = 263)
Life-prolonging treatment	104 (74)	221 (84)
Second-generation hormonal therapy	65 (46)	213 (81)
Abiraterone	22 (16)	153 (58)
Enzalutamide	57 (40)	119 (45)
Docetaxel	29 (21)	25 (10)
Cabazitaxel	84 (60)	114 (43)
Radium 223	3 (2)	11 (4)
Lu-PSMA	2 (1)	3 (1)

Abi = abiraterone; ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; ITT = intention to treat; Lu-PSMA = lutetium-117 prostate-specific membrane antigen-617; SOC = standard of care.

Source: Fizazi et al. (2022).[16]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. Note that in both the overall population and the docetaxel plus ADT population, no interactions between abiraterone and radiotherapy were identified for rPFS, OS, CRPC-free survival or prostate cancer–specific survival after adjusting for randomization stratification factors. Therefore, data were pooled irrespective of radiotherapy.

Overall Survival

OS was a coprimary efficacy outcome in the PEACE-1 trial. OS results in the PEACE-1 trial are summarized in Figure 4 and Table 13.In the docetaxel plus ADT population, 121 of 355 participants (34.1%) in the abiraterone plus docetaxel plus ADT arm and 151 of 355 participants (42.5%) in the docetaxel plus ADT arm died, while OS was censored for the remaining participants. In the docetaxel plus ADT population, median OS was not reached in the abiraterone plus docetaxel plus ADT arm and was 4.4 years (CI not reported) in the docetaxel plus ADT arm. The median OS difference was 0.9 years (95.1% CI, 0.0 years to 2.0 years) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT. The HR for OS was 0.75 (95.1% CI, 0.59 to 0.95; P = 0.017) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT.

Subgroup analyses of OS in the docetaxel plus ADT population and metastatic burden are shown in Figure 4 and Table 13. Overall, the results were consistent with the main analysis. Among patients with high-volume disease in the docetaxel plus ADT population, median OS was 5.1 years in the abiraterone plus docetaxel plus ADT arm and 3.5 years (CI not reported) in the docetaxel plus ADT arm. The median OS difference was 1.1 years (95.1% CI, 0.2 years to 1.9 years) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT. Among patients with low-volume disease in the docetaxel plus ADT population, median OS was not reached in either the abiraterone plus docetaxel plus ADT arm or the docetaxel plus ADT arm, and thus the

median OS difference could not be calculated. Point estimates of the HR for OS were closer to the null with wider CIs among the approximately one-third of with low-volume disease (HR for OS = 0.83; 95.1% CI, 0.50 to 1.39) compared with the approximately two-thirds of patients with high-volume disease (HR for OS = 0.72; 95.1% CI, 0.55 to 0.95). However, the CIs around the HR in both groups were overlapping.

The results of subgroup analyses of OS in the docetaxel plus ADT population by ECOG performance status were also consistent with the main analysis.

Health-Related Quality of Life

HRQoL was a secondary efficacy outcome in the PEACE-1 trial but was still under investigation at the time of publication.

Radiographic PFS

rPFS was a coprimary efficacy outcome in the PEACE-1 trial. rPFS results in the PEACE-1 trial are summarized in Figure 4 and Table 13.[16] In the docetaxel plus ADT population, 139 of 355 patients (39.2%) in the abiraterone plus docetaxel plus ADT arm and 211 of 355 patients (59.4%) in the docetaxel plus ADT arm had rPFS events, while rPFS was censored for the remaining patients. In the docetaxel plus ADT population, median rPFS was 4.5 years (CI not reported) in the abiraterone plus docetaxel plus ADT arm and 2.0 years (CI not reported) in the docetaxel plus ADT arm. The median rPFS difference was 2.2 years (99.9% CI, 0.6 years to 2.7 years) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT. The HR for rPFS was 0.50 (99.9% CI, 0.34 to 0.71; P < 0.0001) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT.

Subgroup analyses of rPFS in the docetaxel plus ADT population by metastatic burden are shown in Figure 5. Overall, the results were consistent with the main analysis. Among patients with high-volume disease in the docetaxel plus ADT population, median rPFS was 4.1 years (CI not reported) in the abiraterone plus docetaxel plus ADT arm and 1.6 years (CI not reported) in the docetaxel plus ADT arm. The median rPFS difference was 2.2 years (99.9% CI, 0.6 years to 3.2 years) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT. Among patients with low-volume disease in the docetaxel plus ADT population, median rPFS was not reached in the abiraterone plus docetaxel plus ADT arm and was 2.7 years (CI not reported) in the docetaxel plus ADT arm, and thus the median rPFS difference could not be calculated. Point estimates of the HR for rPFS were closer to the null with wider CIs among the approximately one-third of patients with low-volume disease (HR for rPFS = 0.58; 99.9% CI, 0.29 to 1.15) compared with the approximately two-thirds of patients with high-volume disease (HR for rPFS = 0.47; 99.9% CI, 0.30 to 0.72); however, the CIs around the HR in both groups overlapped.

The results of subgroup analyses of rPFS in the docetaxel plus ADT population by ECOG performance status were also consistent with the main analysis.

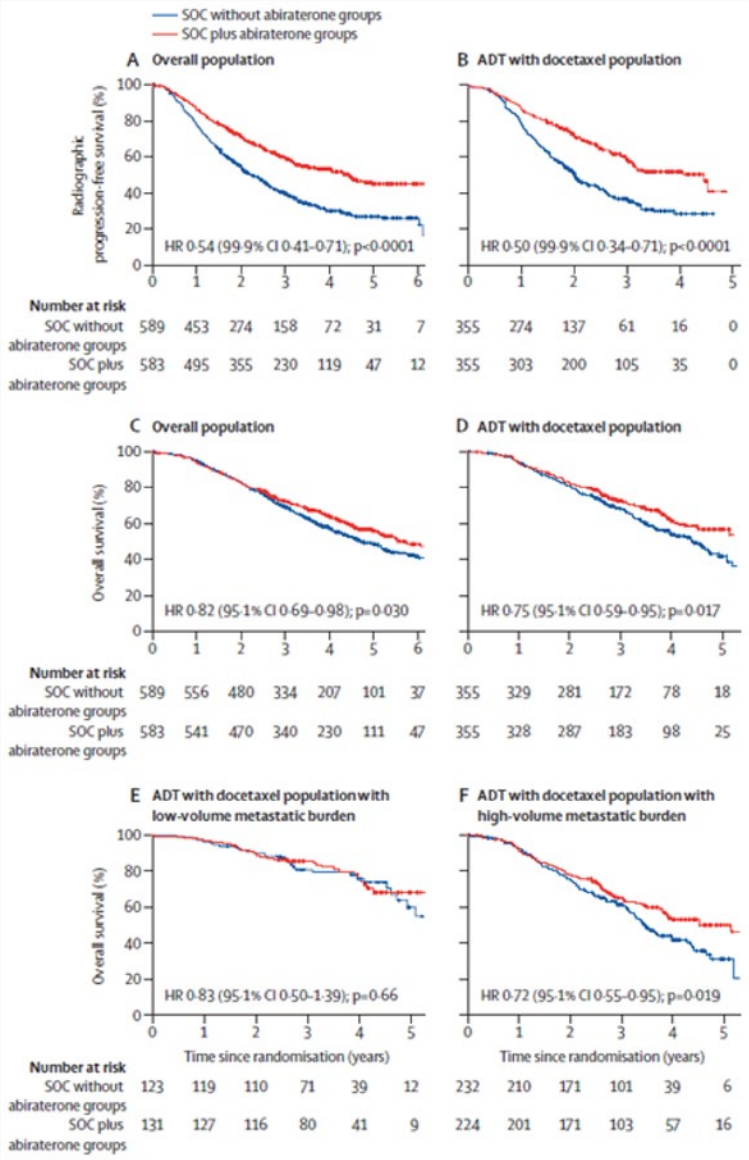
Table 13: Efficacy Outcomes in the ITT Population

Outcome	Patients assessed, n		Median, years		Median difference, years	Hazard ratio	P value
	SOC with abiraterone groups	SOC without abiraterone groups	SOC with abiraterone groups	SOC without abiraterone groups			
Primary outcomes in the overall population							
Overall survival	583	589	5.7	4.7	0.9 (95.1% CI, 0.0 to 2.0)	0.82 (95.1% CI, 0.69 to 0.98)	0.030
rPFS	583	589	4.5	2.2	2.1 (99.9% CI, 0.7 to 2.9)	0.54 (99.9% CI, 0.41 to 0.71)	< 0.0001
Secondary outcomes in the overall population							
CRPC-free survival	583	589	3.8	1.5	2.3 (95% CI, 1.6 to 3.0)	0.40 (95% CI, 0.35 to 0.47)	< 0.0001
Prostate cancer–specific survival	583	589	NR	5.8	NA	0.75 (95% CI, 0.61 to 0.91)	0.0038
Primary outcomes in the ADT with docetaxel population							
Overall survival	355	355	NR	4.4	NA	0.75 (95.1% CI, 0.59 to 0.95)	0.017
rPFS	355	355	4.5	2.0	2.2 (99.9% CI, 0.6 to 2.8)	0.50 (99.9% CI, 0.34 to 0.71)	< 0.0001
Secondary outcomes in the ADT with docetaxel population							
OS in patients with low-volume metastatic burden	131	123	NR	NR	NA	0.83 (95.1% CI, 0.50 to 1.39)	0.66
OS in patients with high-volume metastatic burden	224	232	5.1	3.5	1.1 (95.1% CI, 0.2 to 1.9)	0.72 (95.1% CI, 0.55 to 0.95)	0.019
rPFS in patients with low-volume metastatic burden	129	122	NR	2.7	NA	0.58 (99.9% CI, 0.29 to 1.15)	0.0061
rPFS in patients with high-volume metastatic burden	225	231	4.1	1.6	2.2 (99.9% CI, 0.6 to 3.2)	0.47 (99.9% CI, 0.30 to 0.72)	< 0.0001
CRPC-free survival	355	355	3.2	1.4	2.0 (95% CI, 1.5 to 3.1)	0.38 (95% CI, 0.31 to 0.47)	< 0.0001
Prostate cancer–specific survival	355	355	NR	4.7	NA	0.69 (95% CI, 0.53 to 0.90)	0.0062

ADT = androgen deprivation therapy; CI = confidence interval; CRPC = castration-resistant prostate cancer; ITT = intention to treat; NA = not available; NR = not reached; OS = overall survival; rPFS = radiographic progression-free survival; SOC = standard of care (with or without radiotherapy).

Source: Fizazi et al. (2022).[16]

Figure 4: Kaplan-Meier Estimates of rPFS and OS in the Overall Population and in the ADT with Docetaxel Population in the PEACE-1 Trial

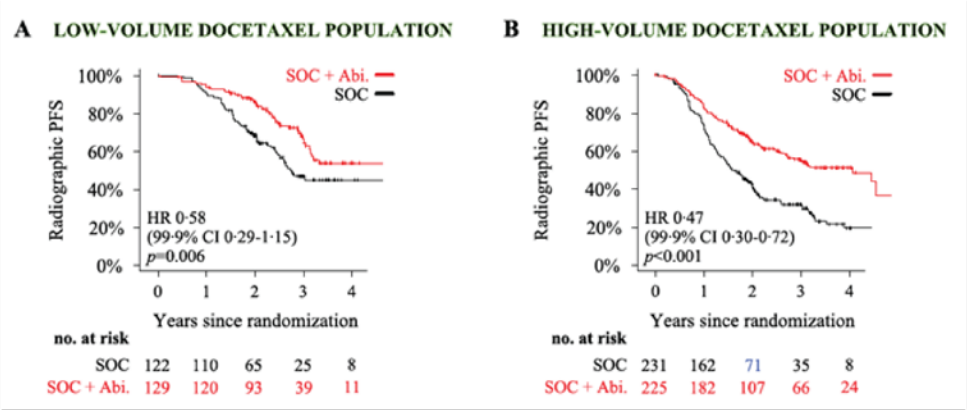


ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; OS = overall survival; rPFS = radiographic progression-free survival; SOC = standard of care (with or without radiotherapy).

Note: Time-to-event curves are presented for rPFS (A) and OS (C) in the overall population, rPFS (B) and OS (D) in the ADT with docetaxel population, and OS in the ADT with docetaxel population in patients with low-volume metastatic burden I and high-volume metastatic burden (F). SOC in the overall population was ADT with or without docetaxel. SOC in the ADT with docetaxel population was ADT with docetaxel.

Source: Fizazi et al. (2022).[16]

Figure 5: Kaplan-Meier Estimates of the rPFS in the ADT + Docetaxel Population in the PEACE-1 trial



Abi = abiraterone; ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; rPFS = radiographic progression-free survival; RT = radiotherapy; SOC = standard of care.

Note: Time-to-event curves are presented for males with low-volume (A) or high-volume (B) disease burden. SOC is ADT with docetaxel with or without RT.

Source: Fizazi et al. (2022).[16]

Time to Castration-Resistant Prostate Cancer

Time to CRPC was not an efficacy outcome in the PEACE-1 trial.

Time to Chemotherapy of Castration-Resistant Prostate Cancer

Time to chemotherapy of CRPC was a secondary efficacy outcome in the PEACE-1 trial but was still under investigation at the time of publication.

