CDA-AMC Reimbursement Review

Provisional Funding Algorithm

Indication: Prostate Cancer

This report supersedes the CADTH Provisional funding algorithm report for Prostate Cancer dated March 2024.

Please always check CADTH Provisional Funding Algorithms | CADTH to ensure you are reading the most recent algorithm report.

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Background

Following a request from jurisdictions, CADTH may design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- CADTH pCODR Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CADTH concerning sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CADTH website for more details.

Provisional funding algorithms also delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on prostate cancer. However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

CADTH published the first rapid provisional funding algorithm for prostate cancer in May 2023 and with an update in October 2023 to incorporate the CADTH recommendations for abiraterone acetate and prednisone for high-risk nonmetastatic prostate cancer (nmPC) and for abiraterone acetate and prednisone or dexamethasone with docetaxel for metastatic castrate-sensitive prostate cancer (mCSPC).

The rapid algorithm report was updated in March 2024 to incorporate the CADTH recommendations for: olaparib (Lynparza) plus abiraterone and prednisone or prednisolone for metastatic castration-resistant prostate cancer (mCRPC) and niraparib (Akeega) plus abiraterone acetate with prednisone or prednisolone for mCRPC.

Jurisdictional cancer drug programs requested an update to this rapid algorithm report in August 2024 to incorporate the CADTH recommendations for:

- relugolix (Orgovyx) for the treatment of advanced prostate cancer.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Advanced Prostate Cancer		
Relugolix (Orgovyx)	June 2024	CADTH recommends that relugolix (Orgovyx) should be reimbursed by public drug plans for the treatment of advanced prostate cancer if the following conditions are met: **Initiation:** 1. Adults (18 years or older) with histologically or cytologically confirmed prostate cancer (PC) who are not candidates for chemotherapy or surgical therapy soon after initiating ADT. 2. Patients should have good performance status. **Renewal:** 3. Assessment for disease progression should be based on clinical, PSA, and radiographic evaluations at least every 3 to 6 months or per physician's discretion. **Discontinuation:** 4. Reimbursement of relugolix should continue until unacceptable toxicity. **Prescribing:** 5. Relugolix should be prescribed by a clinician with expertise in management of PC and ADT. **Pricing:** 6. Relugolix pricing should be negotiated so that it does not exceed the drug program cost of treatment with the least costly ADT reimbursed for the treatment of advanced PC. **Feasibility of adoption:** 7. The feasibility of adoption of relugolix must be addressed. **Guidance on sequencing or treatment considerations:** The eligibility criteria for the HERD trial included patients with any of the following: • evidence of biochemical (PSA) or clinical relapse following local primary intervention • newly diagnosed androgen-sensitive metastatic disease

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		• advanced localized disease unlikely to be cured by primary intervention with either surgery or radiation. (this group included patients with localized or locally advanced disease with higher risk features). pERC agreed with the clinical experts' feedback and stakeholders' feedback indicating that relugolix is appropriate for use as an ADT in the same patient population that injectable ADTs are currently used. pERC agreed with the clinical experts that patients with an ECOG performance status of 2 or 3 could potentially benefit from relugolix. The clinical experts noted that patient preference for oral treatment or preference for rapid return of testosterone to normal levels upon cessation of drug may be factors for using relugolix over existing agents. pERC agreed with the clinical experts that choice of relugolix over other treatments can be made in case of patient preference for oral treatment or preference for rapid return of testosterone to normal levels upon drug cessation. The study did not include abiraterone and apalutamide, which are significant intensification options in this therapeutic area. The sponsor proposed a comprehensive listing for the use of relugolix in combination with all ARATs. However, it may be appropriate to consider restricting combination partners to those explicitly included in the study, such as the use of enzalutamide specifically in the context of metastatic castration-resistant prostate cancer, as suggested by the clinical experts. pERC agreed with the clinical experts and noted the limited evidence on efficacy of relugolix as part of an intensification therapy or in combination with radiation therapy for advanced prostate cancer. In the absence of definitive evidence about the clinical benefit or safety of using relugolix in combination with ARATs, pERC suggests that using relugolix as part of an intensification strategy should be based on the professional judgment of the prescribing clinician. Drug-drug interactions with other systemic therapy should be reviewed carefully.
nmCSPC		
Abiraterone acetate and prednisone	September 8, 2023	The CADTH FMEC recommends that abiraterone acetate with prednisone be reimbursed for patients with high-risk nmPC who are starting long-term ADT if the following conditions are met: **Initiation:** #1.# Abiraterone and prednisone should be reimbursed in patients with very high risk nmPC who meet all the following criteria: #1.1.# node positive, or node negative with 2 of the following: #1.1.1.# Clinical tumour stage T3 or T4 #1.1.2.# Gleason sum score 8 to 10 #1.1.3.# PSA ≥ 40 ng/mL #1.2.# no prior systemic therapy for PC #1.3.# good performance status #2.# Abiraterone acetate and prednisone should not be reimbursed in combination with enzalutamide #3.# Abiraterone acetate and prednisone should not be reimbursed in patients that have biochemical recurrence. **Discontinuation:**

