Canadian Journal of Health Technologies

CADTH

January 2023 Volume 3 Issue 1

CADTH Reimbursement Recommendation

Darolutamide (Nubeqa)

Indication: For the treatment of patients with metastatic castration-sensitive prostate cancer in combination with docetaxel

Sponsor: Bayer Inc.

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Nubeqa?

CADTH recommends that Nubeqa should be reimbursed by public drug plans for the treatment of metastatic castration-sensitive prostate cancer (mCSPC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Nubeqa should only be covered to treat patients with mCSPC who are eligible for chemotherapy and are in relatively good health (i.e., have good performance status). Patients should not have received androgen deprivation therapy (ADT) for metastatic disease for more than 6 months, completed ADT for nonmetastatic disease within the past year, or received other prior systemic therapies for mCSPC.

What Are the Conditions for Reimbursement?

Nubeqa should only be reimbursed if used in combination with docetaxel and ADT and should not be given with other anticancer drugs. It should be prescribed by an oncologist with expertise in the management of prostate cancer, and the price of Nubeqa should be reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that treatment with Nubeqa improves survival in patients with mCSPC compared with currently available treatment alone (docetaxel plus ADT).
- The addition of Nubeqa to docetaxel plus ADT could meet some needs important to patients, including improving survival and delaying the progression to metastatic castration-resistant prostate cancer, the worsening of pain, and complications caused by cancer spreading to the bone.
- Based on CADTH's assessment of the health economic evidence, Nubeqa does not represent good value to the health care system at the public list price. Therefore, a price reduction is required.
- Based on public list prices, Nubeqa is estimated to cost the public drug plans approximately $39 million over the next 3 years.

Additional Information

What Is mCSPC?

Metastatic prostate cancer is prostate cancer that has spread to other parts of the body. mCSPC refers to metastatic prostate cancer that responds to treatment that lowers testosterone levels in the body. Patients with mCSPC often have difficulty urinating and pain due to cancer spreading to the bones. It is estimated that 24,600 people will be diagnosed with prostate cancer in 2022, 9% of whom will have metastatic disease.

Unmet Needs in mCSPC

Available treatments for mCSPC are effective but there is still no cure. There is a need for treatments that can extend survival while improving or maintaining the quality of life of patients.

How Much Does Nubeqa Cost?

Treatment with Nubeqa is expected to cost approximately $3,175 per patient per 28-day cycle.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that darolutamide be reimbursed for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC) in combination with docetaxel only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, multicentre, double-blind, randomized controlled trial (RCT) (ARASENS) demonstrated that treatment with darolutamide in combination with docetaxel and androgen deprivation therapy (ADT) resulted in added clinical benefit for patients with de novo or metachronous mCSPC compared with docetaxel and ADT. The ARASENS trial demonstrated that treatment with darolutamide in combination with docetaxel and ADT was associated with statistically significant and clinically meaningful improvements in overall survival (OS) (hazard ratio [HR] = 0.68; 95% confidence interval [CI], 0.57 to 0.80; P < 0.0001) compared with docetaxel and ADT alone. Analyses of secondary outcomes supported the efficacy of darolutamide plus docetaxel and ADT in delaying progression to metastatic castration-resistant prostate cancer (mCRPC), the need for subsequent antineoplastic therapy, worsening of pain, and symptomatic skeletal events compared with docetaxel plus ADT.

Patients identified a need for treatments that improve survival, delay the onset of symptoms and the need for subsequent chemotherapy, have fewer side effects, maintain health-related quality of life (HRQoL), and are easy to administer. Given all the evidence, pERC concluded that darolutamide in combination with docetaxel and ADT met some of the needs identified by patients in terms of improving survival and delaying the progression to mCRPC, worsening of pain, and symptomatic skeletal events.

Because the comparator in the clinical trial does not reflect the current standard of care, the comparative clinical evidence informing the economic model was based on the sponsor-submitted network meta-analysis (NMA). Using the sponsor-submitted price for darolutamide and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for darolutamide combined with docetaxel plus ADT was $156,172 per quality-adjusted life-year (QALY) gained compared with abiraterone plus ADT. At this ICER, darolutamide plus docetaxel plus ADT is not cost-effective at a $50,000 per QALY gained willingness-to-pay (WTP) threshold for patients with mCSPC. A price reduction is required for darolutamide to be considered cost-effective at a $50,000 per QALY gained WTP threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with darolutamide in combination with docetaxel and ADT should only be initiated in patients with mCSPC who meet all of the following criteria:	Evidence from the ARASENS trial demonstrated that treatment with darolutamide in combination with docetaxel and ADT resulted in clinically meaningful improvement of OS compared with docetaxel plus ADT in patients with mCSPC. The	—