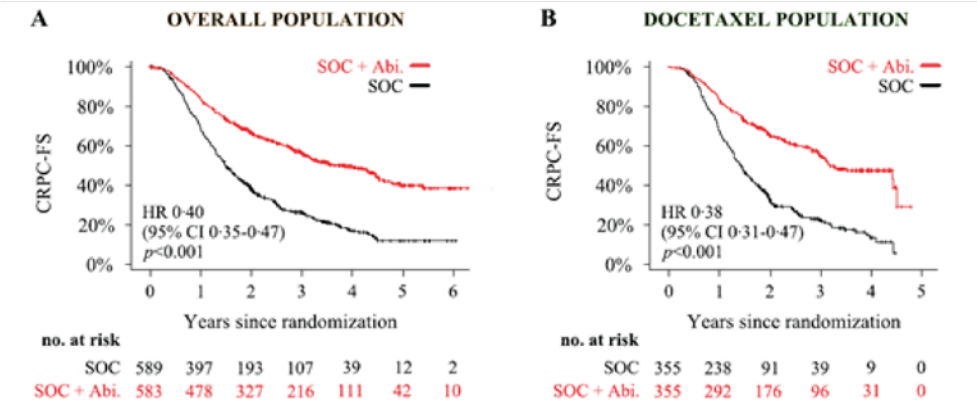
Cancer Symptoms

Time to pain progression was a secondary efficacy outcome in the PEACE-1 trial but was still under investigation at the time of publication.

Castration-Resistant Prostate Cancer-Free Survival

CRPC-free survival was a secondary efficacy outcome in the PEACE-1 trial. This outcome was not part of the statistical hierarchy and results were not adjusted for multiplicity. CRPC-free survival results in the PEACE-1 trial are summarized in Figure 6 and Table 13. In the docetaxel plus ADT population, median CRPC-free survival was 3.2 years (CI not reported) in the abiraterone plus docetaxel plus ADT arm and 1.4 years (CI not reported) in the docetaxel plus ADT arm. The median CRPC-free survival difference was 2.0 years (95% CI, 1.5 years to 3.1 years) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT. The HR for CRPC-free survival was 0.38 (95% CI, 0.31 to 0.47) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT.

Figure 6: Kaplan-Meier Estimates of CRPC-Free Survival in the PEACE-1 trial



Abi = abiraterone; CI = confidence interval; CRPC = castration-resistant prostate cancer; CRPC-FS = castration-resistant prostate cancer-free survival; HR = hazard ratio; SOC = standard of care.

Note: Time-to-event curves are presented for the overall population (A) and the docetaxel population (B).

Source: Fizazi et al. (2022).[16]

Prostate Cancer–Specific Survival

Prostate cancer–specific survival was a secondary efficacy outcome in the PEACE-1 trial. This outcome was not part of the statistical hierarchy and results were not adjusted for multiplicity. Prostate cancer–specific survival results in the PEACE-1 trial are summarized in Figure 7 and Table 13. In the docetaxel plus ADT population, median prostate cancer–specific survival was not reached in the abiraterone plus docetaxel plus ADT arm and was 4.7 years (CI not reported) in the docetaxel plus ADT arm, and thus the median prostate cancer–specific survival difference could not be calculated. The HR for prostate cancer–specific survival was 0.69 (95% CI, 0.53 to 0.90) comparing abiraterone plus docetaxel plus ADT to docetaxel plus ADT.

Serious Genitourinary Event-Free Survival

Serious genitourinary event-free survival was a secondary efficacy outcome in the PEACE-1 trial but was still under investigation at the time of publication.

Objective Response Rate

Objective response rate was not an efficacy outcome in the PEACE-1 trial.

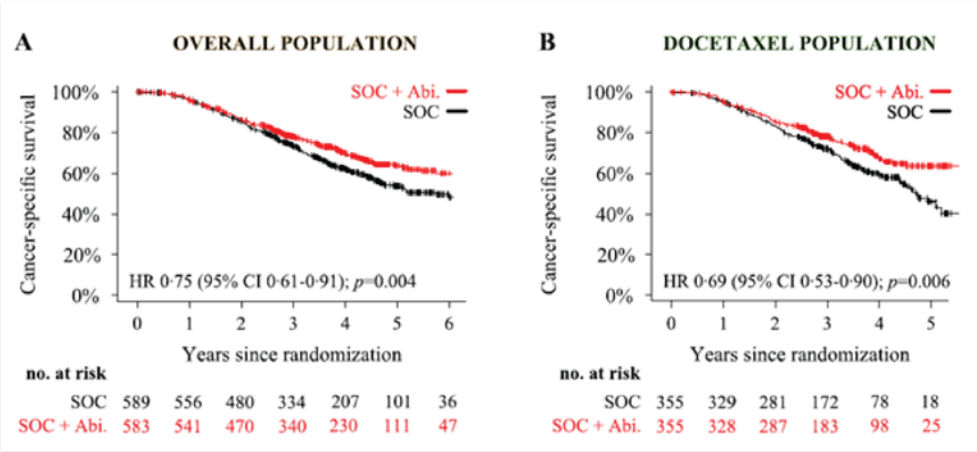
Time to Next Skeletal-Related Event

PSA response rate was a secondary efficacy outcome in the PEACE-1 trial, and was still under investigation at the time of publication.

Time to PSA Progression

Time to PSA progression was not an efficacy outcome in the PEACE-1 trial.

Figure 7: Kaplan-Meier Estimates of Prostate Cancer–Specific Survival in the PEACE-1 trial



Abi = abiraterone; CI = confidence interval; HR = hazard ratio; SOC = standard of care.
Note: Time-to-event curves are presented for the overall population (A) and for the docetaxel population (B).
Source: Fizazi et al. (2022).[16]

PSA Response Rate

PSA response rate was a secondary efficacy outcome in the PEACE-1 trial, and was still under investigation at the time of publication.

PSA Nadir Level

PSA nadir level was not an efficacy outcome in the PEACE-1 trial.

Harms

Only those harms identified in the review protocol are reported below. Refer to Table 14 and Table 15 for detailed harms data.

Adverse Events

All patients in the PEACE-1 trial experienced at least 1 AE during the trial except for 4 patients who received ADT alone.

Severe AEs

In the docetaxel plus ADT population, 217 of 347 patients (62.5%) in the abiraterone plus docetaxel plus ADT arm and 181 of 350 patients (51.7%) in the docetaxel plus ADT arm had severe (grade 3 or higher) AEs. In the ADT population, 149 of 226 patients (65.9%) in the abiraterone plus ADT arm and 97 of 237 patients (40.9%) in the ADT arm had severe AEs.

Frequent severe AEs are described in the Notable Harms section. The most common severe toxicities associated with abiraterone were hypertension and hepatotoxicity, while the most common severe toxicities associated with docetaxel were neutropenia, febrile neutropenia, and peripheral neuropathy.

Serious AEs

Information on SAEs was not provided.

Withdrawals Due to AEs

In the docetaxel plus ADT population, 32 of 347 patients (9.2%) in the abiraterone plus docetaxel plus ADT arm and 1 of 350 patients (0.3%) in the docetaxel plus ADT arm had WDAEs (refer to Exposure to Study Treatments section). In the ADT population, 29 of 226 patients (12.8%) in the abiraterone plus ADT arm and 1 of 237 patients (0.4%) in the ADT arm had WDAEs (refer to Exposure to Study Treatments section).

Mortality

In the docetaxel plus ADT population, 7 of 347 patients (2.0%) in the abiraterone plus docetaxel plus ADT arm and 3 of 350 patients (0.9%) in the docetaxel plus ADT arm had fatal AEs. In the ADT population, 8 of 226 patients (3.5%) in the abiraterone plus ADT arm and 5 of 237 patients (2.1%) in the ADT arm had fatal AEs.

Notable Harms

In the docetaxel plus ADT population, 76 of 347 patients (21.9%) in the abiraterone plus docetaxel plus ADT arm and 45 of 350 patients (12.9%) in the docetaxel plus ADT arm experienced grade 3 or higher hypertension. In the ADT population, 66 of 226 patients (29.2%) in the abiraterone plus ADT arm and 39 of 237 patients (16.5%) in the ADT arm experienced grade 3 or higher hypertension.

In the docetaxel plus ADT population, 20 of 347 patients (5.8%) in the abiraterone plus docetaxel plus ADT arm and 2 of 350 patients (0.6%) in the docetaxel plus ADT arm experienced grade 3 or higher hepatotoxicity. In the ADT population, 14 of 226 patients (6.2%) in the abiraterone plus ADT arm and 3 of 237 patients (1.3%) in the ADT arm experienced grade 3 or higher hepatotoxicity.

In the docetaxel plus ADT population, 17 of 347 patients (4.9%) in the abiraterone plus docetaxel plus ADT arm and 14 of 350 patients (4.0%) in the docetaxel plus ADT arm experienced grade 3 or higher gamma-glutamyl transferase increase. In the ADT population, 6 of 226 patients (2.7%) in the abiraterone plus ADT arm and 4 of 237 patients (1.7%) in the ADT arm experienced grade 3 or higher gamma-glutamyl transferase increase.

In the docetaxel plus ADT population, 15 of 347 patients (4.3%) in the abiraterone plus docetaxel plus ADT arm and 12 of 350 patients (3.4%) in the docetaxel plus ADT arm experienced blood grade 3 or higher blood alkaline phosphatase increase. In the ADT population, 6 of 226 patients (2.7%) in the abiraterone plus ADT arm and 13 of 237 patients (5.5%) in the ADT arm experienced grade 3 or higher blood alkaline phosphatase increase.

In the docetaxel plus ADT population, 34 of 347 patients (9.7%) in the abiraterone plus docetaxel plus ADT arm and 32 of 350 patients (9.1%) in the docetaxel plus ADT arm experienced grade 3 or higher neutropenia. In the ADT population, no patients in the abiraterone plus ADT arm and no patients in the ADT arm experienced blood grade 3 or higher neutropenia.

In the docetaxel plus ADT population, 18 of 347 patients (5.2%) in the abiraterone plus docetaxel plus ADT arm and 19 of 350 patients (5.4%) in the docetaxel plus ADT arm experienced grade 3 or higher febrile

neutropenia. In the ADT population, 2 of 226 patients (0.9%) in the abiraterone plus ADT arm and 1 of 237 patients (0.4%) in the ADT arm experienced grade 3 or higher febrile neutropenia.

In the docetaxel plus ADT population, 4 of 347 patients (1.2%) in the abiraterone plus docetaxel plus ADT arm and 6 of 350 patients (1.7%) in the docetaxel plus ADT arm experienced grade 3 or higher peripheral neuropathy. In the ADT population, 1 of 226 patients (0.4%) in the abiraterone plus ADT arm and no patients in the ADT arm experienced grade 3 or higher peripheral neuropathy.

In the docetaxel plus ADT population, 136 of 347 patients (39.2%) in the abiraterone plus docetaxel plus ADT arm and 119 of 350 patients (34.0%) in the docetaxel plus ADT arm experienced grade 1 or 2 peripheral neuropathy. In the ADT population, 7 of 226 patients (3.1%) in the abiraterone plus ADT arm and 4 of 237 patients (1.7%) in the ADT arm experienced grade 1 or 2 peripheral neuropathy.

Table 14: Adverse Events in the Safety Population

Outcome, n (%)	ADT with docetaxel population		ADT without docetaxel population	
	SOC plus abiraterone groups (with or without radiotherapy) (n = 347)	SOC without abiraterone groups (with or without radiotherapy) (n = 350)	SOC plus abiraterone groups (with or without radiotherapy) (n = 226)	SOC without abiraterone groups (with or without radiotherapy) (n = 237)
Any adverse events	346 (100)	349 (100)	226 (100)	233 (99)
Severe (grade ≥ 3) adverse events	217 (63)	181 (52)	149 (66)	97 (41)
Fatal (grade 5) adverse events	7 (2)	3 (1)	8 (4)	5 (2)
Frequent severe adverse events				
Hypertension	76 (22)	45 (13)	66 (29)	38 (16)
Neutropenia	34 (10)	32 (9)	0	0
Hepatotoxicity	20 (6)	2 (1)	14 (6)	3 (1)
Febrile neutropenia	18 (5)	19 (5)	2 (1)	1 (< 1)
Gamma-glutamyl transferase increase	17 (5)	14 (4)	6 (3)	4 (2)
Erectile dysfunction	7 (2)	5 (1)	12 (5)	13 (5)
Blood alkaline phosphatase increase	15 (4)	12 (3)	6 (3)	13 (5)
Other severe adverse events				
Fatigue	10 (3)	15 (4)	3 (1)	0
Peripheral neuropathy	4 (1)	6 (2)	1 (< 1)	0

ADT = androgen deprivation therapy; SOC = standard of care.

Note: Data are n (%). As the patients were not randomly assigned according to docetaxel prescription, toxicities recorded in the ADT without docetaxel and ADT with docetaxel populations are not directly comparable. Percentages are rounded to the nearest integer. The safety population includes patients who actually received the assigned treatment. Severe adverse events (grade ≥ 3) were considered frequent if they occurred in at least 5% of patients in either group, and are reported in decreasing order of occurrence according to the Medical Dictionary for Regulatory Activities Preferred Term classification.