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		#4.# Abiraterone acetate and prednisone should be discontinued if the patient has any of the following: #4.1.# completed 2 years of therapy #4.2.# significant intolerance of the therapy #4.3.# progression of the cancer **Prescribing:** #5.# Abiraterone acetate and prednisone should be prescribed by clinicians familiar with the treatment of PC and knowledgeable in the management of therapy toxicities. **Pricing:** #6.# Abiraterone acetate should be priced no more than the cheapest generic price. **Guidance on sequencing or treatment considerations:** FMEC agrees with the clinical expert that the definition of "high-risk nmPC" in the STAMPEDE trial is different than that used in the Canadian clinical setting. In the Canadian setting, the patients would be more advanced and represent the very high risk nmPC patient population. The differences in definition of high-risk nmPC between Canadian clinical practice and the STAMPEDE trial are reflected in initiation criteria of the reimbursement recommendation. FMEC agrees with the clinical expert and recommends relapse of 6 months or longer from the completion of abiraterone as an appropriate interval for re-treatment. FMEC agrees with the clinical expert that abiraterone treatment intensification should occur within 3 months of initiating ADT.
nmCRPC		
Darolutamide (Nubega)	April 22, 2020	pERC conditionally recommends the reimbursement of darolutamide in combination with ADT for the treatment of patients with nmCRPC who are at high risk of developing metastases, if the following condition is met: • cost-effectiveness being improved to an acceptable level. High risk is defined as a PSADT of ≤ 10 months during continuous ADT and castration-resistant according to the PCWG2 criteria, which was used in the ARAMIS trial. An absence of metastases was determined by a negative CT scan and a negative bone scan. Patients should have good performance status. Treatment should continue until unacceptable toxicity or radiographic disease progression. pERC made this recommendation because it was satisfied that, compared with ADT monotherapy, there is a net clinical benefit of darolutamide in combination with ADT based on statistically significant and clinically meaningful improvements in MFS and OS, a manageable toxicity profile, and no detriment in QoL. pERC concluded that darolutamide aligns with the following patient values: delay in disease progression and symptoms, prolonged survival, maintenance of QoL, and additional treatment choice. In addition, pERC considered evidence provided through ITCs with apalutamide and enzalutamide, which are relevant comparators in this setting. pERC concluded that there is uncertainty about the comparative efficacy and safety data of darolutamide, apalutamide, and enzalutamide. pERC concluded that, at the submitted price, darolutamide in combination with ADT is not cost-effective compared with ADT monotherapy. The Committee noted that there was considerable uncertainty in the cost-effectiveness estimates compared with relevant comparators (apalutamide and enzalutamide) because of a lack of robust

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		direct or indirect comparative clinical effectiveness data to inform the submitted economic evaluation. **Guidance on sequencing:** pERC was unable to make an informed recommendation on the optimal sequencing of treatments for mCRPC after treatment with darolutamide in the nonmetastatic setting, noting that there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces would need to address this issue upon implementation of reimbursement of darolutamide in combination with ADT and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value.
Enzalutamide (Xtandi)	March 26, 2019	pERC conditionally recommends reimbursement of enzalutamide (Xtandi) in combination with ADT for the treatment of patients with nmCRPC who are at high risk of developing metastases only if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption (budget impact) being addressed. High risk is defined as a PSADT of ≤10 months during continuous ADT. Patients should have good performance status and no risk factors for seizures. Treatment should continue until unacceptable toxicity or radiographic disease progression. pERC made this recommendation because it was satisfied that, compared with ADT monotherapy, there is a net clinical benefit of enzalutamide plus ADT based on statistically significant and clinically meaningful improvements in MFS, a manageable toxicity profile, no significant detriment in QoL, and a need for treatment options in this population of patients who are at increased risk for developing metastases. pERC concluded that enzalutamide aligns with the following patient values: delay in disease progression and symptoms, additional treatment choice, and maintenance of QoL. In addition, the Committee considered evidence provided through indirect treatment comparisons with apalutamide, a relevant comparator in this setting. pERC concluded that enzalutamide and apalutamide may have similar efficacy and safety; however, in the absence of more robust direct evidence from a randomized trial, there is uncertainty about the comparative efficacy and safety data of these 2 regimens. pERC concluded that, at the submitted price and with a lack of a statistically significant OS benefit, enzalutamide plus ADT is not cost-effective compared with ADT monotherapy. pERC also highlighted that the submitted potential budget impact of enzalutamide plus ADT was underestimated and would be substantial. pERC, therefore, had concerns about the capacity of jurisdictions to implement reimbursement of enzalutamide. **Guidance on sequencing:** pERC was unable to make an informed recommendation on the optimal sequencing of treatments for metastatic CRPC after treatment with enzalutamide in the nonmetastatic setting, noting that there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces would need to address this issue upon implementation of reimbursement of enzalutamide plus ADT and noted that a national approach to developing evidence-based clinical practice guidelines addressing sequencing of treatments would be of value.
Apalutamide (Erleada)	November 1, 2018	pERC conditionally recommends reimbursement of apalutamide (Erleada) in combination with ADT for the treatment of patients with CRPC who have no detectable distant metastases by either CT, MRI, or 99mTc bone scan and who are at high risk of developing metastases only if the following condition is met:

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		• cost-effectiveness being improved to an acceptable level. If the aforementioned condition cannot be met, pERC does not recommend reimbursement of apalutamide plus ADT. High risk is defined as a PSADT of 10 months during continuous ADT. Patients should have good performance status and no risk factors for seizures. Treatment should continue until unacceptable toxicity or radiographic disease progression. pERC made this recommendation because it was satisfied that compared with ADT monotherapy, there is a net clinical benefit of apalutamide plus ADT based on statistically significant and clinically meaningful improvements in MFS, significant improvements in time to symptomatic progression, a manageable toxicity profile, no significant detriment in QoL, and a need for treatment options in this population of patients, who are at increased risk for developing metastases. pERC was also satisfied that apalutamide aligns with patient values because of the delay in disease and symptom progression, manageable side effects, offering an additional treatment choice, and lack of detriment in QoL. pERC concluded that at the submitted price and with a lack of a statistically significant OS benefit, apalutamide plus ADT is not cost-effective compared with ADT monotherapy. pERC also highlighted that the submitted potential budget impact of apalutamide plus ADT is underestimated. **Guidance on sequencing:** pERC was unable to make an informed recommendation on the optimal sequencing of treatments for metastatic CRPC after treatment with apalutamide in the nonmetastatic setting, noting that there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces would need to address this issue upon implementation of reimbursement of apalutamide plus ADT and noted that a national approach to developing evidence-based clinical practice guidelines addressing sequencing of treatments would be of value. pERC was unable to make an informed recommendation on the use of apalutamide for patients who have been treated with abiraterone, enzalutamide, or other second-generation antiandrogens through a clinical trial or private drug insurance, as there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces would need to address this issue upon implementation of reimbursement of apalutamide plus ADT and noted that a national approach to developing evidence-based clinical practice guidelines addressing this time-limited need would be of value.
mCSPC		
Abiraterone acetate and prednisone or dexamethasone with docetaxel	September 8, 2023	The CADTH FMEC recommends that abiraterone acetate and prednisone or dexamethasone be reimbursed for the treatment of adults with metastatic castration-sensitive prostate cancer (mCSPC) in combination with docetaxel and androgen deprivation therapy (ADT). **Guidance on sequencing or treatment considerations:** FMEC agrees with the clinical expert that treatment may be given to patients with higher ECOG status at the discretion of the patient and clinician. Indirect comparisons suggest that triplet therapy is associated with greater severe toxicity than ARPI doublet therapy. Cautious use of ARPI plus ADT is preferred for patients with a poor performance status. FMEC agrees with the clinical expert that 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. The trial was stratified by metastatic site, but not high-volume or low-volume disease. Disease volume is an imprecise surrogate for cancer biology. Patients with low-volume disease may be at lower risk, and

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		treatment with a triplet regimen vs. the current SOC (ARPI plus ADT doublet) should be considered clinically on an individual patient basis. As defined in the CHAARTED trial, high volume disease is presence of visceral metastases or 4 or more bone metastasis with at least one outside the spine and pelvis. FMEC agrees with the clinical expert that patients who are unable to tolerate 6 cycles of docetaxel should still be continued on abiraterone plus ADT, which is one of the current SOC treatment options. Patients who are unable to tolerate abiraterone should be eligible to switch to another ARPI. The available data on retreatment with docetaxel for mCRPC after it has been used for mCSPC do not consistently demonstrate clinical benefit. 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 to 2 years). Re-treatment with abiraterone could also be considered if treatment were discontinued due to patient preference and not to toxicity. Re-treatment decisions should be based on patient preference and clinician discretion. FMEC agrees with the clinical expert that patients who recently initiated docetaxel plus ADT before this recommendation being implemented should be eligible to add on abiraterone acetate-prednisone (or dexamethasone) within a period of 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 acetate + ADT should be allowed to switch to the triplet if funding is implemented. The clinical expert suggested this decision would be based on patient preference and clinician discretion but should be made within a restricted time frame (e.g., approximately 4 to 6 months).
Darolutamide (Nubeqa)	January 23, 2023	The CADTH pERC recommends that darolutamide be reimbursed for the treatment of patients with mCSPC in combination with docetaxel only if the following conditions are met: **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: #1.1.# are chemotherapy-eligible #1.2.# have good performance status. #2.# Patients should receive a gonadotropin-releasing hormone concurrently or have 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. **Discontinuation:** #4.# Treatment with darolutamide in combination with docetaxel should be discontinued upon the occurrence of either of the following:

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		#4.1.# disease progression based on clinical, PSA, and radiographic factors #4.2.# 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. **Prescribing:** #6.# Darolutamide in combination with docetaxel should be prescribed by an oncologist with expertise in the management of prostate cancer. #7.# Darolutamide should not be given in combination with anticancer drugs other than with the combination of docetaxel plus ADT. **Pricing:** #8.# A reduction in price.
Abiraterone acetate plus prednisone or prednisolone	May 2021	**Conclusions and implications for decision- or policy-making:** Five SRs and 3 subgroup analyses reporting results from 1 RCT were included to address the clinical effectiveness of abiraterone acetate for the treatment of mCSPC. One economic evaluation was included to address the cost-effectiveness of abiraterone acetate for the treatment of mCSPC. The findings from these publications are largely based on 2 trials with moderate-to-high certainty evidence for key clinical outcomes and generalizable to the mCSPC patient population in Canada and the economic context. Compared to ADT monotherapy, AAP plus ADT was associated with improved overall survival, prostate cancer-specific survival, PFS, and improved quality of life. Although AAP plus ADT did have a favourable association with AEs, such as time to pain progression and deterioration compared with ADT monotherapy, patients treated with AAP plus ADT were at increased risk of grade III to grade V AEs (severe, life-threatening, or fatal) and the risk of treatment discontinuation due to these AEs was higher. Hird et al. (2020) estimated a cost of $276,251.82 per QALY gained, which is higher than traditionally accepted willingness-to-pay thresholds. Despite the recent introduction of a generic product to the market in Canada, the updated ICER was calculated to be $149,022.09 per QALY gained. Future funding decisions for abiraterone acetate in Canada will have to weigh the benefits of a clinically effective treatment against both the evidence regarding AEs and the budgetary implications of such a high-cost treatment.
Enzalutamide (Xtandi)	September 23, 2020	pERC conditionally recommends reimbursement of enzalutamide in combination with ADT for the treatment of patients with mCSPC if the following condition is met: • cost-effectiveness being improved to an acceptable level. pERC was unable to make an informed recommendation on the optimal sequencing of treatments for patients who progress after treatment with enzalutamide in combination with ADT for mCSPC and enter the mCRPC setting. pERC noted that there is insufficient evidence to inform this clinical situation. However, pERC agreed with the pCODR CGP that there is no high-level evidence at present to support the sequencing of ARATs, which have the same mechanism of action. pERC recognized that provinces would need to address this issue upon implementation of reimbursement of enzalutamide in combination with ADT and noted that a national approach to developing clinical practice guidelines addressing the sequencing of treatments would be of value. **Guidance on sequencing:** pERC discussed that there is insufficient evidence at present to make an informed decision on the use of enzalutamide in combination with ADT compared to other androgen receptor-targeted drugs (e.g., apalutamide or abiraterone plus prednisone). pERC was unable to comment on the preferred