Reimbursement condition	Reason	Implementation guidance
1.1. are chemotherapy eligible 1.2. have good performance status.	ARASENS trial included patients with an ECOG performance status of 0 or 1.	
2. Patients should receive a gonadotropin-releasing hormone concurrently or have undergone a bilateral orchiectomy.	In addition to darolutamide and docetaxel, patients enrolled in the ARASENS trial received a gonadotropin-releasing hormone concurrently or had undergone a bilateral orchiectomy.	—
3. Patients should not receive treatment with darolutamide in combination with docetaxel if they meet either of the following criteria: 3.1. received prior treatment with an androgen receptor axis–targeted therapy, chemotherapy, or immunotherapy for prostate cancer 3.2. received ADT in the metastatic setting for more than 6 months or within 1 year of completing adjuvant ADT in the nonmetastatic setting.	Patients who received prior androgen receptor axis–targeted therapy, chemotherapy, or immunotherapy for prostate cancer were excluded from the ARASENS trial. Patients enrolled in the ARASENS trial were ADT naive or initiated ADT no longer than 12 weeks prior.	—
Discontinuation		
4. Treatment with darolutamide in combination with docetaxel should be discontinued upon the occurrence of either of the following: 4.1. disease progression based on clinical, PSA, and radiographic factors 4.2. unacceptable toxicity.	Patients in the ARASENS trial were allowed to continue treatment until symptomatic disease progression or unacceptable toxicity.	—
5. Assessment for disease progression should be based on clinical, PSA, and radiographic evaluations every 3 to 6 months or per physician's discretion.	Treatment response was evaluated every 12 weeks in the ARASENS trial. According to clinical expert input, in clinical practice, clinical and PSA assessments are conducted every 3 months in the first year and every 6 months thereafter.	—
Prescribing		
6. Darolutamide in combination with docetaxel should be prescribed by an oncologist with expertise in the management of prostate cancer.	To ensure that darolutamide in combination with docetaxel is prescribed only for appropriate patients, and that adverse effects are managed appropriately.	—
7. Darolutamide should not be given in combination with anticancer drugs other than with the combination of docetaxel plus ADT.	There is no evidence supporting concomitant use of anticancer drugs other than ADT and docetaxel.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
8. A reduction in price.	The ICER for darolutamide + docetaxel + ADT is $156,172 compared with abiraterone + ADT. A price reduction of at least 58% would be required for darolutamide for the regimen to achieve an ICER of $50,000 per QALY gained compared with abiraterone + ADT.	—

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; mCSPC = metastatic castration-sensitive prostate cancer; OS = overall survival; PSA = prostate-specific antigen; QALY = quality-adjusted life-year.

Discussion Points

- Patients expressed a need for treatments that have long-term efficacy, fewer side effects, and maintain HRQoL. Analyses of secondary outcomes supported the efficacy of darolutamide plus docetaxel and ADT in delaying progression to mCRPC, the need for subsequent antineoplastic therapy, worsening of pain, and symptomatic skeletal events, compared with docetaxel plus ADT. The ARASENS trial assessed HRQoL using the National Comprehensive Cancer Network Prostate Cancer Symptom Index 17 item questionnaire / Functional Assessment of Cancer Therapy (NCCN-FACT FPSI-17) instrument, which captures common symptoms (e.g., pain, difficulty in urination) and treatment-related side effects (e.g., fatigue, weight gain, decreased sexual function) that are relevant to patients. However, due to the limitations with statistical analysis of this outcome, pERC was unable to draw definitive conclusions regarding the effect of darolutamide on HRQoL.
- pERC acknowledged that, when the ARASENS trial was designed, the use of docetaxel plus ADT was standard of care and an appropriate comparator. pERC appreciated that currently the use of docetaxel in the mCSPC setting is low and most people in Canada with mCSPC would now receive an androgen receptor axis–targeted therapy (ARAT) plus ADT. pERC discussed indirect evidence comparing darolutamide plus ADT and docetaxel to other treatments, including docetaxel, abiraterone, enzalutamide, or apalutamide in combination with ADT. The findings from 3 NMAs supported the findings of the ARASENS trial for the comparative survival benefit observed with darolutamide plus ADT and docetaxel compared with ADT and docetaxel, although the findings of these NMAs are associated with uncertainty. The OS results of the indirect comparisons between darolutamide plus ADT and docetaxel with an ARAT plus ADT were uncertain. The main concern across the NMAs was the potential for heterogeneity across studies, which introduces an unknown degree of bias into the results.
- pERC noted that the safety profile of darolutamide plus docetaxel plus ADT was overall similar to that of docetaxel plus ADT in the ARASENS trial, with no additional serious safety concerns.
- pERC discussed the uncertainty around the economic evidence, specifically the imprecise results of the sponsor's indirect treatment comparison between darolutamide plus docetaxel plus ADT versus ARAT plus ADT alone regimens. Therefore, the ICER could be underestimated, and a higher price reduction may be warranted.

Background

Prostate cancer is the most common cancer and the third leading cause of death from cancer in men living in Canada. It is estimated that 24,600 people will be diagnosed with prostate cancer in 2022. mCSPC refers to cancer that responds to ADT. Bone metastasis is common and often accompanied by bone pain. Disease-related skeletal complications, such as pathological fracture and spinal cord compression, can occur. Progression to mCRPC, a disease state associated with morbidity and poor HRQoL and prognosis, occurs despite standard-of-care treatment. The median survival for mCSPC is approximately 5 years, with large variability in survival among patients.

Treatment intensification with docetaxel or an ARAT in addition to ADT is the current standard of care in patients with mCSPC. This treatment has been shown to improve survival and delay disease progression, although it is not curative. Recently, triplet therapy with abiraterone and prednisone plus docetaxel and ADT is also observed in clinical practice in light of new clinical trial evidence. This triplet therapy is under review at CADTH for mCSPC concurrently.