Source: Fizazi et al. (2022).[16]

Table 15: Expected Frequent Severe Adverse Events[a] – Safety Population

Safety population Expected frequent adverse events, n (%)	Treatment allocation			
	ADT with docetaxel population (SOC = ADT + DXL ± RT)		ADT population (SOC = ADT ± RT)	
	SOC + Abi Arm B+D (n = 347)	SOC Arm A+C (n = 350)	SOC + Abi Arm B+D (n = 226)	SOC Arm A+C (n = 237)
Severe adverse events (grade 3 to 5)				
Hypertension	76 (22)	45 (13)	66 (29)	38 (16)
Neutropenia	34 (10)	32 (9)	0 (0)	0 (0)
Hepatotoxicity	20 (6)	2 (1)	14 (6)	3 (1)
Febrile neutropenia	18 (5)	19 (5)	2 (1)	1 (0)
Gamma-glutamyltransferase increased	17 (5)	14 (4)	6 (3)	4 (2)
Erectile dysfunction	7 (2)	5 (1)	12 (5)	13 (5)
Blood alkaline phosphatase increased	15 (4)	12 (3)	6 (3)	13 (5)
Expected fatigue events				
Grade 3 to 5 events	10 (3)	15 (4)	3 (1)	0 (0)
Grade 1 to 2 events	234 (67)	242 (69)	83 (37)	61 (26)
Expected peripheral neuropathy events				
Grade 3 to 5 events	4 (1)	6 (2)	1 (0)	0 (0)
Grade 1 to 2 events	136 (39)	119 (34)	7 (3)	4 (2)

Abi = abiraterone; ADT = androgen deprivation therapy; DXL = docetaxel; RT = radiotherapy; SOC = standard of care.

Note: Data are n (%). As the patients were not randomly assigned according to docetaxel prescription, toxicities recorded in the ADT without docetaxel and ADT with docetaxel populations are not directly comparable. Percentages are rounded to the nearest integer. The safety population includes patients who actually received the assigned treatment.

[a]Severe adverse events (grade ≥ 3) are reported according to the Medical Dictionary for Regulatory Activities Preferred Term classification. Severe adverse events were considered frequent if they occurred in at least 5% of patients in either group.

Source: Fizazi et al. (2022).[16]

Critical Appraisal

Internal Validity

The PEACE-1 trial (N = 1,173)[16] was an open-label, randomized, phase III study in which males with de novo mCSPC receiving ADT with or without docetaxel could also receive abiraterone and/or radiotherapy in randomized fashion. The study was not designed or reported with regulatory rigour for filing, and the triplet regimen of abiraterone with prednisone or dexamethasone plus docetaxel plus ADT has not been reviewed by Health Canada. Therefore, there is greater uncertainty in the evidence because of the limited ability for critical appraisal.

Randomization and concealment of allocation appeared to be overall successful in balancing baseline demographic and disease characteristics between the study arms. According to the clinical expert CADTH consulted for this review, there were no baseline imbalances of potential prognostic significance that would limit interpretation of the study results; furthermore, losses to follow-up were minimal (approximately 2% to 3%, depending on the study arm) and any resulting selection bias was unlikely to meaningfully impact the study results. The outcomes used in the trial (OS, rPFS, CRPC-free survival, prostate cancer–specific survival) were appropriately defined and commonly used in trials of investigational agents in patients with mCSPC. However, although standardized RECIST version 1.1[17] was used for imaging assessments, imaging was only performed for patients where progression was suspected clinically, and the assignment of rPFS events was performed by investigators who were not blinded to study drug group assignment. Thus, observer bias and information bias may have affected the study results, although the direction of the resulting bias was not clear.

Details of the randomization procedure were limited (a minimization algorithm was used). During the study, no information was provided on protocol deviations or on censoring rules for rPFS. It was evident from the age range of study participants that the inclusion criterion related to age (18 years to 80 years) was violated in some cases. Generally, reasons for rPFS censoring could include no progression at date of last contact, lack of baseline tumour assessments, missed assessments on trial, and initiation of new anticancer therapy. Therefore, potential imbalances in reasons for censoring could not be evaluated along with any resulting biases.

Several statistical issues should be considered when interpreting the results of the PEACE-1 trial. While statistical tests and power were overall appropriate, the primary objective, interventions, and statistical analysis changed over the course of the study. Changes to the study protocol and statistical analysis plan were stated to have been made, without reference to the outcome data collected in the study, but this assumption could not be verified. The original primary objective of evaluating the efficacy of abiraterone plus ADT doublet therapy versus ADT alone in patients with mCSPC was modified to evaluating the efficacy of triplet (abiraterone plus docetaxel plus ADT) versus doublet (docetaxel plus ADT) therapy. Use of docetaxel was initially forbidden, then optional, then required as part of standard of care. In addition, the split of alpha between rPFS (0.001) and OS (0.049) was not explained and may have been selected based on the anticipated relative ease or difficulty in detecting differences in these outcomes. Subgroup analyses were not powered to evaluate individual strata, and for the clinically relevant subgroup analysis by metastatic burden, randomization was stratified by metastatic sites while data were presented for high versus low metastatic burden (not the stratification factor).

Data for several outcomes of interest identified in the CADTH review protocol (HRQoL, time to chemotherapy of CRPC, time to pain progression, serious genitourinary event-free survival, time to next skeletal-related event, and PSA response rate) were not provided in the publication of the PEACE-1 trial. According to the authors, these outcomes were “still under investigation” and the rationale for not presenting these data was unclear. The timeline on which these data will be made available was also unclear.

External Validity

According to the clinical expert CADTH consulted for this review, the PEACE-1 trial participants recruited based on eligibility criteria are likely similar to the patient population who would be candidates for triplet therapy with abiraterone plus docetaxel plus ADT in Canada. The clinical expert did not consider the eligibility criteria related to requirements for public or private insurance and comorbidities as likely to eliminate a substantial number of patients who might be candidates for triplet therapy, despite lack of screening failure rates and reasons for screening failures. Similarly, the clinical expert considered the baseline demographic and disease characteristics in the PEACE-1 trial to be representative of the patients who would be candidates for triplet therapy in Canadian practice. According to the clinical expert consulted by CADTH for this review, there are no major differences in treatment of castration-sensitive prostate cancer in Europe and North America. This contrasted with the industry input received for this review, which suggested that because the study was conducted primarily in France, generalizability to Canada will require further investigation.

There were differing options from stakeholders for this review on generalizability of the study results to subpopulations of males with mCSPC. The clinical expert consulted by CADTH for this review indicated that while the PEACE-1 study population included males with de novo mCSPC, due to their eligibility to receive radiation treatment, there is no reason to expect that some patients treated with local therapy who then had metastases at recurrence would not benefit from treatment. In contrast, industry input suggested that reimbursement should be restricted to males with de novo mCSPC. Similarly, although the clinical expert did not endorse use of triplet therapy for all males with mCSPC, they emphasized that reimbursement should not be restricted by metastatic burden or risk category; industry input suggested that reimbursement should be restricted to patients with high-volume and/or high-risk disease. The clinical expert said that funding recommendations should not be grounded in subgroup analyses that were not used as stratification factors and not powered to detect differences in individual strata (e.g., patients with low-volume disease). Such subgroup analyses should be considered hypothesis generating. The clinical expert relayed that CIs for effect estimates in strata were consistent with the main analysis and, as such, reimbursement should be based on the entire mCSPC population rather than subgroups. In addition, abiraterone is sometimes given with dexamethasone rather than prednisone in a subset of patients, but was not used in the trial; the clinical expert indicated that the study results would nevertheless be generalizable to patients receiving dexamethasone.

Changes to the PEACE-1 study in terms of standard of care (ADT alone, then ADT with or without docetaxel, then ADT plus docetaxel) resulted in heterogeneity of the standard of care used as reference in the study. The protocol amendment that made docetaxel use a requirement may have resulted in the recruitment of patients who, while fit to receive docetaxel, would not have benefited from treatment according to current guidelines (e.g., low-volume and/or low-risk disease). The only comparator in the PEACE-1 trial (docetaxel plus ADT) was not viewed by the clinical expert to reflect the current standard of care for most patients with mCSPC, which would be doublet therapy with an ARPI plus ADT. Other triplet therapies with ARPIs (apalutamide, enzalutamide, darolutamide) plus docetaxel plus ADT have also been studied; the darolutamide triplet has recently been conditionally recommended for funding in Canada. The clinical expert agreed with industry input for this review that the PEACE-1 study did not evaluate the contribution of

docetaxel to the efficacy of the triplet therapy (versus abiraterone plus ADT doublet therapy). It was unclear if requiring a blood test around day 6 of each docetaxel cycle (for early neutropenia detection) aligns with clinical practice in Canada, which could limit generalizability of harms outcomes.

Indirect Evidence

Search and Selection Methods

Given the lack of trials directly comparing abiraterone plus docetaxel plus ADT to relevant comparators in patients with mCSPC (aside from docetaxel plus ADT), this review took into account available indirect evidence. A focused literature search for ITCs dealing with mCSPC was conducted using MEDLINE All (1946 to present) on September 16, 2022. No filters were applied to limit the retrieval by study type, and no limits were placed on publication date or language. A search update was run on March 07, 2023, to capture ITCs published since the original search. The results were screened by 2 reviewers to identify any indirect comparisons fulfilling the PICO framework criteria (i.e., aside from study design) outlined in Table 6.

Included ITCs

The initial literature search identified a total of 40 records. After title and abstract screening, 7 full-text articles were reviewed and 6 NMAs included.[18-23] One ITC was deemed ineligible as all ARPI plus docetaxel plus ADT triplet therapies were pooled together and considered a single treatment node.[46]

Methods of Included Network Meta-Analyses

The systematic reviews contributing to each NMA aimed to include RCTs of patients with mCSPC who were treated with abiraterone plus docetaxel plus ADT or relevant comparators.[18-23] Frequently reported outcomes were OS[18-23] and PFS;[19,21-23] fewer NMAs also reported time to CRPC,[18,19] AEs,[19,22] or serious AEs.[18,19,21] In each systematic review, authors searched multiple electronic databases (at minimum, PubMed, Embase, and another).[18-23] Some also searched relevant conference proceedings and clinical trial registries.[19,20,22,23] The last search for each review occurred between April 2022 and July 2022.

In all systematic reviews, study selection was performed independently in duplicate with discrepancies resolved by consensus; this was also the case for data extraction except for Mandel et al. (2022),[20] where data extraction methods were not reported. The risk of bias of the included RCTs was appraised using version 1.0[18-20,22] or 2.0[21,23] of the Cochrane Risk of Bias tool (at the study level, except for Riaz et al.,[21] which appraised risk of bias at the outcome level). In 5 of the NMAs,[18,19,21-23] each treatment represented a single node, whereas the Mandel et al. (2022)[20] NMA pooled all ARPIs into a single node. The Mandel et al. (2022)[20] and Yanagisawa et al. (2022)[23] studies performed frequentist random effects NMAs; the Jian et al. (2022)[19] and Sathianathen et al. (2022)[22] studies performed Bayesian fixed effects NMAs; the Dou et al. (2023)[18] (Bayesian) and Riaz et al. (2023)[21] (frequentist) meta-analyses chose fixed effects versus random effects models based on I^2 or the sparsity of the networks, respectively. Relevant subgroup analyses included disease volume (3 NMAs[21-23]), metastatic presentation (3 NMAs[21-23]), and performance status (1 NMA[21]). The Riaz et al. (2023)[21] meta-analysis appraised the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for each comparison-outcome.

Results of Included NMAs

Characteristics of Included NMAs

The NMAs overlapped substantially in their included RCTs (refer to Table 16); Riaz et al. (2023)[21] was the most comprehensive in terms of the RCTs included; Dou et al. (2023),[18] Sathianathen et al. (2022),[22] and Yanagisawa et al. (2022)[23] included all of the same trials except for the Southwest Cancer Chemotherapy Study Group (SWOG) 1216,[47] which investigated orteronel plus ADT and nonsteroidal antiandrogens plus ADT (not of interest to the CADTH review). In general, the networks formed by the RCTs in each NMA were sparse with individual comparisons informed by 1 or 2 RCTs. Most evidence was indirect, and as such there were few closed loops. The RCTs were most commonly connected by docetaxel plus ADT and/or ADT alone, as these were the most frequently occurring comparators.

Characteristics of the NMAs and the RCTs contained within them are shown in Table 17. There was some heterogeneity in patient characteristics across the included NMAs, particularly in disease volume and metastatic presentation, when this was reported. Performance status and risk category in the various trials were rarely reported, though the Mandel et al. (2022)[20] study seemed to have a wide variation in risk category according to Gleason score (8 or more versus less than 8). The length of follow-up across the RCTs was highly variable.