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		treatment choice for patients but recognized that provinces will need to address this issue upon implementation of reimbursement of other androgen receptor-targeted drugs. pERC was unable to make an informed recommendation on the optimal sequencing of treatments for patients who progress after treatment with enzalutamide in combination with ADT for mCSPC and enter the mCRPC setting. pERC noted that there is insufficient evidence to inform this clinical situation. However, pERC agreed with the pCODR CGP that there is currently no high-level evidence to support the sequencing of ARATs, which have the same mechanism of action. pERC recognized that provinces would need to address this issue upon implementation of reimbursement of enzalutamide in combination with ADT and noted that a national approach to developing clinical practice guidelines addressing the sequencing of treatments would be of value. pERC noted that despite the fact that the ARCHES trial allowed sequential docetaxel and enzalutamide; and the ENZAMET trial allowed concurrent docetaxel and enzalutamide, there is currently insufficient data to support this approach in the context of Canada. Enzalutamide should not be routinely combined with or sequenced right after docetaxel therapy.
Apalutamide (Erleada)	April 22, 2020	pERC conditionally recommends funding apalutamide (Erleada) in combination with ADT for patients with mCSPC only if the following condition is met: • cost-effectiveness improved to an acceptable level. Patients must be castration sensitive (i.e., no prior ADT or within 6 months of beginning ADT), with good performance status. Treatment should be continued until unacceptable toxicity or disease progression. **Guidance on sequencing:** pERC discussed that there is currently insufficient evidence to make an informed decision on the use of apalutamide plus ADT compared to other ARAT therapies (e.g., abiraterone, enzalutamide), pERC was unable to comment on the preferred treatment choice for patients but recognized that provinces will need to address this issue upon implementation of reimbursement of other ARAT therapies. pERC was unable to make an informed recommendation on the optimal sequencing of treatments for patients who progress after treatment with apalutamide plus ADT for mCSPC and enter the mCRPC setting. pERC noted that there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces would need to address this issue upon implementation of reimbursement of apalutamide plus ADT and noted that a national approach to developing clinical practice guidelines addressing sequencing of treatments would be of value.
mCRPC		
Olaparib (Lynparza) with abiraterone	February 2024	The CADTH pCODR Expert Review Committee (pERC) recommends that olaparib and abiraterone acetate with prednisone or prednisolone be reimbursed for the first-line treatment of adult patients with deleterious or suspected deleterious germline and/or somatic *BRCA* mutated metastatic castration resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated only if the following conditions are met: #1.# Olaparib and abiraterone should be reimbursed in the first-line treatment of adults (18 years or older) with all of the following: #1.1.# mCRPC #1.2.# positive for a germline and/or somatic *BRCA1* or *BRCA2* gene alteration