Darolutamide has been approved by Health Canada for the treatment of patients with mCSPC in combination with docetaxel. Darolutamide is an ARAT. It is available as a 300 mg oral tablet; the dosage recommended in the product monograph is 600 mg taken twice daily, equivalent to a total daily dose of 1,200 mg, until disease progression or unacceptable toxicity. Patients receiving darolutamide should also receive a gonadotropin-releasing hormone analogue concurrently or have had a bilateral orchiectomy.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III RCT, 1 sponsor-provided indirect treatment comparison (ITC), and 2 published ITCs in patients with mCSPC
- patients' perspectives gathered by patient groups, including the Canadian Cancer Survivor Network (CCSN) and the Canadian Cancer Society (CCS)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with mCSPC
- input from 7 clinician groups, including the British Columbia Cancer Agency; the Canadian Cancer Society; genitourinary oncologists from the Maritime provinces; the Allan Blair Cancer Centre; the Ottawa Hospital Cancer Centre – Genitourinary Oncology Group; Ontario Health – Cancer Care Ontario, Genitourinary Cancer Drug Advisory Committee; and the Genitourinary Disease Site Group of the Cancer Centre of Southeastern Ontario
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups, the CCSN and CCS, submitted patient group input for this review. CCSN gathered data through an online survey with responses from 24 patients with prostate cancer (6 of whom were diagnosed with metastatic disease) and 2 caregivers. The CCS conducted surveys and interviews with 39 patients with mCSPC and with 2 caregivers. In both submissions, all patients were from Canada and 8 patients had experience with darolutamide.

The CCS respondents indicated that symptoms associated with mCSPC had a moderate to severe negative impact on their ability to engage in sexual activity, work, exercise, travel, fulfilling family obligations, and maintaining their mental health. Common side effects following treatments that are currently available that were mentioned by patients in both submission groups included changes in libido and sexual function, hot flashes, fatigue, loss of muscle mass, incontinence, and weight gain. Five patients from the CCSN submission rated how their experience with darolutamide compared with other treatments. Four of these patients indicated that darolutamide was easier to use and better addressed disease progression, 3 patients stated that they experienced a reduction in side effects compared with current treatments, and 1 indicated that it controlled their symptoms better. Adverse events identified among respondents with experience with darolutamide were consistent with those of currently available treatments. Across both submissions, respondents reported that they would like to see future treatments that delay the onset of symptoms, delay the need for chemotherapy, have fewer side effects, improve survival, are easy to use, and allow them to maintain their HRQoL.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts noted that although there are currently 2 available treatment intensification strategies using chemotherapy or ARAT that can improve long-term outcomes compared with ADT alone, they are not curative. There remains a compelling need to extend survival longer while improving and maintaining quality of life overall. The clinical experts expected triplet therapy with darolutamide plus docetaxel and ADT to be considered as a first-line treatment option for patients with mCSPC who are eligible for cytotoxic chemotherapy. The clinical experts noted that a major shift in the prescribing pattern is unlikely in the absence of direct evidence between darolutamide triplet therapy versus ARAT plus ADT, the most common regimen currently prescribed in Canada.

The clinical experts noted that there is no consensus among clinicians in Canada on which patients should be offered triplet therapy; it usually involves a case-by-case discussion between the patient and the treating physician. The clinical experts agreed that triplet therapy with darolutamide, docetaxel, and ADT should be available to all patients with mCSPC who are candidates for cytotoxic chemotherapy.

The clinical experts noted that treatment response is generally evaluated based on clinical status, radiologic response, and PSA response, and the frequency of assessment is highly variable in clinical practice. The clinical experts noted that treatment discontinuation is considered in patients who have unacceptable toxicities or disease progression (clinical, PSA, and/or radiologic progression). In addition, the clinical experts noted rapid progression

and the absence of ongoing clinical benefit may warrant the initiation of a subsequent line of therapy.

Clinician Group Input

Clinician group input was received from 7 groups: the British Columbia Cancer Agency (12 clinicians); the Canadian Cancer Society (12 clinicians); genitourinary oncologists from the Maritime provinces (5 clinicians); the Allan Blair Cancer Centre (5 clinicians); the Ottawa Hospital Cancer Centre – Genitourinary Oncology Group (3 clinicians); the Ontario Health – Cancer Care Ontario, Genitourinary Cancer Drug Advisory Committee (4 clinicians); and the Genitourinary Disease Site Group of the Cancer Centre of Southeastern Ontario (2 clinicians). The various clinician groups noted that current treatment goals are to reduce symptom burden, prolong survival, and delay disease progression. The clinician groups noted that current treatment for mCSPC includes either chemotherapy (docetaxel) or a second-generation androgen receptor inhibitor (i.e., abiraterone acetate plus prednisone, enzalutamide, or apalutamide) in combination with ADT. The clinician groups noted that mCSPC is incurable, and many patients fail systemic treatment shortly after treatment initiation. The groups emphasized a significant unmet need for treatments that further improve survival, increase HRQoL, and increase duration of treatment response while providing less toxicity burden. In terms of place in therapy, the clinician groups stated that darolutamide would be used as a first-line treatment for mCSPC in combination with ADT and docetaxel in patients who are fit for chemotherapy. The submissions stated that response to treatment would be assessed using PSA response, radiographic response, and clinical assessment (i.e., worsening pain or symptoms). Treatment would typically be discontinued upon disease progression (PSA, radiological, or symptomatic progression) or unacceptable toxicity.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The comparator in the ARASENS trial is ADT + docetaxel. Other publicly funded comparators in this therapeutic space include apalutamide + ADT, enzalutamide + ADT, and abiraterone + prednisone + ADT. Patients receiving ARAT + ADT may have been sequentially treated with docetaxel. How does darolutamide + ADT + docetaxel compare with other publicly funded alternatives?	pERC noted that the CADTH clinical review reported that the comparative efficacy between darolutamide + ADT and docetaxel vs. enzalutamide + ADT, apalutamide + ADT, and abiraterone + prednisone + ADT on OS, time to CRPC, and rPFS in adults with mCSPC was assessed in the 3 NMAs included. However, there was uncertainty with the evidence due to methodological limitations as well as wide confidence intervals, which preclude definitive conclusions.
There is currently a nonsponsored reimbursement review underway for abiraterone + prednisone + ADT + docetaxel for mCSPC (PEACE-1 trial)	pERC noted that the CADTH clinical review identified no comparative evidence between darolutamide triplet therapy and abiraterone triplet therapy. The absence of such evidence represents an evidence gap in the treatment of mCSPC.