Table 16: Primary Study Overlap Across the Included NMAs in the PEACE-1 Trial

Trial name Year	Treatments within trial	Inclusion of trials within NMAs					
		Dou et al. (2023)	Riaz et al. (2023)	Jian et al. (2022)	Mandel et al. (2022)	Sathianathen et al. (2022)	Yanagisawa et al. (2022)
ARASENS 2022[38]	Docetaxel + ADT Darolutamide + docetaxel + ADT	Yes	Yes	Yes	Yes	Yes	Yes
PEACE-1 2022[16]	Docetaxel + ADT Abiraterone + docetaxel + ADT	Yes	Yes	Yes	Yes	Yes	Yes
SWOG 1216 2022[47]	TAK + ADT NSAA + ADT	No	Yes	No	No	No	No
TITAN 2019[48]	Apalutamide + ADT ADT alone	Yes	Yes	Yes	Yes	Yes	Yes
ARCHES 2019[49]	Enzalutamide + ADT ADT alone	Yes	Yes	Yes	Yes	Yes	Yes
ENZAMET 2019[50]	Enzalutamide + ADT NSAA + ADT	Yes	Yes	Yes	Yes	Yes	Yes
LATITUDE 2017[43]	Abiraterone + ADT ADT alone	Yes	Yes	No	No	Yes	Yes

Trial name Year	Treatments within trial	Inclusion of trials within NMAs					
		Dou et al. (2023)	Riaz et al. (2023)	Jian et al. (2022)	Mandel et al. (2022)	Sathianathen et al. (2022)	Yanagisawa et al. (2022)
STAMPEDE 2017[44]	Abiraterone + ADT Docetaxel + ADT ADT alone	Yes[a]	Yes[a]	No	Yes[a]	Yes	Yes[b]
CHAARTED 2015[30]	Docetaxel + ADT ADT alone	Yes	Yes	No	Yes	Yes	Yes
GETUG-AFU1 2013[51]	Docetaxel + ADT ADT alone	Yes	Yes	No	Yes	Yes	Yes

ADT = androgen deprivation therapy; NSAA = nonsteroidal antiandrogen; NMA = network meta-analysis; TAK = orteronel.

[a]Groups C and G included in the analysis.

[b]Groups B, C, E, and G included in the analysis.

Sources: Dou et al. (2023),[18] Riaz et al. (2023),[21] Jian et al. (2022),[19] Mandel et al. (2022),[20] Sathianathen et al. (2022),[22] Yanagisawa et al. (2022).[23]

Table 17: Characteristics of the NMAs and Their Included Trials

NMA author and year	Number of RCTs (number of patients)	Patient characteristics (range)[a]	Relevant comparisons (vs. abiraterone + docetaxel + ADT)	Outcomes presented	Median follow-up (months)
Dou et al. (2023)	9 (11,058)	• Age (median): 63 years to 70 years • Disease volume (% high): 34% to 82% • Presentation (% de novo): NR • Performance status: NR • Risk category: NR	• Abiraterone + ADT • Docetaxel + ADT • Apalutamide + ADT • Enzalutamide + ADT • Darolutamide + docetaxel + ADT	• OS • Time to CRPC • Severe adverse events grade ≥ 3	43 to 73
Riaz et al. (2023)	10 (11,043)	• Age (median): 63 years to 70 years • Disease volume (% high): 43% to 80% • Presentation (% de novo): 67% to 100% • Performance status: NR • Risk category: NR	• Abiraterone + ADT • Docetaxel + ADT • Apalutamide + ADT • Enzalutamide + ADT • Darolutamide + docetaxel + ADT	• OS • PFS • Grade ≥ 3 AEs	43 to 79
Jian et al. (2022)	5 (5,804)	• Age (median): 63 years to 69 years • Disease volume (% high): 62% to 72% • Presentation (% de novo): NR • Performance status (% ECOG performance status of 0): 63% to 75% • Risk category (Gleason ≥ 8): 67% to 82%	Docetaxel + ADT	• OS • PFS • AEs • Grade ≥ 3 AEs • Time to CRPC	NR

NMA author and year	Number of RCTs (number of patients)	Patient characteristics (range)[a]	Relevant comparisons (vs. abiraterone + docetaxel + ADT)	Outcomes presented	Median follow-up (months)
Mandel et al. (2022)	8 (9,702)	• Age (median): 62 years to 70 years • Disease volume (% high): 41% to 82% • Presentation (% de novo): 67% to 100% • Performance status: NR • Risk category (Gleason ≥ 8): 24% to 98%	ARPI + ADT	OS	34 to 68
Sathianathen et al. (2022)	9 (10,065)	• Age (median): NR • Disease volume (% high): 48% to 80% • Presentation (% de novo): 11% to 100% • Performance status: NR • Risk category: NR	Docetaxel + ADT	• OS • PFS	40 to 83
Yanagisawa et al. (2022)	9 (7,679)	• Age (median): 63 years to 70 years • Disease volume (% high): 47% to 82% • Presentation (% de novo): 58% to 100% • Performance status: NR • Risk category: NR	• Docetaxel + ADT • Abiraterone + ADT	• OS • PFS	34 to 84

ADT = androgen deprivation therapy; AE = adverse events; ARPI = androgen receptor pathway inhibitor; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; NMA = network meta-analysis; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; vs. = versus.

[a]Some NMAs presented patient characteristics by treatment group; the data were not combined for presentation in this table.

Sources: Dou et al. (2023),[18] Riaz et al. (2023),[21] Jian et al. (2022),[19] Mandel et al. (2022),[20] Sathianathen et al. (2022),[22] Yanagisawa et al. (2022).[23]

Findings of Included NMAs

Overall Survival

All 6 NMAs reported on the effect of abiraterone plus docetaxel plus ADT versus 1 or more comparators of interest on OS (Table 18).[18-23] The NMAs in the Dou et al. (2023)[18] and Riaz et al. (2023)[21] studies were most comprehensive in the comparisons presented. Across 5 NMAs,[18,19,21-23] abiraterone plus docetaxel plus ADT was consistently favoured over docetaxel plus ADT, although in most cases the CIs or CrIs also included the potential of little-to-no difference between the treatments. Results for the comparisons to abiraterone plus ADT (3 NMAs[18,21,23]), apalutamide plus ADT (2 NMAs[18,21]), enzalutamide plus ADT (2 NMAs[18,21]), ARPI as a group plus ADT (1 NMA[20]), and darolutamide plus docetaxel plus ADT (3 NMAs[18,19,21]) were affected by imprecision, such that either group could be favoured.

Subgroup analyses by metastatic presentation and disease volume for the comparison to docetaxel plus ADT (3 NMAs[21-23]) and darolutamide plus docetaxel plus ADT (1 NMA[21]) showed results consistent with the main analyses. Subgroup analyses by metastatic presentation for comparisons to abiraterone plus ADT (2 NMAs[21,23]) were consistent with the main analyses. In subgroup analyses by disease volume, point estimates favoured abiraterone plus ADT (2 NMAs[21,23]) as well as apalutamide or enzalutamide plus ADT (1 NMA[21]) over abiraterone plus docetaxel plus ADT among those with low-volume disease; however, there was considerable uncertainty in these findings due to wide CIs or CrIs. Findings for high-volume disease were consistent with the main analysis. In 1 NMA,[21] subgroup analyses by performance status were consistent with the main analysis.

Table 18: OS With Abiraterone Plus Docetaxel Plus ADT Versus Relevant Comparators – Relative Effect

Comparator	HR (95% CI or CrI)[a]					
	Dou et al. (2023)	Riaz et al. (2023)[b]	Jian et al. (2022)	Mandel et al. (2022)	Sathianathen et al. (2022)	Yanagisawa et al. (2022)
Docetaxel + ADT	0.75 (0.59 to 0.95)	0.75 (0.59 to 0.95)	0.75 (0.59 to 0.95)	NR	0.70 (0.56 to 0.86)	0.75 (0.58 to 0.97)
Abiraterone + ADT	0.89 (0.66 to 1.20)	0.88 (0.67 to 1.16)	NR	NR	NR	0.81 (0.58 to 1.14)
Apalutamide + ADT	0.89 (0.64 to 1.24)	0.89 (0.64 to 1.23)	NR	NR	NR	NR
Enzalutamide + ADT	0.87 (0.64 to 1.19)	0.87 (0.62 to 1.23)	NR	NR	NR	NR
ARPI + ADT	NR	NR	NR	0.91 (0.69 to 1.21)	NR	NR
Darolutamide + docetaxel + ADT	1.10 (0.82 to 1.48)	1.10 (0.82 to 1.48)	1.11 (0.83 to 1.49)	NR	NR	NR

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; CI = confidence interval; CrI = credible interval; HR = hazard ratio; NR = not reported; OS = overall survival; vs. = versus.

[a]HR < 1 favours abiraterone plus docetaxel plus ADT.

[b]In Riaz et al. (2023),[21] the authors reported the following certainty of evidence for abiraterone plus docetaxel plus ADT: high certainty of benefit vs. docetaxel plus ADT; low certainty of benefit vs. abiraterone plus ADT, apalutamide plus ADT, and enzalutamide plus ADT; low certainty of harm vs. darolutamide plus docetaxel plus ADT.

Sources: Dou et al. (2023),[18] Riaz et al. (2023),[21] Jian et al. (2022),[19] Mandel et al. (2022),[20] Sathianathen et al. (2022),[22] Yanagisawa et al. (2022).[23]

Progression-Free Survival

Four NMAs[19,21-23] reported on the effect of abiraterone plus docetaxel plus ADT versus 1 or more comparators of interest on PFS (Table 19). The NMA by Riaz et al. (2023)[21] was most comprehensive in the comparisons presented. Abiraterone plus docetaxel plus ADT was consistently favoured over docetaxel plus ADT across 4 NMAs[19,21-23] and abiraterone plus ADT across 2 NMAs.[21,23] For the comparison with abiraterone plus ADT, in both cases the CIs or CrIs also included the potential of little-to-no difference between the treatments. Results for the comparisons to apalutamide plus ADT (1 NMA[21]) and enzalutamide plus ADT (1 NMA[21]) were

affected by imprecision, such that either group could be favoured. No NMAs compared abiraterone plus docetaxel plus ADT to darolutamide plus docetaxel plus ADT.

Two NMAs[21,23] performed subgroup analyses by disease volume, with results for the comparisons to abiraterone plus ADT and docetaxel plus ADT that were consistent with the main analysis. In the NMA by Riaz et al. (2023),[21] subgroup analyses for low-volume disease favoured apalutamide plus ADT and enzalutamide plus ADT over abiraterone plus docetaxel plus ADT; however, there was considerable uncertainty in these findings due to wide CIs. Findings for the high-volume population were consistent with the main analysis.

Time to Castration Resistance

Two NMAs[18,19] reported on the effect of abiraterone plus docetaxel plus ADT versus 1 or more comparators of interest on time to castration resistance (Table 20). Abiraterone plus docetaxel plus ADT was favoured over docetaxel plus ADT across the 2 NMAs,[18,19] apalutamide plus ADT in 1 NMA,[18] and enzalutamide plus ADT in 1 NMA.[18] Results for the comparison to darolutamide plus docetaxel plus ADT (2 NMAs[18,19]) was affected by imprecision, such that either group could be favoured. No NMAs compared abiraterone plus docetaxel plus ADT to abiraterone plus ADT and no subgroup analyses were presented.

Other Efficacy Outcomes

None of the included NMAs reported on serious genitourinary event-free survival, cancer symptoms, CRPC-free survival, prostate cancer–specific survival, objective response rate, PSA response rate, or PSA nadir level. Riaz et al. (2023)[21] intended to analyze data for HRQoL, but did not because of the limited available data. Jian et al. (2022)[19] intended to report on time to PSA progression, time to next skeletal-related event, and time to chemotherapy for CRPC; however, data were not available for any comparisons of interest.

Adverse Events

Only the NMA by Jian et al. (2022)[19] reported on overall frequencies of AEs, and the only comparison of interest was to docetaxel plus ADT. Findings of the analysis favoured docetaxel plus ADT (OR = 1.91; 95% CrI, 1.27 to 2.86). No subgroup analyses were presented.

Grade 3 or Higher AEs

Three NMAs[18,19,21] reported on the effect of abiraterone plus docetaxel plus ADT versus 1 or more comparators of interest on grade 3 or higher AEs (Table 21). The NMA by Riaz et al. (2023)[21] was most comprehensive in the comparisons presented. Docetaxel plus ADT was favoured over abiraterone plus docetaxel plus ADT across the 3 NMAs.[18,19,21] The remaining comparisons were reported only in the Riaz et al. (2023).[21] NMA, with abiraterone plus ADT, apalutamide plus ADT, enzalutamide plus ADT, and darolutamide plus docetaxel plus ADT all favoured over abiraterone plus docetaxel plus ADT. The comparison to darolutamide plus docetaxel plus ADT also included the potential for no difference between treatments. No subgroup analyses were presented.

Table 19: Progression-Free Survival With Abiraterone Plus Docetaxel Plus ADT Versus Relevant Comparators – Relative Effect

Comparator	HR (95% CI or CrI)[a]			
	Riaz et al. (2023)[b]	Jian et al. (2022)	Sathianathen et al. (2022)	Yanagisawa et al. (2022)
Docetaxel + ADT	0.50 (0.35 to 0.72)	0.49 (0.39 to 0.61)	0.43 (0.20 to 0.91)	0.50 (0.40 to 0.62)
Abiraterone + ADT	0.61 (0.41 to 0.91)	NR	NR	0.70 (0.53 to 0.93)
Apalutamide + ADT	0.70 (0.45 to 1.08)	NR	NR	NR
Enzalutamide + ADT	0.88 (0.56 to 1.39)	NR	NR	NR

ADT = androgen deprivation therapy; CI = confidence interval; CrI = credible interval; HR = hazard ratio; NR = not reported; vs. = versus.

[a]HR < 1 favours abiraterone plus docetaxel plus ADT.