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		#1.3.# have not received prior treatment with an ARPi in the mCSPC or nmCRPC setting #1.4.# have not received prior treatment with a PARP inhibitor #1.5.# have not received CYP-17 inhibitor (e.g., abiraterone) for mCRPC for a prolonged time period. #2.# Patients should have good performance status. #3.# Reimbursement of olaparib and abiraterone should continue until disease progression or unacceptable toxicity. #4.# Olaparib and abiraterone should be reimbursed when prescribed by a clinician with expertise in treating mCRPC in an outpatient oncology clinic and with expertise in systemic therapy. #5.# Olaparib and abiraterone should not be reimbursed when administered in combination with other anticancer drugs. #6.# A reduction in price. #7.# The feasibility of adoption of olaparib and abiraterone must be addressed. **Guidance on sequencing:** The experts indicated that for patients with a known *BRCA1* or *BRCA2* mutation, first-line PARP inhibitor (e.g., olaparib) and abiraterone would be preferred over other available systemic treatment options, unless there is a contraindication for the patients, or the patients could not tolerate the incremental toxicities related to the combination therapy. In terms of sequencing, the experts suggested that in patients with mCRPC with *BRCA1* or *BRCA2* mutation, olaparib and abiraterone can be given first, followed by radium, docetaxel or cabazitaxel. Of note, there is no direct or indirect evidence comparing olaparib and abiraterone to the treatments listed in the population included under the Health Canada indication. pERC agreed with the clinical experts.
Niraparib-abiraterone acetate (Akeega)	February 2024	The CADTH pCODR Expert Review Committee (pERC) recommends that niraparib and abiraterone acetate with prednisone or prednisolone be reimbursed for the first-line treatment of adults with deleterious or suspected deleterious *BRCA* mutated (germline and/or somatic) metastatic castration resistant prostate cancer (mCRPC), who are asymptomatic or mildly symptomatic, and in whom chemotherapy is not clinically indicated only if the following conditions are met: #1.# Niraparib and abiraterone should be reimbursed in the first-line treatment of adults (18 years or older) with all of the following: #1.1.# mCRPC #1.2.# positive for a germline and/or somatic *BRCA1* or *BRCA2* gene alteration #1.3.# have not received prior treatment with an ARPi for mCSPC or nmCRPC #1.4.# Have not received prior systemic therapy for mCRPC, except for < 4 months of abiraterone acetate with prednisone for mCRPC #1.5.# Have not received prior treatment with a PARP inhibitor for mCRPC #2.# Patients should have good performance status. #3.# Reimbursement of niraparib and abiraterone acetate should continue until disease progression or unacceptable toxicity. #4.# Niraparib and abiraterone should be reimbursed when prescribed by a clinician with expertise in treating mCRPC in an outpatient oncology clinic and with expertise in systemic therapy.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		#5.# Niraparib and abiraterone acetate with prednisone or prednisolone should not be reimbursed when administered in combination with other anticancer drugs. #6.# A reduction in price.
Lutetium vipivotide tetraxetan (Pluvicto)	March 22, 2023	The CADTH pERC recommends that lutetium [^{177}Lu] vipivotide tetraxetan be reimbursed for the treatment of adults with PSMA-positive mCRPC who have received at least 1 ARPI and at least 1 taxane-based chemotherapy, only if the following conditions are met: **Initiation:** #1.# Treatment with ^{177}Lu vipivotide tetraxetan should only be initiated in patients with mCRPC who are: #1.1.# PSMA positive as per the criteria used in VISION #1.2.# previously treated an APRI and at least one prior taxane-containing regimen #1.3.# in good performance status. **Discontinuation:** #2.# Treatment with ^{177}Lu vipivotide tetraxetan should be discontinued upon the occurrence of any of the following: #2.1.# Disease progression based on clinical, PSA, and radiographic factors. #2.2.# Unacceptable toxicity. #3.# Assessment for disease progression should be based on clinical and radiographic evaluations every 3 months, or as per physician's discretion. **Prescribing:** #4.# ^{177}Lu vipivotide tetraxetan should be prescribed by an oncologist with expertise in the management of prostate cancer. #5.# ^{177}Lu vipivotide tetraxetan should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. #6.# ^{177}Lu vipivotide tetraxetan should not be prescribed in combination with anticancer therapies other than ADT. #7.# Reimbursement should be limited to a maximum of 6 cycles. **Pricing:** #8.# A reduction in price. **Feasibility of adoption:** #9.# The feasibility of adoption of ^{177}Lu vipivotide tetraxetan must be addressed. #10.# Organizational feasibility must be addressed so that jurisdictions have the infrastructure in place to implement treatment with ^{177}Lu vipivotide tetraxetan: #10.1.# Access to specialized facilities that can administer radiopharmaceuticals. #10.2.# Access to PSMA PET-CT diagnostic testing.
Olaparib (Lynparza)	April 21, 2021	pERC conditionally recommends reimbursement of olaparib as monotherapy for the treatment of adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes *BRCA* or *ATM* who have progressed following prior treatment with a new hormonal drug or ARAT if the following condition is met: • cost-effectiveness being improved to an acceptable level. Eligible patients should have a good performance status and treatment should be continued until disease progression or unacceptable toxicity.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		pERC made this recommendation because it was satisfied that there is a net clinical benefit of olaparib compared with investigators' choice of an ARAT based on statistically significant and clinically meaningful improvements in rPFS and OS, a manageable toxicity profile, and no detrimental impact on QoL. However, given the lack of robust direct or indirect comparative data, pERC was unable to conclude on the relative efficacy and safety of olaparib compared with other relevant treatment options, such as taxane-based chemotherapy (i.e., docetaxel, cabazitaxel) or radium-223. pERC also concluded that olaparib aligns with the following patient values: delays disease progression, the onset of symptoms, pain progression, and skeletal-related events; has manageable side effects with no negative impact on QoL; fulfills an unmet need; and offers an additional treatment option with a convenient oral route of administration. pERC concluded that olaparib was not cost-effective at the submitted price vs. available comparators in Canada and that a reduction in drug price would be required to improve its cost-effectiveness to an acceptable level. pERC also noted that the CADTH base-case estimates are informed by the sponsor-submitted indirect treatment comparison, which is highly uncertain. pERC noted that the budget impact of introducing olaparib may potentially be underestimated due to the uncertainty associated with the availability of HRR mutation testing and detection rates.
Enzalutamide (Xtandi)	June 22, 2015	pERC recommends funding enzalutamide (Xtandi) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for patients with asymptomatic or mildly symptomatic mCRPC who have evidence of disease progression following ADT, which generally includes an LHRH agonist or orchiectomy, who have not received prior chemotherapy for mCRPC and who have an ECOG performance status of 0 or 1, and no risk factors for seizures. Treatment should be until disease progression or the initiation of chemotherapy. pERC made this recommendation because it was satisfied that enzalutamide has a net clinical benefit compared with placebo based on a clinically meaningful improvement in overall survival and a manageable toxicity profile. In addition, pERC concluded that treatment with enzalutamide aligns with patient values. However, at the submitted price and the Economic Guidance Panel's range of estimated incremental cost-effectiveness ratios, enzalutamide could not be considered cost-effective compared with placebo. In the absence of a direct comparison of clinical effectiveness with abiraterone and prednisone, the uncertainty in the economic analyses was too great for the Committee to determine enzalutamide's net clinical benefit or cost-effectiveness relative to abiraterone and prednisone. **Guidance on sequencing:** There is currently no evidence available on the effectiveness of enzalutamide in patients with mCRPC who progress after receiving abiraterone and prednisone or vice versa. Therefore, pERC was unable to make an informed recommendation on sequencing.
Abiraterone acetate (Zytiga)	October 22, 2013	The pCODR pERC recommends funding abiraterone acetate conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for patients with asymptomatic or mildly symptomatic mCRPC after failure of ADT, which generally includes an LHRH agonist or orchiectomy, who have not received prior chemotherapy and who have ECOG performance status 0 or 1. pERC made this recommendation because it was satisfied that abiraterone plus prednisone has a net clinical benefit compared with prednisone alone and aligns with patient values. However, at the submitted price and the range of estimated incremental cost-