Implementation issues	Response
How does darolutamide + ADT + docetaxel compare with abiraterone + prednisone + ADT + docetaxel?	
Considerations for initiation of therapy	
Patients with regional lymph node metastases only were not eligible for the ARASENS trial. If darolutamide + ADT + docetaxel is recommended for reimbursement, should patients with regional lymph node metastases only be excluded?	pERC and the clinical experts agreed that there is no compelling reason to exclude patients with regional lymph node metastases and these patients could potentially benefit from darolutamide + ADT+ docetaxel in the long-term.
ARASENS eligibility criteria included ECOG performance status of 0 or 1. Are the results of the trial generalizable to patients with an ECOG performance status ≥ 2?	pERC and the clinical experts noted that the performance status requirement for determining treatment eligibility is less stringent in clinical practice. One clinical expert also noted that it is known that patients with a poor performance status will unlikely tolerate cytotoxic chemotherapy; however, some patients initially present with an ECOG performance status > 2 and experience profound and rapid clinical improvement after lead-in treatment with ADT. These patients may be candidates for darolutamide plus docetaxel and ADT. pERC agreed with the clinical experts that patients with poor baseline performance status should not be necessarily excluded from treatment and their overall medical status should be thoroughly assessed.
Should patients who received ADT in the adjuvant setting and completed therapy more than 1 year prior (i.e., considered hormone sensitive) be eligible for darolutamide + ADT + docetaxel?	pERC agreed with the clinical experts that, to receive triplet therapy, patients should have hormone sensitivity at the onset of treatment. Therefore, patients who received ADT in the adjuvant setting and completed therapy more than 1 year prior should be eligible for darolutamide + ADT + docetaxel.
Are the ARASENS trial results consistent among patients with high-risk and low-risk disease?	pERC noted that the CADTH clinical review reported that the ARASENS trial assessed subgroups of patients with a baseline Gleason score of less than 8 or at least 8, and the results were consistent across the subgroups.
In the ARASENS trial, patients had to have started ADT (± first-generation antiandrogen) but not longer than 12 weeks before randomization. CADTH recommendations for apalutamide and enzalutamide + ADT for mCSPC specified the patient must not have had prior ADT in the metastatic setting or be within 6 months of initiating ADT in the metastatic setting. Should criteria for darolutamide + ADT+ docetaxel align?	pERC agreed with the clinical experts that it would be appropriate to use darolutamide + ADT + docetaxel in patients who are naive to ADT or who had received ADT within 6 months of starting the intensification because it is reasonable to expect that they have hormone sensitivity at the onset of treatment.
Considerations for discontinuation of therapy	
Should patients who are unable to tolerate 6 cycles of docetaxel be eligible to continue with darolutamide + ADT?	pERC and the clinical experts agreed that patients who are unable to tolerate docetaxel should be eligible to continue with darolutamide + ADT.
Should patients unable to tolerate darolutamide be eligible to switch to an alternative ARAT + docetaxel + ADT provided all other criteria are met?	The clinical experts noted that it is unlikely that patients are unable to tolerate darolutamide; however, in the case of intolerance to darolutamide, a switch to a different ARAT (i.e., abiraterone) +

Implementation issues	Response
	docetaxel + ADT or an ARAT + ADT combination is considered clinically appropriate. However, pERC has not reviewed any evidence to support switching to another ARAT in this setting.
In the ARASENS trial, darolutamide was continued until symptomatic disease progression or unacceptable toxicity. In the CADTH recommendations for enzalutamide and apalutamide + ADT for mCSPC, treatment was to be discontinued until disease progression or unacceptable toxicity. Should the discontinuation criteria for darolutamide align with previous CADTH recommendations?	pERC and the clinical experts noted that disease progression is generally determined based on a combination of clinical, PSA, and radiologic factors in clinical practice. pERC agreed with the clinical experts that it is reasonable to align discontinuation criteria for darolutamide with other ARATs.
Generalizability	
Should patients who recently initiated docetaxel + ADT for mCSPC be eligible to add on darolutamide? If so, what is the appropriate time frame?	pERC and the clinical experts noted there is currently no clinical evidence to inform the addition of darolutamide in patients who recently initiated docetaxel + ADT. The clinical experts indicated that the addition of darolutamide to docetaxel + ADT would be reasonable if done within the first 6 months of therapy. pERC indicated that the addition of darolutamide to docetaxel + ADT would be reasonable if the patient is receiving docetaxel and shows no progression of disease.
Should patients receiving ARAT (apalutamide, enzalutamide, or abiraterone + prednisone) + ADT for mCSPC be eligible to switch to darolutamide + ADT + docetaxel at the time of funding?	pERC and the clinical experts noted there is currently no evidence to inform switching from an existing ARAT + ADT to darolutamide + ADT + docetaxel. pERC and the clinical experts noted that this is an unlikely clinical scenario because it would be unusual in clinical practice to consider switching the treatment regimen in patients who have well-controlled disease on an established regimen. They also noted that it would be uncommon for a treating physician to consider switching from ARAT plus ADT to triplet therapy, except in the early phase of treatment (i.e., within 3 months of ADT initiation).