[b]In Riaz et al. (2023),[21] the authors reported the following certainty of evidence for abiraterone plus docetaxel plus ADT: high certainty of benefit vs. abiraterone plus ADT; moderate certainty of benefit vs. docetaxel plus ADT; low certainty of benefit vs. apalutamide plus ADT and enzalutamide plus ADT.

Sources: Riaz et al. (2023),[21] Jian et al. (2022),[19] Sathianathen et al. (2022),[22] Yanagisawa et al. (2022).[23]

Table 20: Time to Castration Resistance With Abiraterone Plus Docetaxel Plus ADT Versus Relevant Comparators – Relative Effect

Comparator	HR (95% CrI)[a]	
	Dou et al. (2023)	Jian et al. (2022)
Docetaxel + ADT	0.38 (0.34 to 0.42)	0.38 (0.31 to 0.47)
Apalutamide + ADT	0.68 (0.58 to 0.81)	NR
Enzalutamide + ADT	0.59 (0.50 to 0.70)	NR
Darolutamide + Docetaxel + ADT	1.06 (0.93 to 1.20)	1.08 (0.82 to 1.41)

ADT = androgen deprivation therapy; CrI = credible interval; HR = hazard ratio; NR = not reported.

[a]HR < 1 favours abiraterone plus docetaxel plus ADT.

Sources: Dou et al., 2023,[18] Jian et al., 2022.[19]

Table 21: Grade 3 or Higher Adverse Events With Abiraterone Plus Docetaxel Plus ADT Versus Relevant Comparators – Relative Effect

Comparator	OR or RR (95% CI or CrI)[a]		
	Dou et al. (2023)	Riaz et al. (2023)[b]	Jian et al. (2022)
Docetaxel + ADT	1.60 (1.20 to 2.10)	1.22 (1.07 to 1.39)	1.56 (1.15 to 2.11)
Abiraterone + ADT	NR	1.23 (1.04 to 1.47)	NR
Apalutamide + ADT	NR	1.45 (1.18 to 1.78)	NR
Enzalutamide + ADT	NR	1.80 (1.39 to 2.34)	NR
Darolutamide + Docetaxel + ADT	NR	1.16 (1.00 to 1.35)	NR

ADT = androgen deprivation therapy; CI = confidence interval; CrI = credible interval; NR = not reported; OR = odds ratio; RR = risk ratio; vs. = versus.

[a]OR or RR < 1 favours abiraterone plus docetaxel plus ADT.

[b]Results are presented as risk ratios. The authors reported the following certainty of evidence for abiraterone plus docetaxel plus ADT: high certainty of harm vs. abiraterone plus ADT and docetaxel plus ADT; moderate certainty of harm vs. darolutamide plus docetaxel plus ADT, apalutamide plus ADT, and enzalutamide plus ADT.

Sources: Dou et al. (2023),[18] Riaz et al. (2023),[21] Jian et al. (2022).[19]

Notable Harms

One NMA[19] reported on the effect of abiraterone plus docetaxel plus ADT versus docetaxel plus ADT on hypertension, neutropenia, and febrile neutropenia. Docetaxel plus ADT was favoured for hypertension (OR = 1.91; 95% CI, 1.27 to 2.86), but the CIs were wide, which introduced uncertainty for neutropenia (OR = 1.02; 95% CI, 0.62 to 1.65) and febrile neutropenia (OR = 0.82; 95% CI, 0.45 to 1.50).[19] One NMA[23] reported on the effect of abiraterone plus docetaxel plus ADT versus abiraterone plus ADT for febrile neutropenia. In this analysis, abiraterone plus ADT was favoured (OR = 23.91; 95% CI, 6.05 to 94.52).[23] No other notable harms of interest were reported within the included NMAs and no subgroup analyses were presented.

Other Harms Outcomes

WDAEs and deaths due to AEs were not reported within any of the included NMAs.

Critical Appraisal of Included Network Meta-Analyses

Four[19,21-23] of the 6 systematic reviews with NMA were informed by an a priori protocol. Though there was some variation in the comprehensiveness of the search strategies, across the NMAs the methods used to identify eligible RCTs were adequate to minimize the risk of error and bias. Based on the reported information, analysis methods across the NMAs generally appeared appropriate; however, model parameters (i.e., selection of priors, assessment of model fit, convergence) and assessments of consistency and heterogeneity (when relevant) were not always presented. The NMAs largely overlapped in the primary studies included. There was some discordance in the risk of bias appraisals presented; however, according to the authors of the systematic reviews, the included RCTs were at low risk of bias for objective outcomes, whereas there was some concern for bias in subjective outcomes (e.g., PFS, AEs) because several of the RCTs were open-label.

Clinical and methodological heterogeneity was noted in patient population (e.g., the STAMPEDE trial included a subset of patients with high-risk localized prostate cancer), metastatic presentation, disease volume, outcome definitions and ascertainment methods (e.g., PFS), length of follow-up, study design features (e.g., blinded versus open-label), prior treatment with docetaxel, use of subsequent treatments, and potential differences in standard of care due to the 10-year time period across which the included RCTs were published. These sources of heterogeneity challenged the plausibility of the transitivity assumption underlying the NMA. The networks were sparse (several comparisons informed by few trials), and all evidence for the comparisons of interest was indirect (aside from the comparison to docetaxel plus ADT). As a result, several comparison-outcomes were affected by important imprecision that reduced the certainty of the effect estimates; CIs or CrIs often included the potential for no important difference between treatments, or that either treatment could be favoured. Because there were few trials per comparison, where this was planned, formal assessments of the risk of publication bias were not possible. Of note, most of the contributing RCTs were industry-sponsored. Subgroup findings were often informed by post hoc within-trial subgroup analyses without stratification; therefore, prognostic balance in these comparisons may not be ensured.

Across the NMAs, clinically relevant outcomes were considered, including OS, PFS, and AEs. Several important efficacy outcomes that may be of particular relevance to patients (e.g., HRQoL, symptoms, time to skeletal-related event) were either not considered or could not be analyzed due to insufficient data.

Other Relevant Evidence

No other relevant evidence was identified for this review.

Economic Evidence

As this review is part of the CADTH nonsponsored reimbursement review program in which an application filed by a sponsor is absent, CADTH does not have access to an economic model for abiraterone plus docetaxel plus ADT in this clinical condition. As a result, the economic review consists of only a cost comparison for abiraterone plus docetaxel plus ADT compared with appropriate comparators for the treatment of patients with mCSPC.[52]

CADTH Analyses

The comparators presented in Table 22 are deemed appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on the respective product monographs and validated by clinical experts. If discrepancies in dosing between the product monograph and clinical practice were noted, the dose specified by clinical experts was used. As abiraterone does not have a Health Canada indication for mCSPC, dosing was based on the PEACE-1 trial[16] and validated by clinical experts consulted by CADTH for this review. Based on public list prices from the Ontario Drug Benefit Formulary accessed in June 2023, abiraterone 250 mg and 500 mg tablets are priced at $26.03 and $52.06, respectively.[53] Pricing for comparator products was also based on publicly available list prices.

Clinical expert feedback obtained by CADTH indicated that there are 3 distinct treatment options available for patients with mCSPC: ADT monotherapy; a doublet therapy that includes an ARPI (i.e., abiraterone, apalutamide, enzalutamide, and darolutamide) in combination with ADT; or a triplet therapy that includes a taxane (docetaxel) and an ARPI in combination with ADT (note: currently, darolutamide is the only ARPI indicated for triplet therapy). As such, the appropriate comparators for this cost comparison were identified to be ADT monotherapy, abiraterone plus ADT, enzalutamide plus ADT, apalutamide plus ADT, and darolutamide plus docetaxel plus ADT. Results of the cost comparison demonstrate that, over a 28-day cycle, ABI + DOC + ADT ranges from $4,494 to $4,665. At this cost, ABI + DOC + ADT represents an incremental cost compared with doublet therapy (i.e., 28-day costs for ABI + ADT = $3,169 to $3,340; ENZ + ADT = $3,522 to $3,693; APA + ADT = $3,740 to $3,911; DOC + ADT = $1,577 to $1,748), and ADT monotherapy (28-day costs = $252 to $423). In aggregate, the potential incremental 28-day cost of ABI + DOC + ADT ranges from $685 to $4,425. Alternatively, ABI + DOC + ADT represents cost savings from $75 to $441 when compared to DAR + DOC + ADT (28-day costs = $4,752 to $4,923). 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 22. A scenario analysis exploring abiraterone pricing from another alternative jurisdiction is presented in Table 25.

Table 22: CADTH Cost Comparison Table for Abiraterone with Prednisone plus Docetaxel for the Treatment of mCSPC

Treatment	Strength/concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	28-day cost ($)
Abiraterone acetate (generic)	250 mg 500 mg	Tab	26.0313 52.0625	1,000 mg daily	104.13	2,916
Docetaxel (generic)	80 mg/4.0 mL 160 mg/8.0 mL	4 mL vial 8 mL vial	497.0000[a] 990.0000[a]	75 mg/m^2 as a 1-hour IV fusion every 3 weeks for 6 cycles[b]	47.14	1,320
Dexamethasone (generic)	0.5 mg 4 mg	Tab	0.1564 0.6112	8 mg 3 times before docetaxel infusion	0.17	5
Prednisone (generic)	5 mg 50 mg	Tab	0.0220 0.1735	10 mg daily	0.044	1
ADT[c]					9.01 to 15.10	252 to 423
ABI + DOC + ADT					160.49 to 166.58	4,494 to 4,665
Antiandrogen						
Abiraterone acetate (generic)	250 mg 500 mg	Tab	26.0313 52.0625	1,000 mg daily	104.13	2,916
Prednisone (generic)	5 mg 50 mg	Tab	0.0220 0.1735	10 mg daily	0.044	1
ADT[c]					9.01 to 15.10	252 to 423
ABI + ADT					113.18 to 119.27	3,169 to 3,340
Enzalutamide (Xtandi)	40 mg	Cap	29.1954[d]	160 mg daily	116.78	3,270
ADT[c]					9.01 to 15.10	252 to 423
ENZ + ADT					125.79 to 131.88	3,522 to 3,693
Darolutamide (Nubeqa)	300 mg	Tab	28.3440[d]	600 mg twice daily	113.38	3,175
Docetaxel (generic)	80 mg/4.0 mL 160 mg/8.0 mL	4 mL vial 8 mL vial	497.0000[a] 990.0000[a]	75 mg/m^2 as a 1-hour IV fusion every 3 weeks for 6 cycles[b]	47.14	1,320

Treatment	Strength/concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	28-day cost ($)
Dexamethasone (generic)	0.5 mg 4 mg	Tab	0.1564 0.6112	8 mg 3 times before docetaxel infusion	0.17	5
ADT[c]					9.01 to 15.10	252 to 423
DAR + DOC + ADT					169.70 to 175.79	4,752 to 4,923
Androgen synthesis inhibitor						
Apalutamide (Erleada)	60 mg	Tab	31.1400[d]	240 mg daily	124.56	3,488
ADT[c]					9.01 to 15.10	252 to 423
APA + ADT					133.57 to 139.66	3,740 to 3,911
Antineoplastic agent						
Docetaxel (generic)	80 mg/4.0 mL 160 mg/8.0 mL	4 mL vial 8 mL Vial	497.0000[a] 990.0000[a]	75 mg/m^2 as a 1-hour IV fusion every 3 weeks for 6 cycles[b]	47.14	1,320
Dexamethasone (generic)	0.5 mg 4 mg	Tab	0.1564 0.6112	8 mg 3 times before docetaxel infusion	0.17	5
ADT[c]					9.01 to 15.10	252 to 423
DOC + ADT					56.32 to 62.41	1,577 to 1,748

ABI + ADT = abiraterone acetate with prednisone in combination with androgen deprivation therapy; ABI + DOC + ADT = abiraterone acetate with prednisone plus docetaxel in combination with androgen deprivation therapy; ADT = androgen deprivation therapy; APA + ADT = apalutamide in combination with androgen deprivation therapy; Cap = capsule; DAR + DOC + ADT = darolutamide plus docetaxel in combination with androgen deprivation therapy; DOC + ADT = docetaxel in combination with androgen deprivation therapy; ENZ + ADT = enzalutamide in combination with androgen deprivation therapy; mCSPC = metastatic castration-sensitive prostate cancer; Tab = tablet.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2023) unless otherwise indicated, and do not include dispensing fees.[53] All dosing is from respective product monographs, unless otherwise indicated.[34,52,54,55]

Note: In all treatments where docetaxel is used, patients are premedicated with dexamethasone.

[a]Wholesale price reported by IQVIA DeltaPA, June 2023.[56] The 20 mg/mL strength is marketed in Canada for docetaxel (per the Health Canada Drug Product Database);[57] however, CADTH could not obtain a current price for this product from IQVIA.

[b]Docetaxel costs based on an average body surface area assumed to be equal to 1.8 m^2.

[c]CADTH notes that the ADT degarelix (Firmagon) had a significantly more expensive first cycle and a daily cost of $742 and $26.50, respectively. The subsequent 28-day cycle and daily costs are $274 and $9.79, which fall within the range highlighted in Table 22.