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		effectiveness ratios, abiraterone plus prednisone cost could not be considered effective compared with prednisone alone. **Guidance on sequencing:** There is currently no evidence available on the effectiveness of re-treatment with abiraterone postchemotherapy in those patients who progress after receiving abiraterone in the prechemotherapy setting or the optimal sequencing of other therapies in mCRPC. Therefore, pERC concluded that the optimal sequencing of abiraterone and other treatments in mCRPC is still unknown and pERC was unable to make an informed recommendation on re-treatment with abiraterone in the postchemotherapy setting. However, pERC recognized that provinces would need to address this issue upon implementation of abiraterone funding in the prechemotherapy setting.
Enzalutamide (Xtandi)	July 23, 2013	pERC recommends funding enzalutamide (Xtandi) for the treatment of patients with mCRPC who have progressed on docetaxel-based chemotherapy. Funding should be for patients who have an ECOG performance status of ≤ 2 and no risk factors for seizures. pERC made this recommendation because it was satisfied enzalutamide has a net clinical benefit compared with placebo and is marginally cost-effective compared with best supportive care. pERC was also satisfied that enzalutamide would be an alternative to abiraterone for patients in the postdocetaxel setting but would not be an add-on therapy to abiraterone treatment. pERC also considered that, despite the limitations of the indirect comparison, the cost-effectiveness of enzalutamide is likely comparable to the cost-effectiveness of abiraterone, based on the Economic Guidance Panel's best estimates of cost-effectiveness and assuming similar pricing of the 2 therapies. **Guidance on sequencing:** There is no evidence available on sequential treatment of enzalutamide and other therapies in the postdocetaxel setting for patients with metastatic castration-resistant prostate cancer. Therefore, pERC considered that the optimal sequencing of these treatments is still unknown and pERC was unable to make an informed recommendation on sequencing of enzalutamide and other treatments postdocetaxel.

AAP = abiraterone acetate with prednisone; ADT = androgen deprivation therapy; AE = adverse event; ARAT = androgen receptor axis-targeted therapy; ARPI = androgen receptor pathway inhibitor; CGP = Clinical Guidance Panel; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; FMEC = Formulary Management Expert Committee; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LHRH = luteinizing hormone-releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; MFS = metastasis-free survival; nmCRPC = nonmetastatic castration-resistant prostate cancer; nmCSPC = nonmetastatic castration-sensitive prostate cancer; nmPC = risk nonmetastatic prostate cancer; OS = overall survival; pCODR = pan-Canadian Oncology Drug Review; PCWG2 = Prostate Cancer Working Group 2; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PC = prostate cancer; PFS = progression-free survival; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time; PSMA = prostate-specific membrane antigen; QALY = quality-adjusted life-year; QoL = quality of life; RCT = randomized controlled trial; SOC = standard of care; SR = systematic review.

Notes: Hormone-sensitive prostate cancer and castration-sensitive prostate cancer are used interchangeably and describe the same clinical state. Furthermore, hormone-resistant prostate cancer, hormone-refractory prostate cancer or castration-resistant prostate cancer all describe the same clinical state.