ADT = androgen deprivation therapy; ARAT = androgen receptor axis–targeted therapy; ECOG = Eastern Cooperative Oncology Group; mCSPC = metastatic castration-sensitive prostate cancer; rPFS = radiographic progression-free survival.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The CADTH systematic review identified 1 relevant study, ARASENS, which was a phase III, double-blind RCT comparing darolutamide (600 mg twice daily) versus placebo, both in combination with docetaxel (75 mg/m^2 via IV infusion every 21 days for 6 cycles) and ADT in patients with de novo or metachronous mCSPC (N = 1,306) in a first-line metastatic setting. Patients were randomized to the treatment arms in a 1:1 ratio and continued treatment until disease progression (symptomatic disease progression or a change of therapy) or unacceptable toxicity. The primary end point was OS; the secondary end points were time to castration-resistant prostate cancer (CRPC), time to initiation of subsequent systemic

antineoplastic therapy, time to pain progression, time to first symptomatic skeletal event, and symptomatic skeletal event–free survival.

In the final efficacy analysis (data cut-off on October 25, 2021), the median age of patients at baseline was 67.0 years (range, 41 to 89 years). The majority of patients were white (52.0%) or Asian (36.4%) and had stage IV disease at initial diagnosis (87.6%), an ECOG performance status of 0 (71.1%), and bone metastases (82.8%) at baseline. Most patients did not receive prior local therapy, and no patients had prior systemic antineoplastic therapy for prostate cancer other than ADTs.

Efficacy Results

Overall Survival

In the final analysis for OS (primary outcome), the median duration of follow-up in the darolutamide plus docetaxel and ADT arm and the placebo plus docetaxel and ADT arm was 43.7 months (standard deviation [SD] = not reported) and 42.4 months (SD = not reported), respectively. The median OS was not reached in the darolutamide plus docetaxel and ADT arm (OS = 48.9 months; 95% CI, 44.4 to not reached) in the placebo plus docetaxel and ADT arm, which corresponded to an HR of 0.68 (95% CI, 0.57 to 0.80; P < 0.0001) in favour of darolutamide.

Time to Castration-Resistant Prostate Cancer

The median time to CRPC (secondary outcome) was not reached in the darolutamide plus docetaxel and ADT arm; in the placebo plus docetaxel and ADT arm, median time to CRPC was 19.1 months (95% CI, 16.5 to 21.8 months) , with an HR of 0.36 (95% CI, 0.30 to 0.42; P < 0.0001) in favour of darolutamide.

Time to Initiation of Subsequent Systemic Antineoplastic Therapy

The median time to initiation of subsequent systemic antineoplastic therapy (secondary outcome) was not reached in the darolutamide plus docetaxel and ADT arm; in the placebo plus docetaxel and ADT arm, median time to initiation of subsequent systemic antineoplastic therapy was 25.3 months (95% CI, 23.1 to 28.8 months) , with an HR of 0.39 (95% CI, 0.33 to 0.46; P < 0.0001) in favour of darolutamide.

Time to Pain Progression

The median time to pain progression (secondary outcome) was not reached in the darolutamide plus docetaxel and ADT arm; in the placebo plus docetaxel and ADT arm, median time to pain progression was 27.5 months (95% CI, 22.0 to 36.1 months) , with an HR of 0.79 (95% CI, 0.66 to 0.95; P = 0.0058) in favour of darolutamide.

Health-Related Quality of Life

HRQoL (exploratory outcome) was measured using the NCCN-FACT FPSI-17 questionnaire. The mean total score and subscale scores were similar between treatment arms at baseline and remained stable at most assessment time points until near the end of the treatment when the scores trended toward deterioration in both arms. There was no notable difference in the mean change in score from baseline between treatment arms at most time points; however, the difference between treatments was not statistically tested.

Objective Response Rate

This outcome was not measured in the study.

Time to First Symptomatic Skeletal Event

The median time to first symptomatic skeletal event (secondary outcome) was not reached in both treatment arms, and the HR was 0.71 (95% CI, 0.54 to 0.94; P = 0.0081) in favour of darolutamide.

Symptomatic Skeletal Event–Free Survival

The median symptomatic skeletal event–free survival (secondary outcome) was 51.2 months (95% CI, 47.2 to not reached) in the darolutamide plus docetaxel and ADT arm; in the placebo plus docetaxel and ADT arm, symptomatic skeletal event–free survival was 39.7 months (95% CI, 36.0 to 42.3 months) , with an HR of 0.61 (95% CI, 0.52 to 0.72; P < 0.0001) in favour of darolutamide.

Prostate-Specific Antigen Outcomes

The following analyses were exploratory, and the difference between treatment arms was not adjusted for multiplicity.

The median time to PSA progression was not reached in the darolutamide plus docetaxel and ADT arm, and was 22.4 months (95% CI, 22.1 to 27.6 months) in the placebo plus docetaxel and ADT arm, with an HR of 0.26 (95% CI, 0.21 to 0.31).