[d]Price reported by Ontario Exceptional Access Program (accessed June 2023).[58]

Issues for Consideration

- Abiraterone acetate with prednisone and enzalutamide is undergoing a concurrent nonsponsored reimbursement review by CADTH for the treatment of patients with high-risk nonmetastatic prostate cancer in combination with ADT.[59]
- The list prices for abiraterone vary across jurisdictions. Pricing in Table 22 is based on Ontario list prices,[53] and CADTH noted that some jurisdictions have lower list prices. For example, in Nova Scotia, abiraterone is priced as $7.6563 and $15.3125 per 250 mg tablet and 500 mg tablet, respectively, as of June 1, 2023.[60] The reimbursement of abiraterone for the treatment of mCSPC can lead to increased or decreased treatment acquisition costs, depending on the treatment regimen and the jurisdiction's prices. To highlight this uncertainty, CADTH conducted a scenario analysis exploring abiraterone costs from an alternative jurisdiction (i.e., Nova Scotia) (refer to Table 25).
- The CADTH pan-Canadian Oncology Drug Review Expert Committee (pERC) has previously reviewed abiraterone for mCRPC.[15] pERC issued a recommendation on October 22, 2013, to reimburse with clinical criteria and/or conditions, specifying that abiraterone was not cost-effective at the submitted price.[15] The price submitted by the sponsor for abiraterone for mCRPC ($28.33 per 250 mg tablet) with the earlier review is higher than the current public list prices of generic abiraterone ($26.03 per 250 mg tablet).[53]
- As abiraterone with prednisone plus docetaxel is used as an add-on therapy to ADT, in addition to treatment costs, pharmacy dispensing fees could increase should the regimen be reimbursed by drug plans.
- No cost-effectiveness studies conducted in Canada were identified based on a literature search conducted on June 6, 2023.

Discussion

Summary of Available Evidence

One open-label, randomized, phase III study (PEACE-1, N = 1,173) contributed evidence to this report. This study was designed to evaluate the efficacy and safety of triplet therapy with abiraterone plus docetaxel plus ADT versus docetaxel plus ADT (both with or without radiotherapy) in males with de novo mCSPC. The study participants were adult males with de novo mCSPC, with ECOG performance status of 0 or 1 (or 2 due to bone pain), who were clinically fit to receive docetaxel (once this was allowed via protocol amendment), who had received ADT for no more than 3 months before randomization, and who had received ADT for at least 6 weeks before the first docetaxel dose. Study participants were randomized 1:1:1:1 to receive standard of care (ADT with or without 6 cycles of IV docetaxel), standard of care plus radiotherapy, standard of care plus abiraterone (1,000 mg per day orally), or standard of care plus radiotherapy plus abiraterone. Treatment with ADT and abiraterone was continuous while on study, until disease progression or unacceptable toxicity. The coprimary outcomes were rPFS and OS, while secondary outcomes with available data included CRPC-free survival and prostate cancer–specific survival; other secondary outcomes were not analyzed at the time

of publication. According to the clinical expert CADTH consulted for this review, the eligibility criteria for the PEACE-1 trial (after protocol amendment for docetaxel fitness) and the baseline characteristics of the PEACE-1 study population were broadly representative of patients with mCSPC who would be candidates for this triplet therapy in Canada. Most study participants (78% to 79%) were from France, and the median age was 66 years in both the abiraterone plus docetaxel plus ADT and docetaxel plus ADT arms. Approximately two-thirds had ECOG performance status of 0 or 1, more than 90% had bone and/or visceral metastases, approximately two-thirds had high-volume disease, and more than three-quarters had Gleason scores of 8 to 10.

Indirect evidence was considered given the lack of trials comparing abiraterone plus docetaxel plus ADT directly to relevant comparators in patients with mCSPC, aside from docetaxel plus ADT. Six relevant NMAs were identified and included. The NMAs overlapped substantially in their included RCTs. Comparisons were made with docetaxel plus ADT, various ARPIs plus ADT, and darolutamide plus docetaxel plus ADT. Frequently reported outcomes were OS and PFS; fewer NMAs also reported time to CRPC, AEs, or serious AEs. In some cases, subgroup analyses by disease volume, metastatic presentation, and performance status were available. There was some heterogeneity in patient characteristics across the included NMAs, particularly in disease volume and metastatic presentation, when this was reported. This, and other sources of clinical and methodological heterogeneity challenged the plausibility of the underlying transitivity assumption and resulted in several comparison-outcomes being affected by substantial imprecision.

Interpretation of Results

Efficacy

Direct Evidence

According to the clinical expert CADTH consulted for this review, the PEACE-1 study demonstrated clinically relevant improvements in rPFS (median difference = 2.2 years; 99.9% CI, 0.6 years to 2.8 years; HR = 0.50; 99.9% CI, 0.34 to 0.71; P < 0.0001) and OS (median difference not estimable because it was not yet reached in the abiraterone plus docetaxel plus ADT group; HR = 0.75, 95.1% CI, 0.59 to 0.95; P = 0.017) for the triplet of abiraterone plus docetaxel plus ADT versus the doublet of docetaxel plus ADT. The clinical expert emphasized that the only comparator in the PEACE-1 trial (docetaxel plus ADT) does not reflect the current standard of care for most patients with mCSPC, which would be doublet therapy with an ARPI plus ADT. Other triplet therapies with ARPIs (apalutamide, enzalutamide, darolutamide) plus docetaxel plus ADT have also been studied with the darolutamide triplet, having been recently conditionally recommended for funding in Canada. The clinical expert agreed with industry input for this review that the PEACE-1 study did not evaluate the contribution of docetaxel to the efficacy of the triplet therapy (versus abiraterone plus ADT doublet therapy). In the PEACE-1 trial, efficacy data were not presented for the ADT population and thus descriptive comparisons of OS and rPFS between the triplet and abiraterone plus ADT doublet were not possible. According to the clinical expert, the available data from multiple studies suggest that ARPI plus ADT doublet therapy has similar efficacy to docetaxel plus ADT doublet therapy, but is less toxic; while the relative efficacy of different ARPIs (abiraterone, apalutamide, enzalutamide, darolutamide) as elements of triplet regimens with docetaxel and ADT is not clear.

CADTH received contrasting views on the appropriate population for reimbursement of the triplet therapy under review based on the PEACE-1 study results. The clinical expert consulted for this review indicated that although the study population was restricted to those with de novo mCSPC, some males who had previously received local therapy for prostate cancer and then had metastases could also be expected to benefit from triplet therapy. In contrast, industry input suggested that reimbursement should be restricted to males with de novo mCSPC (the study population). Similarly, while the clinical expert emphasized that reimbursement should not be restricted by metastatic burden or risk category, industry input suggested that reimbursement should be restricted to patients with bone and/or visceral metastases (because more than 90% of the PEACE-1 study population had these), high-volume disease (because descriptive subgroup analyses more clearly suggested benefit in these patients), and/or high-risk disease (because current guidelines recommend use of docetaxel in these patients). Note that subgroup analyses were not powered to assess difference in efficacy between strata, and patients with low-volume disease made up approximately one-third of the study population.

Indirect Evidence

Similar to the findings of the PEACE-1 trial, the included NMAs reported that abiraterone plus docetaxel plus ADT was consistently favoured over docetaxel plus ADT for OS, PFS, and time to castration resistance, although in most cases the CIs or CrIs for OS also included the potential of little-to-no difference between the treatments. The findings related to efficacy outcomes for comparisons to abiraterone plus ADT, apalutamide plus ADT, enzalutamide plus ADT, and darolutamide plus docetaxel plus ADT were inconsistent and often affected by substantial imprecision. Additional uncertainty was introduced due to several sources of clinical and methodological heterogeneity, which challenged the plausibility of underlying transitivity assumption of the NMAs. Other outcomes of importance to patients (e.g., HRQoL, symptoms, time to skeletal-related event) were either not considered or could not be analyzed due to insufficient data.

Harms

Direct Evidence

Safety data from the PEACE-1 trial were reported in limited detail. The available data suggested that the most common severe (grade 3 or higher) toxicities associated with abiraterone were hypertension (22% to 29% of abiraterone-treated patients versus 13% to 17% of non-abiraterone-treated patients) and hepatotoxicity (6% of abiraterone-treated patients versus 1% of non-abiraterone-treated patients), while the most common severe toxicities associated with docetaxel were neutropenia (approximately 10% of docetaxel-treated patients versus no events in non-docetaxel-treated patients), febrile neutropenia (approximately 5% of docetaxel-treated patients versus less than 1% of non-docetaxel-treated patients), and peripheral neuropathy (1% to 2% of docetaxel-treated patients versus less than 1% of non-docetaxel-treated patients). Grade 1 or 2 peripheral neuropathy was more common in patients receiving docetaxel (34% to 39% of docetaxel-treated patients versus 2% to 3% of non-docetaxel-treated patients). Toxicities associated with abiraterone led to treatment discontinuation more frequently (9% to 13% of abiraterone-treated patients) than in non-abiraterone-treated patients (0.3% to 0.4%).

As for efficacy outcomes, the PEACE-1 study did not rigorously evaluate the contribution of docetaxel to the safety of the triplet therapy (triplet versus abiraterone plus ADT doublet therapy), either because docetaxel use was forbidden or because it was required for most patients in the trial. The clinical expert CADTH consulted for this review said that care must be taken to avoid misinterpreting the safety data from the PEACE-1 trial, as the lack of relevant comparators with lower toxicity could lead to a perception of under-reported toxicity of the triplet regimen. The clinical expert explained that the most common grade 3 or higher toxicities are asymptomatic (e.g., hypertension, hypokalemia, transaminitis), treatable without dose reduction, and laboratory based, and thus easily documented; by contrast, the grade 3 or higher toxicities of other ARPIs are symptomatic, often require dose reduction, and are more subject to reporting bias. For this reason, the clinical expert expected that abiraterone would be better tolerated than other ARPIs, especially in older patients.

Indirect Evidence

NMA results suggested a greater risk AEs with abiraterone plus docetaxel plus ADT compared to docetaxel plus ADT. In addition, risk of grade 3 or higher AEs was increased with abiraterone plus docetaxel plus ADT relative to abiraterone plus ADT, docetaxel plus ADT, apalutamide plus ADT, enzalutamide plus ADT, and darolutamide plus docetaxel plus ADT. Relative to docetaxel plus ADT, abiraterone plus docetaxel plus ADT demonstrated a greater risk greater risk of hypertension; estimates for neutropenia and febrile neutropenia were affected by uncertainty due to wide CIs. The risk of febrile neutropenia was increased with abiraterone plus docetaxel plus ADT compared to abiraterone plus ADT. Uncertainty was introduced due to the indirect nature of most estimates (aside from the comparison to docetaxel plus ADT) and several sources of clinical and methodological heterogeneity, which challenged the underlying transitivity assumption of the NMAs.

Cost

Based on publicly available list prices, abiraterone with prednisone plus docetaxel in combination with ADT (ABI + DOC + ADT) is expected to have a 28-day cost of between $4,494 and $4,665 per patient depending on the ADT prescribed. The 28-day cost of abiraterone plus docetaxel plus ADT is higher than ADT monotherapy (incremental cost ranging from $4,071 to $4,413 per patient), and doublet therapies (i.e., incremental costs for ABI + ADT = $1,154 to $1,496; APA + ADT = $583 to $925; and ENZ + ADT = $801 to $1,143 per patient). Recently, the triplet of darolutamide plus docetaxel in combination with ADT (DAR + DOC + ADT) received a positive recommendation from CADTH;[24] at the submitted price for darolutamide, darolutamide plus docetaxel plus ADT is expected to have a slightly greater 28-day cost than abiraterone plus docetaxel plus ADT (incremental cost ranging from $87 to $429 per patient). As the current standard-of-care treatment for mCSPC patients is ADT monotherapy, or an ARPI in combination with ADT, the addition of docetaxel to the abiraterone plus ADT doublet will be more expensive than current standard of care ($697 to $4,403). These incremental costs or savings are based on publicly available list prices from Ontario and may not reflect actual prices paid by public drug plans in Canada. These findings were observed to be sensitive to the price of abiraterone. In a scenario analysis that employed alternative abiraterone drug pricing from Nova Scotia, abiraterone plus docetaxel plus ADT became less expensive than the doublet therapies of apalutamide plus ADT and enzalutamide plus ADT (i.e., incremental 28-day cost savings for APA + ADT = $1,132 to 1,474; ENZ + ADT = $914 to $1,256).

Conclusions

Evidence from the PEACE-1 study suggested that, compared with a docetaxel plus ADT doublet, the triplet regimen of abiraterone with prednisone plus docetaxel plus ADT was associated with potentially clinically meaningful prolongation of OS and rPFS among males with de novo mCSPC. The study provided no evidence regarding the comparative efficacy of the triplet under review versus the current standard of care in most patients (ARPI plus ADT doublets) or versus other triplet regimens (e.g., darolutamide plus docetaxel plus ADT). Indirect evidence (6 ITCs) was consistent with the trial evidence for the comparison of the triplet under review versus docetaxel plus ADT doublet therapy. The indirect evidence also suggested a potential advantage of the triplet under review versus abiraterone plus ADT doublet for PFS and versus apalutamide plus ADT and enzalutamide plus ADT doublets for time to castration resistance. Overall, the indirect evidence regarding the comparative efficacy of the triplet under review versus ARPI plus ADT doublets or a darolutamide plus docetaxel plus ADT triplet was associated with uncertainty due to limited assessment of ITC assumptions, risk of bias issues, and a lack of head-to-head trials in patients with mCSPC. Evidence from the PEACE-1 study suggested that the main severe (grade 3 or higher) toxicities associated with abiraterone were hypertension and hepatotoxicity, while the main severe toxicities associated with docetaxel were neutropenia, febrile neutropenia, and peripheral neuropathy. The indirect evidence regarding harms was consistent in suggesting greater risk of grade 3 or higher toxicities with the abiraterone plus docetaxel plus ADT triplet compared with either abiraterone plus ADT or docetaxel plus ADT doublets and other ARPI plus ADT doublets (e.g., apalutamide, enzalutamide). Together, these results were partially aligned with some outcomes identified as important to patients with mCSPC (prolonged survival) but alignment with other outcomes (maintained HRQoL, convenient administration, limited side effects) was less clear.