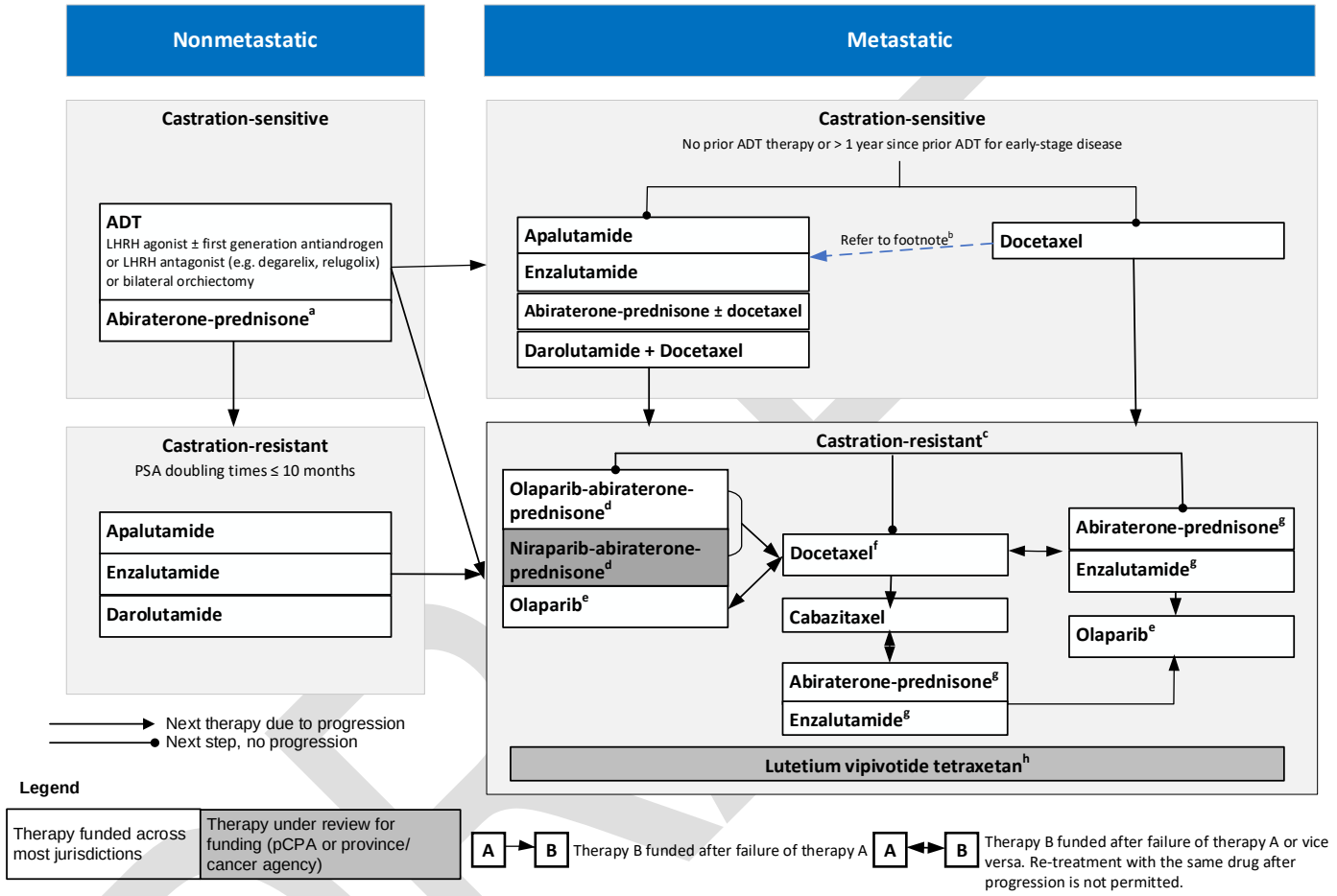
ARAT and ARPI are generally referring to the same group of medications resulting in the reduction of the androgen level. Some recommendations have referred to ARPI in the reimbursement conditions (e.g., lutetium vipivotide tetraxetan), while others have referred to ARAT in the reimbursement reports (e.g., apalutamide and enzalutamide). Both ARATs and ARPIs would include androgen receptor antagonists such as enzalutamide, darolutamide and apalutamide and androgen synthesis inhibitors such as abiraterone.

Table 2: CADTH Implementation Advice Panels on Prostate Cancer

Topic (date of publication)	Implementation advice
Guidance for PSMA-PET Implementation (August 30, 2023)	Guidance for PSMA-PET Implementation • All 3 PSMA-PET radiopharmaceuticals (^{68}Ga gozetotide, ^{18}F-DCFPyl, ^{18}F-PSMA-1007) are appropriate for use in identifying patient eligibility when validated criteria and thresholds are used and image interpretation and assessment are conducted by an appropriately trained PET-interpreting physician. • The VISION trial criterion used for defining a positive lesion was uptake greater than normal liver parenchyma with ^{68}Ga gozetotide. Liver parenchyma can be used as a threshold for ^{18}F-DCFPyl, which exhibits physiological activity in the liver like ^{68}Ga gozetotide. • For PSMA-PET radiopharmaceuticals that exhibit higher normal liver uptake or hepatobiliary excretion (e.g., ^{18}F-PSMA-1007), set detection thresholds are appropriate for confirming PSMA positivity. • The acquisition and implementation of additional PSMA-PET radiopharmaceuticals are not anticipated to increase the target population or number of patients eligible for Pluvicto beyond those that have been reported by CADTH, although this may change as data emerge to improve methods used to define eligibility criteria. • There may be opportunities to refine the patient cohorts that will most benefit from therapy as evidence matures regarding PSMA-PET eligibility criteria and thresholds. • The system costs associated with PSMA-PET imaging drugs for this class of therapy and relevant implementation, capacity, and equity in access factors should be considered for usability in clinical practice.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Prostate Cancer



ADT = androgen deprivation therapy; ARAT = androgen receptor axis-targeted therapy; ARPI = androgen receptor pathway inhibitor; LHRH = luteinizing hormone-releasing hormone; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; nmPC = nonmetastatic prostate cancer; PARP = poly-(ADP-ribose) polymerase; pCPA = pan-Canadian Pharmaceutical Alliance; PSA = prostate-specific antigen PSMA = prostate-specific membrane antigen.

Notes: ADT is available to continue in all settings. LHRH antagonist options can include degarelix and relugolix. All drugs are subject to explicit funding criteria that may vary between provinces.

[a] Abiraterone-prednisone should be reimbursed in patients with very high-risk nmPC, per the initiation criteria, which are as follows: node positive or node negative with 2 of the following: clinical tumour stage T3 or T4, Gleason sum score 8 to 10, PSA ≥ 40 ng/mL. Abiraterone-prednisone should not be reimbursed in combination with enzalutamide. A relapse of 6 months or longer from the completion of abiraterone is an appropriate interval for re-treatment.
[b] Can add apalutamide or enzalutamide if within 3 months of therapy with no disease progression, otherwise can continue ADT alone.
[c] Radium 223 is a funded option in many jurisdictions across Canada for metastatic castration-resistant prostate cancer for appropriate patients.