The risk difference in absolute PSA response rate (the proportion of patients with a PSA level less than 0.2 ng/mL) between treatment arms was 25.0% (95% CI, 20.0% to 29.9%) at 6 months, and 34.2% (95% CI, 29.2% to 39.1%) at 12 months.

The relative 90% PSA response rate (proportion of patients with at least 90% PSA reduction) was numerically higher in the darolutamide plus docetaxel and ADT arm than the placebo plus docetaxel and ADT arm at 3, 6, and 12 months. Analyses of relative 50% and 30% PSA response rate showed similar findings.

Harms Results

Almost all patients reported at least 1 treatment-emergent adverse event (TEAE) in both treatment arms (99.5% of patients in the darolutamide plus docetaxel and ADT arm; 99.8% of patients in the placebo plus docetaxel and ADT arm). There was no notable difference in the TEAEs between treatment arms, except for the incidence of decreased appetite of any grade and hypertension of grade 3 or higher, both of which were numerically higher in the darolutamide plus docetaxel and ADT arm than the placebo plus docetaxel and ADT arm (decreased appetite of any grade: 18.6% versus 13.1%; hypertension of grade 3 or higher: 6.6% versus 3.2%). In the darolutamide plus docetaxel and ADT arm, 44.8% of patients reported at least 1 serious TEAE; 42.3% of patients in the placebo plus docetaxel and ADT arm reported at least 1 serious TEAE. The most common serious TEAE in both arms was febrile neutropenia (6.1% and 6.0%, respectively).

The proportion of patients who discontinued darolutamide or placebo due to a TEAE was 13.5% in the darolutamide plus docetaxel and ADT arm, and 10.6% in the placebo plus docetaxel and ADT arm, whereas the proportion of patients who discontinued docetaxel due to a TEAE was 8.0% in the darolutamide plus docetaxel and ADT arm, and 10.3% in the placebo plus docetaxel and ADT arm. Death events were reported in 35.1% of patients in the darolutamide plus docetaxel and ADT arm, and 46.8% of patients in the placebo plus docetaxel and ADT arm. The majority of deaths were attributed to disease progression in both treatment arms.

Critical Appraisal

Appropriate methods of randomization were used in the study. Reporting bias in favour of the darolutamide arm might have been involved for subjective efficacy outcomes (i.e., time to pain progression, time to first symptomatic skeletal event, symptomatic skeletal event–free survival, and HRQoL) as a result of unblinding by error, although the extent of bias was likely to be small because of the small number of unblinded patients (in the darolutamide triplet arm, in the placebo arm). Many important protocol deviations ( ) were reported that, according to the sponsor, were due to the use of broad and conservative definitions for important deviations; these were not expected to compromise study data. The sponsor noted that none of the important protocol deviations were considered major according to the old International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH E3) classification. The statistical analyses were generally well-designed, with adequate sample size and power considerations and multiplicity adjustments for all secondary outcomes using a hierarchal gatekeeping approach. However, HRQoL, PSA outcomes, and subgroup analyses were not adjusted for multiplicity and were considered exploratory due to increased risk of type II error. There is also uncertainty in the HRQoL outcomes because of the high risk of bias in measuring the outcome and the large losses to follow-up. The clinical experts noted the duration of follow-up for OS (median approximately 3.5 years) was adequate for assessing the efficacy and safety of systemic treatments for mCSPC, although longer follow-up would increase certainty of the OS results.

In consultation with the clinical experts, the inclusion and exclusion criteria of the trial were generally reflective of the treatment eligibility criteria in clinical practice; however, the exclusion of patients with significant comorbidities (e.g., cardiovascular diseases) and poor performance status may limit the generalizability of study results because this patient population is commonly seen in clinical practice. ARATs were the most commonly used subsequent antineoplastic therapy in the darolutamide arm. However, the clinical experts noted that the use of a second-line ARAT is unlikely to be adopted in clinical practice because second- or later-line re-treatment with an alternate ARAT is not funded by most jurisdictions. Although the comparator regimen, docetaxel plus ADT, is an appropriate and relevant comparator, it accounts for a small proportion of treatment regimens prescribed for chemotherapy-eligible patients with mCSPC in Canada. Without direct evidence, the comparative efficacy of darolutamide plus docetaxel and ADT versus ARAT plus ADT, the most commonly prescribed treatment regimen for mCSPC, is unknown and represents a gap in evidence. The clinical experts considered the benefits of darolutamide plus docetaxel and ADT in survival and delaying disease progression to be clinically meaningful. The clinical relevance of the HRQoL outcome was uncertain because, as per the clinical experts, the NCCN-FACT FPSI-17 instrument is not routinely administered in clinical practice. Nevertheless, the instrument does capture common symptoms (e.g., pain, difficulty in urination) and treatment-related side effects (e.g., fatigue, weight gain, decreased sexual function), which are very relevant in the clinical assessment of these patients in practice, according to the clinical experts.

Indirect Comparisons

Description of Studies

As part of the development of a global cost-effectiveness model for darolutamide in mCSPC, the sponsor conducted and submitted an NMA that was used to inform these analyses. The sponsor-submitted ITC first conducted a systematic literature review (SLR) to identify evidence for inclusion in a global ITC. The relative efficacy of darolutamide plus ADT and

docetaxel from the ARASENS trial was indirectly compared with alternative treatments for patients with mCSPC via [redacted] NMA. Comparators of interest for the sponsor-submitted NMA included abiraterone and prednisone, apalutamide, enzalutamide, and docetaxel in combination with ADT. Outcomes of interest included OS, time to CRPC, and radiographic PFS.