As a cost-effectiveness analysis was not submitted, the cost-effectiveness of abiraterone plus docetaxel plus ADT in comparison with the appropriate comparators for the treatment of mCSPC could not be determined. As the current standard of care is ADT monotherapy, or an ARPI or taxane as an add-on therapy to ADT (doublet therapy), results of the cost comparison demonstrate that the reimbursement of abiraterone plus docetaxel plus ADT is expected to increase overall treatment costs (incremental costs from $697 to $4,403 per patient per 28-day period) based on Ontario list prices. These findings were found to be sensitive to the price of abiraterone. In a scenario analysis using the list price of abiraterone from Nova Scotia, the results differed in that abiraterone plus docetaxel plus ADT was found to be less expensive than apalutamide plus ADT and enzalutamide plus ADT. In both analyses, abiraterone plus docetaxel plus ADT was always more expensive than ADT monotherapy and abiraterone plus ADT, but always less expensive than darolutamide plus docetaxel plus ADT. Other costs such as administration costs were not considered as part of the cost comparison. To adequately consider this alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of this treatment compared with all current standard-of-care treatments would be required.

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52. APO-Abiraterone (abiraterone acetate): 250 mg and 500 mg film-coated oral tablets [product monograph]. Toronto (ON): Apotex Inc; 2021 Apr 01: https://pdf.hres.ca/dpd_pm/00060444.PDF. Accessed 2022 Dec 15.
53. Ontario Ministry of Health, Ontario Ministry of Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2022; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2022 Sept 15.
54. Docetaxel Injection (docetaxel): 10 mg/ mL one-vial formulation as 20 mg/2 mL, 80 mg/8 mL, or 160 mg/16 mL solution for intravenous infusion [product monograph]. Boucherville (QC): Sandoz Canada Inc.; 2020 Nov 17: https://pdf.hres.ca/dpd_pm/00058887.PDF. Accessed 2022 Dec 15.
55. Xtandi (enzalutamide capsules): 40 mg oral capsules [product monograph]. Markham (ON): Astellas Pharma Canada, Inc.; 2022 Jan 24: https://pdf.hres.ca/dpd_pm/00064474.PDF. Accessed 2022 Dec 15.
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61. Eligard (leuprolide acetate for injection): 7.5 mg (1-Month), 22.5 mg (3-Month), and 30 mg (4-Month), powder for solution, subcutaneous injection for sustained release [product monograph] and Eligard (leuprolide acetate for injectable suspension): 45 mg (6-Month) powder for suspension, for subcutaneous injection for sustained release [product monograph]. Oakville (ON): Innomar Strategies Inc.; 2022 Oct 31: https://pdf.hres.ca/dpd_pm/00068018.PDF. Accessed 2022 Dec 15.

62. Lupron (leuprolide acetate injection): 5 mg/mL sterile solution for subcutaneous injection [product monograph] and Lupron Depot (leuprolide acetate for depot suspension): 3.75 mg/syringe (1-Month slow release), 7.5 mg/syringe (1-Month slow release), 11.25 mg/syringe (3-Month slow release), 22.5 mg/syringe (3-Month slow release), or 30 mg/syringe (4-Month slow release), pre-filled dual-chamber syringe containing sterile lyophilized microspheres for intramuscular injection [product monograph]. St-Laurent (QC): AbbVie Corporation; 2021 Nov 18: https://pdf.hres.ca/dpd_pm/00063626.PDF. Accessed 2022 Dec 15.

63. Zeulide Depot (leuprolide acetate for depot suspension): 3.75 mg (1-Month) and 22.5 mg (3-Month), lyophilized powder (suspension after reconstitution with diluent) for intramuscular injection [product monograph]. Mississauga (ON): Verity Pharmaceuticals Inc.; 2021 Aug 03: https://pdf.hres.ca/dpd_pm/00062368.PDF. Accessed 2022 Dec 15.

64. Trelstar (triptorelin for injectable suspension): 3.75 mg per vial (1 month sustained-release formulation), 11.25 mg per vial (3 month sustained-release formulation), or 22.5 mg (6 month sustained-release formulation), powder for intramuscular injection [product monograph]. Montreal (QC): Knight Therapeutics, Inc; 2022: https://pdf.hres.ca/dpd_pm/00067340.PDF. Accessed 2022 Dec 15.

Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: September 19, 2022

Alerts: Biweekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits:

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

Table 23: 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
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.dq	Candidate term word (Embase)
.pt	Publication type

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

Multi-Database Strategy

1. Abiraterone Acetate/
2. (abretone* or abiraterone* or abiratas* or abirapro* or zaitiga* or zaytiga* or CB 7598 or CB7598 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* or EM5OCB9YJ6 or G819A456D0).ti,ab,kf,ot,hw,nm,rn
3. or/1-2
4. Prednisone/
5. (prednicen* or prednico* or prednidib* or prednilonga or prednison or prednisone or prednisona or prednisonum or prednitone or prednizon or Apo-Prednisone* or ApoPrednisone* or adasone* or ancortone* or biocortone* or cartancyl* or colisone* or cortan* or cortidelt* or cortiprex* or cotone* or cutason* or dacorten* or dacortin* or decort* or de-cort* or dekortin* or delitisone* or dellacort* or delta-cort* or deltacort* or delta-dome* or deltadome* or delta-e or deltae or delta-prenovis* or deltaprenovis* or deltasone* or deltison* or deltra or dehydrocortison* or di-adreson* or diadreson* or drazone or econosone* or encorton* or enkorto* or fernisone* or fiasone* or hostacortin* or incocortyl* or in-sone* or insone* or juvason* or kortancyl* or liquid Pred* or lisacort* or lodotra* or lodtra* or me-korti* or mekorti* or meprison* or metacort* or meticort* or nisona* or nizon* or novoprednison* or nurison* or orisane* or orasone* or panafcort* or panasol* or paracort* or parmenison* or pehacort* or precort* or predeltin* or predniment* or predno* or preson* or pronison* or pronizon* or pulmison* or rayos* or rectodelt* or servison* or sone* or steerometz* or sterapred* or supercortil or ultracorten* or urtilon* or winpred* or wojtab* or AI3-52939 or AI352939 or CCRIS-2646 or CCRIS2646 or EINECS 200-160-3 or EINECS 2001603 or EINECS200-160-3 or EINECS2001603 or HSDB-3168 or HSDB-3168 or nsc-10023 or nsc10023 or orb-101 or orb101 or U-6020 or U6020 or VB0R961HZT).ti,ab,kf,ot,hw,nm,rn
6. exp dexamethasone/
7. (ozurdex* or dexamethason* or dexametason* or hexadecadrol* or decameth or decaspray* or dexason* or dexpak* or maxidex* or millicorten* or oradexon* or decaject* or hexadrol* or aeroseb-D or aeroseb-dex* or anaflogistico* or aphtasolon* or auxiron* or azium* or bisu DS or calonat* or corsone* or cortisumman* or decacortin* or decaderm* or decadron* or decagel* or decalix* or decasone* or dectancyl* or dekacort* or deltafluoren* or dergramin* or desadrene* or desametasone* or desamethasone* or desameton* or deseronil* or dex-ide or dexa mamallet* or dexa-cortidelt* or dexa-cortisyl* or dexa-scheroson* or dexa-sine* or dexacort* or dexacortal* or dexacortin* or dexadeltone* or dexafarma* or dexalona* or dexameth* or dexapolcort* or dexapos* or dexaprol* or dexinolon* or dexinoral* or dexone* or dextelan* or dezone* or dinormon* or

fluormethylprednisolon* or fluormone* or fluorocort* or fortecortin* or gammacorten* or HL-dex* or isopto-dex* or lokalison F or loverine* or luxazone* or mediamethasone* or methylfluorprednisolone* or mexidex* or mymethasone* or ocu-trol or pet derm III or policort* or prednisolon F or prednisolone F or spoloven* or sunia Sol D or superprednol* or turbinaire* or visumetazone* or adrecort* or adrenocot* or aeroseb dex* or aflucoson* or aflucosone* or alfalyl* or arcodexan* or artrosone* or bidexol* or calonat* or cebedex* or colofoam* or corsona* or cortastat* or cortidex* or cortidrona* or cortidrone* or dacortina fuerte* or dacortine fuerte* or dalalone* or danasone* or de-sone la or decadeltosona* or decadeltosone* or decadion* or decadran* or decaesadril* or decamethasone* or decasterolone* or decdan* or decilone* or decofluor* or delladec* or deronil* or desacort* or desalark* or desigdron* or dexa cortisyl* or dexa dabrosan* or dexa korti* or dexa scherosan* or dexa scherozon* or dexa-p or dexacen 4 or dexachel* or dexacorten* or dexacortisyl* or dexadabroson* or dexadecadrol* or dexadrol* or dexagel* or dexagel* or dexagen* or dexahelvacort* or dexakorti* or dexalien* or dexalocal* or dexame* or dexamecortin* or dexameson* or dexamethazon* or dexamethonium* or dexamonozon* or dexan* or dexapot* or dexascheroson* or dexascherozon* or dexionil* or dexmethsone* or dexona* or dextrasone* or dezone* or dibasona* or dexamethasone* or esacortene* or exadion* or firmalone* or fluormethyl prednisolone* or fluorodelta* or fluoromethylprednisolone* or grosodexon* or hexadecadiol* or hexadiol* or isnacort* or isopto dex* or isopto maxidex* or isoptodex* or isoptomaxidex* or marvidione* or megacortin* or mephameson* or metasolon* or methazon ion* or methazone ion* or methazonion* or metisone lafi* or mexasone* or millicortenol* or neoforderx* or neofordex* or nisomethasona* or novocort* or oftan-dexa* or opticorten* or opticortinol* or oradexan* or orgadrone* or pidexon* or posurdex* or predni f tablinen* or predni-f or prednisolone f or prodexon* or sanamethasone* or santenson* or santeson* or sawasone* or solurex* or sterasone* or thilodexine* or triamcimetil* or vexamet* or visumethazone* or tobradex* or maxitrol* or AI3-50934 or AI350934 or CCRIS 7067 or CCRIS7067 or DXMS or EINECS 200-003-9 or EINECS 2000039 or EINECS200-003-9 or EINECS2000039 or HSDB 3053 or HSDB3053 or MK 125 or MK125 or NSC 34521 or NSC34521 or 7S5I7G3JQL).ti,ab,kf,ot,hw,rn,nm

8. or/4-7
9. Docetaxel/
10. (docetaxel* or docetaxol* or taxoltere* or taxotere* or axtere* or daxotel* or dexotel* or docefrez* or oncodocel* or taxanit* or taxespira* or taxoter* or texot* or RP-56976 or RP56976 or NSC-628503 or NSC628503 or NSC-759850 or NSC 759850 or bind-014 or “bind 014” or bs-102 or bs102 or crix-301 or crix301 or lit-976 or lit976 or xrp-6976 or xrp6976 or sid-530 or sid530 or ckd-810 or ckd810 or 699121PHCA or 15H5577CQD).ti,ab,kf,ot,hw,nm,rn
11. exp chemoradiotherapy/ or exp chemotherapy, adjuvant/ or consolidation chemotherapy/ or induction chemotherapy/ or remission induction/
12. (chemotherap* or chemohormon* or chemoradiotherap* or radiochemotherap*).ti,ab,kf
13. (adjuvant drug adj3 therap*).ti,ab,kf
14. or/9-13