[d] For those with somatic or germline *BRCA* mutations who have not received a prior ARPi (in the mCSPC or nmCRPC setting), prior systemic therapy for mCRPC (except for < 4 months of abiraterone acetate with prednisone for mCRPC), or a prior PARP inhibitor.
[e] For somatic or germline *BRCA* or *ATM* mutations, if not received previously and if there is disease progression following an ARAT.
[f] Subsequent docetaxel is available if progression is longer than 3 months after prior docetaxel, otherwise cabazitaxel should be offered.
[g] In some provinces, ARAT with a different mechanism of action may be available following progression on a previous ARAT.
[h] Treatment should be initiated in those who are PSMA positive (per the criteria in the VISION trial) and who were previously treated with an ARPI and at least 1 prior taxane-containing regimen.

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Description of the Provisional Funding Algorithm

Nonmetastatic Castration-Sensitive Prostate Cancer

In prostate cancer, androgen deprivation therapy (ADT) is the backbone therapy and is continued in all settings. It is currently the main treatment option for patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC). ADT can include an LHRH agonist plus or minus first generation antiandrogen, or a luteinizing hormone-releasing hormone (LHRH) antagonist or bilateral orchiectomy. LHRH antagonist options can include degarelix and relugolix. All drugs are subject to explicit funding criteria that may vary between provinces.

Abiraterone-prednisone is available to patients with very high-risk nmCSPC who meet the initiation criteria. The initiation criteria are node positive or node negative with 2 of the following: clinical tumour stage T3 or T4, Gleason sum score of 8 to 10, prostate-specific antigen (PSA) of 40 ng/mL or greater. It is noted that abiraterone-prednisone should not be reimbursed in combination with enzalutamide.

Nonmetastatic Castration-Resistant Prostate Cancer

For patients who progress to nmCRPC and who are at high risk of developing metastases — that is, who have a prostate-specific antigen doubling time of 10 months or less during continuous ADT — the following 3 treatment options are available, given in combination with ADT: apalutamide, enzalutamide, and darolutamide.

Metastatic Castration-Sensitive Prostate Cancer

For patients who develop or are diagnosed with mCSPC and who had no prior ADT or who have had a period of at least 1 year since prior ADT for early-stage disease, the 2 following options are available:

- chemotherapy with docetaxel
- treatment with an androgen receptor axis-targeted therapy (ARAT) or an androgen receptor pathway inhibitor (ARPI), any of these given in combination with ADT.

Treatment options in the latter category include apalutamide, enzalutamide, the combination of abiraterone-docetaxel plus prednisone, and darolutamide-docetaxel. For those who started with docetaxel, there is the option to add apalutamide and enzalutamide, if the patients is within 3 months of therapy with no disease progression.

CADTH notes that there is currently insufficient evidence to recommend 1 of these drugs over any other. In addition, there is no high-level evidence to inform the optimal sequencing of treatments and to support the sequencing of drugs that have the same mechanism of action.

Metastatic Castration-Resistant Prostate Cancer

Patients with mCRPC may have the following treatment options:

- olaparib plus abiraterone and niraparib-abiraterone are treatment options available in the first-line setting for patients with deleterious or suspected deleterious germline and/or somatic *BRCA*-mutated mCRPC in whom chemotherapy is not clinically indicated and who have not received a prior ARPi (in the mCSPC or nmCRPC setting), prior systemic therapy for mCRPC (except for < 4 months of abiraterone acetate plus prednisone for mCRPC), or prior poly-(ADP-ribose) polymerase (PARP) inhibitor (Note

that both olaparib plus abiraterone and niraparib-abiraterone are under review for funding.)

- chemotherapy with docetaxel
- olaparib (in patients with deleterious or suspected deleterious germline and/or somatic mutations in the homologous recombination repair genes *BRCA* or *ATM* who have progressed following prior treatment with an ARAT)
- either of the following drugs:
  - enzalutamide
  - abiraterone plus prednisone.

In the case of treatment failure with docetaxel, patients may receive cabazitaxel, another taxane-based chemotherapy. Patients may also be treated with either enzalutamide or the combination of abiraterone plus prednisone.

At any time, patients may become eligible to receive olaparib if they meet the specific mutation criteria for deleterious or suspected deleterious germline and/or somatic mutations in the homologous recombination repair genes *BRCA* or *ATM* and have progressed following prior treatment with a new hormonal drug or ARAT.

Patients may be eligible for lutetium vipivotide tetraxetan if they meet the initiation criteria, which include patients with mCRPC who are prostate-specific membrane antigen (PSMA) positive, per the criteria used in the VISION trial, and who were previously treated with an APRI and at least 1 prior taxane-containing regimen. After receiving lutetium vipivotide tetraxetan, a patient may be eligible for olaparib if they meet the specific mutation criteria, or alternative chemotherapy if indicated. Note that lutetium vipivotide is currently under review for funding.

Additional Remarks

CADTH was unable to make an informed recommendation on the preferred treatments of choice and on optimal sequencing of treatments for patients in the various prostate cancer settings but recognizes that provinces will need to address this issue upon the implementation of reimbursement recommendations, especially considering the coexistence of various androgen receptor-targeted therapies.

In addition, the 2 reviews (abiraterone acetate for nmCSPC and mCSPC) reflected in the previous provisional funding algorithm stem from the Formulary Management Expert Committee (FMEC) via the nonsponsored review procedures. When sponsors of the branded drug have declined to file an application with CADTH, CADTH will consider reviewing a drug through the nonsponsored reimbursement review process. This can address clinical indications for which a pharmaceutical manufacturer has not applied for a Health Canada Notice of Compliance (i.e., off-label use) when there is evidence for use of the drug for the condition of interest in clinical practice in Canada (e.g., integration of the drug into clinical practice guidelines, consultations with clinical specialists). For full eligibility criteria, please refer to the nonsponsored review procedures.