Two additional NMAs were identified in the CADTH literature search (Menges et al. [2022] and Yanagisawa et al. [2022]). The objective of the published SLR and NMA by Menges et al. (2022) was to assess the clinical effectiveness regarding survival and HRQoL, safety, and benefit-harm balance of metastatic hormone sensitive prostate cancer treatments, including docetaxel, abiraterone, enzalutamide, apalutamide, darolutamide, and radiotherapy (alone or in combination with ADT) via frequentist, random-effects NMA. Outcomes of interest evaluated in the study included OS, PFS, HRQoL, and adverse events (AEs); however, results for PFS and HRQoL were not available for comparisons involving darolutamide, and AEs were not available as comparisons were only made to ADT monotherapy, so were not of interest to this review.

The objective of the published SLR and NMA by Yanagisawa et al. (2022) was to analyze the benefit of triplet combination therapies with androgen receptor signalling inhibitors (abiraterone acetate, apalutamide, darolutamide, and enzalutamide) in combination with docetaxel and ADT compared with available treatment regimens in patients with metastatic hormone sensitive prostate cancer via frequentist, random-effects NMA. Outcomes of interest included OS, PFS, and AEs; however, results for PFS were not available for comparisons involving darolutamide, and comparisons for AEs were only made to ADT monotherapy, so were not of interest to this review.

Efficacy Results

The sponsor-submitted NMA included a total of [redacted] trials. In the [redacted] NMA for OS, darolutamide plus ADT plus docetaxel was favoured over ADT plus docetaxel ([redacted]) and ADT alone ([redacted]); however, comparisons between darolutamide plus ADT plus docetaxel and enzalutamide ([redacted]), apalutamide ([redacted]), and abiraterone acetate ([redacted]) were affected by imprecision, precluding conclusions about comparative efficacy. For time to CRPC, darolutamide plus ADT plus docetaxel was favoured over apalutamide + ADT ([redacted]), abiraterone plus ADT ([redacted]), docetaxel plus ADT ([redacted]), and ADT alone ([redacted]), but the comparison to enzalutamide plus ADT ([redacted]) was imprecise, precluding conclusions about comparative efficacy. Results for sensitivity analyses using [redacted] models were consistent with the base case analyses, although the 95% credible intervals were wider.

The NMA by Menges et al. (2022) included a total of 10 studies. In the frequentist, random-effects NMA for OS, darolutamide plus ADT and docetaxel was favoured over ADT and docetaxel (HR = 0.68; 95% CI, 0.57 to 0.81). The comparisons of darolutamide plus ADT and docetaxel to abiraterone acetate plus ADT and prednisone, enzalutamide plus ADT, apalutamide plus ADT, and apalutamide plus ADT plus docetaxel were affected by imprecision, precluding conclusions.

The NMA by Yanagisawa et al. (2022) included a total of 8 studies. In the frequentist, random-effects NMA for OS, darolutamide plus ADT and docetaxel was favoured over ADT and docetaxel (HR = 0.68; 95% 0.56 to 0.82) and ADT and abiraterone acetate (HR = 0.74; 95% CI, 0.55 to 0.99). No analyses were conducted for other comparators of interest.

Harms Results

Harms results were only reported for the published NMAs although most comparisons were only conducted versus ADT monotherapy. No harms results were reported in the sponsor-submitted NMA. Results of an NMA focusing on AEs conducted by Yanagisawa et al. (2022) also showed wide CIs for the comparison of darolutamide plus ADT and docetaxel to abiraterone and ADT (odds ratio = 26.62; 95% CI, 7.46 to 94.99), precluding conclusions.

Critical Appraisal

Appraisal points across the 3 NMAs were similar. The sponsor-submitted NMA and both published NMAs were informed by SLRs; however, no information was provided in the sponsor-submitted report on the methods of study selection or data extraction (i.e., duplicate reviewers) or a risk of bias assessment. Both published NMAs followed appropriate methods for identification, inclusion, and assessment of studies. Both published NMAs also conducted a quality assessment using the Cochrane risk of bias 2.0 tool; however, the results for the individual domains varied despite the authors reaching the same conclusion that the studies were at a low risk of bias.

In general, the treatments included in the NMAs were considered appropriate, although there were some treatments, such as ADT monotherapy (included in all NMAs) and radiotherapy, which were not considered relevant comparators for this review. Additionally, the sponsor-submitted NMA did not consider the combination of abiraterone plus ADT and docetaxel, which the clinical experts consulted by CADTH noted was a relevant treatment option currently in Canada. The clinical experts also reported that the combination has recently begun to be used by some clinicians in light of new clinical trial evidence and it would not have been considered relevant at the time the NMA was conducted by the sponsor. The outcomes assessed across NMAs were also appropriate; however, important outcomes, such as AEs and HRQoL, were not considered in the sponsors NMA. Although HRQoL and AEs were evaluated across the published NMAs, comparisons either did not include darolutamide plus ADT and docetaxel or they used ADT monotherapy as a reference so were not included in this report. Across the NMAs, most comparisons were based on single trials, and all evidence for comparisons to darolutamide plus ADT and docetaxel was indirect, which increases the uncertainty of the estimates of comparative efficacy. Additionally, results for OS were generally in favour of darolutamide plus ADT and docetaxel over ADT and docetaxel, although there were wide 95% CIs, suggesting uncertainty and imprecision in the comparative efficacy estimates.