15. 3 and 8 and 14
16. 15 use medall
17. *abiraterone acetate/ or *abiraterone/
18. (abretone* or abiraterone* or abiratas* or abirapro* or zaitiga* or zaytiga* or CB 7598 or CB7598 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
19. or/17-18
20. *prednisone/
21. (prednicen* or prednico* or prednidib* or prednilonga or prednison or prednisone or prednisona or prednisonum or prednitone or prednizon or Apo-Prednisone* or ApoPrednisone* or adasone* or ancortone* or biocortone* or cartancyl* or colisone* or cortan* or cortidelt* or cortiprex* or cotone* or cutason* or dacorten* or dacortin* or decort* or de-cort* or dekortin* or delitisone* or dellacort* or delta-cort* or deltacort* or delta-dome* or deltadome* or delta-e or deltae or delta-prenovis* or deltaprenovis* or deltasone* or deltison* or deltra or dehydrocortison* or di-adreson* or diadreson* or drazone or econosone* or encorton* or enkorto* or fernisone* or fiasone* or hostacortin* or incocortyl* or in-sone* or insone* or juvason* or kortancyl* or liquid Pred* or lisacort* or lodotra* or lodtra* or me-korti* or mekorti* or meprison* or metacort* or meticort* or nisona* or nizon* or novoprednison* or nurison* or orisane* or orasone* or panafcort* or panasol* or paracort* or parmenison* or pehacort* or precort* or predeltin* or predniment* or predno* or preson* or pronison* or pronizon* or pulmison* or rayos* or rectodelt* or servison* or sone* or steerometz* or sterapred* or supercortil or ultracorten* or urtilon* or winpred* or wojtab* or AI3-52939 or AI352939 or CCRIS-2646 or CCRIS2646 or EINECS 200-160-3 or EINECS 2001603 or EINECS200-160-3 or EINECS2001603 or HSDB-3168 or HSDB-3168 or nsc-10023 or nsc10023 or orb-101 or orb101 or U-6020 or U6020 or VB0R961HZT).ti,ab,kf,dq
22. *Dexamethasone/
23. (ozurdex* or dexamethason* or dexametason* or hexadecadrol* or decameth or decaspray* or dexason* or dexpak* or maxidex* or millicorten* or oradexon* or decaject* or hexadrol* or aeroseb-D or aeroseb-dex* or anaflogistico* or aphtasolon* or auxiron* or azium* or bisu DS or calonat* or corsone* or cortisumman* or decacortin* or decaderm* or decadron* or decagel* or decalix* or decasone* or dectancyl* or dekacort* or deltafluoren* or dergramin* or desadrene* or desametasone* or desamethasone* or desameton* or deseronil* or dex-ide or dexa mamallet* or dexa-cortidelt* or dexa-cortisyl* or dexa-scheroson* or dexa-sine* or dexacort* or dexacortal* or dexacortin* or dexadeltone* or dexafarma* or dexalona* or dexameth* or dexapolcort* or dexapos* or dexaprol* or dexinolon* or dexinoral* or dexone* or dextelan* or dezone* or dinormon* or fluormethylprednisolon* or fluormone* or fluorocort* or fortecortin* or gammacorten* or HL-dex* or isopto-dex* or lokalison F or loverine* or luxazone* or mediamethasone* or methylfluorprednisolone* or mexidex* or mymethasone* or ocu-trol or pet derm III or policort* or prednisolon F or prednisolone F or spoloven* or sunia Sol D or superprednol* or turbinaire* or visumetazone* or adrecort* or

adrenocot* or aeroseb dex* or aflucoson* or aflucosone* or alfalyl* or arcodexan* or artrosone* or bidexol* or calonat* or cebedex* or colofoam* or corsona* or cortastat* or cortidex* or cortidrona* or cortidrone* or dacortina fuerte* or dacortine fuerte* or dalalone* or danasone* or de-sone la or decadeltosona* or decadeltosone* or decadion* or decadran* or decaesadril* or decamethasone* or decasterolone* or decdan* or decilone* or decofluor* or delladec* or deronil* or desacort* or desalark* or desigdron* or dexa cortisyl* or dexa dabrosan* or dexa korti* or dexa scherosan* or dexa scherozon* or dexa-p or dexacen 4 or dexachel* or dexacorten* or dexacortisyl* or dexadabroson* or dexadecadrol* or dexadrol* or dexagel* or dexagel* or dexagen* or dexahelvacort* or dexakorti* or dexalien* or dexalocal* or dexame* or dexamecortin* or dexameson* or dexamethazon* or dexamethonium* or dexamonozon* or dexan* or dexapot* or dexascheroson* or dexascherozon* or dexionil* or dexmethsone* or dexona* or dextrasone* or dezone* or dibasona* or dexamethasone* or esacortene* or exadion* or firmalone* or fluormethyl prednisolone* or fluorodelta* or fluoromethylprednisolone* or grosodexon* or hexadecadiol* or hexadiol* or isnacort* or isopto dex* or isopto maxidex* or isoptodex* or isoptomaxidex* or marvidione* or megacortin* or mephameson* or metasolon* or methazon ion* or methazone ion* or methazonion* or metisone lafi* or mexasone* or millicortenol* or neoforderx* or neofordex* or nisomethasona* or novocort* or oftan-dexa* or opticorten* or opticortinol* or oradexan* or orgadrone* or pidexon* or posurdex* or predni f tablinen* or predni-f or prednisolone f or prodexon* or sanamethasone* or santenson* or santeson* or sawasone* or solurex* or sterasone* or thilodexine* or triamcimetil* or vexamet* or visumethazone* or tobradex* or maxitrol* or AI3-50934 or AI350934 or CCRIS 7067 or CCRIS7067 or DXMS or EINECS 200-003-9 or EINECS 2000039 or EINECS200-003-9 or EINECS2000039 or HSDB 3053 or HSDB3053 or MK 125 or MK125 or NSC 34521 or NSC34521 or 7S5I7G3JQL).ti,ab,kf,dq

24. or/20-23
25. *docetaxel/
26. (docetaxel* or docetaxol* or taxoltere* or taxotere* or axtere* or daxotel* or dexotel* or docefrez* or oncodocel* or taxanit* or taxespira* or taxoter* or texot* or RP-56976 or RP56976 or NSC-628503 or NSC628503 or NSC-759850 or NSC 759850 or bind-014 or “bind 014” or bs-102 or bs102 or crix-301 or crix301 or lit-976 or lit976 or xrp-6976 or xrp6976 or sid-530 or sid530 or ckd-810 or ckd810 or 699121PHCA or 15H5577CQD).ti,ab,kf,dq
27. exp *chemotherapy/ or exp *cancer chemotherapy/ or exp *combination chemotherapy/
28. (chemotherap* or chemohormon* or chemoradiotherap* or radiochemotherap*).ti,ab,kf,dq
29. (adjuvant drug adj3 therap*).ti,ab,kf,dq
30. or/25-29
31. 19 and 24 and 30
32. 31 use oemezd
33. 32 not (conference abstract or conference review).pt
34. 16 or 33
35. remove duplicates from 34

Clinical Trials Registries

ClinicalTrials.gov

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

[Search -- abiraterone AND (prednisone OR dexamethasone) AND docetaxel | Prostate Cancer]

WHO ICTRP

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

[Search terms -- abiraterone AND (prednisone OR dexamethasone) AND docetaxel]

Health Canada's Clinical Trials Database

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

[Search terms -- abiraterone AND castration-sensitive prostate cancer]

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 AND prednisone AND docetaxel) OR (abiraterone AND dexamethasone AND docetaxel)]

Grey Literature

Search dates: September 07, 2022, to September 19, 2022

Keywords: [Abiraterone, prednisone, dexamethasone, docetaxel, metastatic castration sensitive prostate cancer, mCSPC, metastatic hormone sensitive prostate cancer, and mHSPC]

Limits: Publication years: 2017 to present for guidelines, no limits for other sections

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)
- Internet Search

Appendix 2: Cost Comparison Table

Table 24: CADTH Cost Comparison Table of ADT for Patients With mCSPC

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dose	Daily cost ($)	28-day cost ($)
ADTs						
Leuprolide acetate						
Leuprolide acetate (Eligard)	7.5 mg 22.5 mg 30 mg 45 mg	Lyophilized powder for injection, prefilled syringe	310.7200 891.0000 1,285.2000 1,645.0000	7.5 mg monthly 22.5 mg every 3 months 30 mg every 3 months 45 mg every 6 months	9.01 to 11.10	252 to 311
Leuprolide acetate (Lupron depot)	3.75 mg 7.5 mg 11.25 mg 22.5 mg 30 mg	Prefilled syringe	389.1300 387.9700 1,159.5200 1,071.0000 1,428.0000	7.5 mg monthly 22.5 mg every 3 months 30 mg every 4 months	11.74 to 13.86	329 to 388
Leuprolide acetate (Zeulide depot)	3.75 mg 22.5 mg	Lyophilized powder for injection	304.0000 873.0000	3.75 mg monthly 22.5 mg every 3 months	9.59 to 10.86	269 to 304
Other LHRH agonists						
Goserelin depot (Zoladex)	3.6 mg 10.8 mg	Depot	422.6778 1,204.7322	3.6 mg monthly 10.8 mg every 3 months	15.10 13.24	423 371
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 11.25 mg every 3 months 22.5 mg every 6 months	9.10 to 12.37	255 to 346
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	Cycle 1: 26.50 Subsequent: 9.79	Cycle 1: 742 Subsequent: 274

Drug/comparator	Strength	Dosage form	Price ($)	Recommended dose	Daily cost ($)	28-day cost ($)
				monthly 1 month after starting dose		

ADT = androgen deprivation therapy; LHRH = luteinising hormone-releasing hormone; mCSPC = metastatic castration-sensitive prostate cancer.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2023), unless otherwise indicated, and do not include dispensing fees.[53]

Note: All dosing is from respective product monographs, unless otherwise indicated.[37,61-64]

Note: This table has not been copy-edited.

Table 25: CADTH Cost Comparison Table of ADT for Patients With mCSPC Using Nova Scotia List Prices (Scenario Analysis)

Treatment	Strength/concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	28-day cost ($)
Abiraterone acetate (generic)	250 mg 500 mg	Tab	7.6563 15.3125	1,000 mg daily	30.63	858
Docetaxel (generic)	80 mg/4.0 mL 160 mg/8.0 mL	4 mL vial 8 mL vial	497.0000[a] 990.0000[a]	75 mg/m^2 as a 1-hour IV fusion every 3 weeks for 6 cycles[b]	47.14	1,320
Dexamethasone (generic)	0.5 mg 4 mg	Tab	0.1564 0.6112	8 mg 3 times before docetaxel infusion	0.17	5
Prednisone (Generic)	5 mg 50 mg	Tab	0.0401 0.1735	10 mg daily	0.080	2
ADT[c]					9.01 to 15.10	252 to 423
ABI + DOC + ADT					87.03 to 93.12	2,437 to 2,608
Antiandrogen						
Abiraterone acetate (generic)	250 mg 500 mg	Tab	7.6563 15.312 5	1,000 mg daily	30.63	858
Prednisone (generic)	5 mg 50 mg	Tab	0.0401 0.1735	10 mg daily	0.080	2
ADT[c]					9.01 to 15.10	252 to 423
ABI + ADT					39.72 to 45.81	1,112 to 1,283
Enzalutamide (Xtandi)	40 mg	Cap	29.1953	160 mg daily	116.78	3,270
ADT[c]					9.01 to 15.10	252 to 423
ENZ + ADT					125.79 to 131.88	3,522 to 3,693
Darolutamide (Nubeqa)	300 mg	Tab	28.3440	600 mg twice daily	113.38	3,175
Docetaxel (generic)	80 mg/4.0 mL 160 mg/8.0 mL	4 mL Vial 8 mL Vial	497.0000[a] 990.0000[a]	75 mg/m^2 as a 1-hour IV fusion every 3 weeks for 6 cycles[b]	47.14	1,320

Treatment	Strength/concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	28-day cost ($)
Dexamethasone (Generic)	0.5 mg 4 mg	Tab	0.1564 0.6112	8 mg 3 times before docetaxel infusion	0.17	5
ADT[c]					9.01 to 15.10	252 to 423
DAR + DOC + ADT					169.70 to 175.79	4,752 to 4,923
Androgen synthesis inhibitor						
Apalutamide (Erleada)	60 mg	Tab	31.1400	240 mg daily	124.56	3,488
ADT[c]					9.01 to 15.10	252 to 423
APA + ADT					133.57 to 139.66	3,740 to 3,911
Antineoplastic agent						
Docetaxel (generic)	80 mg/4.0 mL 160 mg/8.0 mL	4 mL Vial 8 mL Vial	497.0000[a] 990.0000[a]	75 mg/m^2 as a 1-hour IV fusion every 3 weeks for 6 cycles[b]	47.14	1,320
Dexamethasone (Generic)	0.5 mg 4 mg	Tab	0.1564 0.6112	8 mg 3 times before docetaxel infusion	0.17	5
ADT[c]					9.01 to 15.10	252 to 423
DOC + ADT					56.32 to 62.41	1,577 to 1,748

ABI + ADT = abiraterone acetate with prednisone in combination with androgen deprivation therapy; ABI + DOC + ADT = abiraterone with prednisone plus docetaxel in combination with androgen deprivation therapy; ADT = androgen deprivation therapy; APA + ADT = apalutamide in combination with androgen deprivation therapy; Cap = capsule; DAR + DOC + ADT = darolutamide plus docetaxel in combination with androgen deprivation therapy; DOC + ADT = docetaxel in combination with androgen deprivation therapy; ENZ + ADT = enzalutamide in combination with androgen deprivation therapy; mCSPC = metastatic castration-sensitive prostate cancer; Tab = tablet.

Note: All prices are from the Nova Scotia Formulary (accessed June 2023) unless otherwise indicated, and do not include dispensing fees.[60] All dosing is from respective product monographs, unless otherwise indicated.[34,52,54,55]

Note: In all treatments where docetaxel is used, patients are premedicated with dexamethasone.

[a]Wholesale price reported by IQVIA DeltaPA, June 2023.[56] 20 mg/mL strength is marketed in Canada for docetaxel (per the Health Canada Drug Product Database);[57] however, CADTH could not obtain a current price for this product from IQVIA.

[b]Docetaxel costs based on an average body surface area assumed to be equal to 1.8 m^2.

[c]CADTH notes that the ADT degarelix (Firmagon) had a significantly more expensive first cycle and daily cost of $742 and $26.50, respectively. The subsequent 28-day cycle and daily costs are $274 and $9.79, which fall within the range highlighted in Table 24.

Note: This table has not been copy-edited.

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