The main concern across the NMAs was the potential for heterogeneity across studies that would result in violation of the underlying transitivity assumption and introduce an unknown degree of bias into the results. In the sponsor-submitted NMA, potential effect modifiers were considered from results of the ARASENS subgroup analysis, but consultation with clinical experts or other empirical evidence was not reported. There were notable differences in study design (i.e., blinded versus open label) and baseline characteristics that could have changed relative treatment effects that were identified but were not accounted for (i.e., PSA level and prostate cancer stage). Other differences evident across studies were prior treatment requirements, the time period during which the studies were undertaken, and follow-up duration. Baseline characteristics were not available for all factors of interest across all studies. Although many baseline characteristics seemed similar across trials, other differences across studies (e.g., study design, prior treatment, outcome definitions, length of follow-up, and time period during which the studies were undertaken) were not feasible to address. In the NMA by Menges et al. (2022), the authors noted that transitivity was

assessed using epidemiologic criteria and the presence of potential effect modifiers, along with considerations of clinical plausibility. No rationale or further discussion of the transitivity assessment was provided in the publication or supplementary material; therefore, it is difficult to conclude whether the transitivity assumption was met. Heterogeneity was assessed visually and by means of I^2 values; it was reported to be low for OS in the overall NMA. Some potentially important effect modifiers were reported in the study but were not adjusted for or discussed (e.g., use of prior therapy, Gleason score), and follow-up duration varied across studies. In the Yanagisawa et al. (2022) NMA, potential sources of heterogeneity were evaluated in the initial meta-analysis via the Cochrane Q test; however, the results did not suggest any important heterogeneity, so it was not explored in the NMA. As a result, it was unclear if the transitivity assumption was met. Additionally, no consideration was given to treatment effect modifiers, thus the impact of any potential effect modifiers remains unknown. The authors noted that the publications included in the NMA included different patient populations with regards to proportions of patients with de novo disease and disease burden. As such, the findings of all the NMAs, although supportive of the ARASENS trial, were highly uncertain due to the methodological limitations and wide credible intervals and CIs.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target population	Patients with mCSPC eligible for chemotherapy, which is aligned with the reimbursement request
Treatments	Darolutamide + docetaxel + ADT
Dose regimen	600 mg darolutamide twice daily, in combination with docetaxel and ADT
Submitted price	Darolutamide, 300 mg tablet: $28.34
Treatment cost	28-day darolutamide cost: $3,175 28-day regimen cost (darolutamide + docetaxel + ADT): $4,755 to $4,923
Comparators	Docetaxel + ADT Abiraterone and prednisone + ADT Apalutamide + ADT Enzalutamide + ADT ADT alone (degarelix, leuprorelin, goserelin, or triptorelin)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (25 years)

Component	Description
Key data source	• Phase III, double-blinded RCT (ARASENS) comparing darolutamide + docetaxel + ADT to docetaxel + ADT. • A systematic literature review and NMA were conducted to assess the survival of other relevant comparators compared to darolutamide + docetaxel + ADT.
Key limitations	• The OS extrapolations chosen for the trial data resulted in overestimates of survival when compared with the general Canadian population. • There was uncertainty in the relative treatment effects given the imprecision in the NMA and other limitations. • Docetaxel costs were underestimated in the sponsor's base case compared with CADTH sources. • Subsequent therapy in the ARASENS trial did not align with expected clinical practice in Canada, where clinicians indicated that ARATs would not be used subsequent to each other. • All relevant AEs were not included and treatment waning of darolutamide + docetaxel + ADT was not considered.
CADTH reanalysis results	• In the CADTH base case, CADTH used alternate OS extrapolations for darolutamide + docetaxel + ADT and docetaxel + ADT, along with updated costs for docetaxel. • Results of the CADTH base case suggest that darolutamide + docetaxel + ADT is more costly and more effective than abiraterone + ADT (incremental costs: $121,237; incremental QALYs: 0.77), resulting in an ICER of $156,172 per QALY gained. • A price reduction of 58% for darolutamide would be required for darolutamide + docetaxel + ADT to be considered cost-effective at a $50,000 per QALY gained threshold.
Key scenario analyses	• Due to the uncertainty surrounding the OS extrapolations, a scenario analyses involving Weibull extrapolations resulted in an ICER for darolutamide + docetaxel + ADT of $180,113 per QALY gained. Another scenario analysis was performed in which no difference in OS was assumed between darolutamide + docetaxel + ADT and those comparators for whom the NMA results were insignificant, which resulted in an ICER of $520,548 per QALY gained compared with abiraterone + ADT and price reduction of 75% for darolutamide.

ADT = androgen deprivation therapy; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; OS = overall survival; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: ADT costs for combination therapies were not properly incorporated, drug costs for treatment regimen under review were underestimated, and market uptake of darolutamide plus docetaxel and ADT was underestimated. The CADTH reanalysis included updating docetaxel and comparator costs, increasing the market share of darolutamide plus docetaxel and ADT, and including ADT costs as a background therapy to all combination therapies. Based on the CADTH base case, the expected budget impact for funding darolutamide was $5,208,502 in year 1, $12,422,270 in year 2, and $22,084,198 in year 3, for a 3-year expected budget impact of $39,714,970.

CADTH

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: November 9, 2022

Regrets: None

Conflicts of interest: None