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CADTH Reimbursement Recommendation

Olaparib (Lynparza)

Indication: In combination with abiraterone and prednisone or prednisolone for the 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. BRCA mutation must be confirmed before olaparib treatment is initiated.

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Lynparza?

CADTH recommends that Lynparza, in combination with abiraterone with prednisone or prednisolone, should be reimbursed by public drug plans for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Lynparza should only be covered to treat patients with mCRPC who have BRCA mutations, who have not been treated with an androgen receptor pathway inhibitor (ARPi), who have not been treated with a poly-(ADP ribose) polymerase (PARP) inhibitor for mCRPC, and who have not been treated with a CYP-17 inhibitor for mCRPC for more than 4 months. Also, the patients should be in relatively good health.

What Are the Conditions for Reimbursement?

Lynparza, in combination with abiraterone with prednisone or prednisolone, should only be reimbursed if it is prescribed by a clinician with expertise in treating prostate cancer with systemic anticancer therapy and if the costs of both Lynparza and abiraterone are reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Lynparza and abiraterone with prednisone or prednisolone may delay the progression of disease (based on medical imaging) and improve survival in patients with BRCA-mutated mCRPC compared with placebo and abiraterone with prednisone or prednisolone.
- Lynparza may meet some of the important needs to patients, such as prolonging survival.
- Based on CADTH's assessment of the health economic evidence, Lynparza, combined with abiraterone, does not represent good value to the health care system at the public list price. Given the cost of Lynparza and abiraterone, which must be taken in combination, a price reduction for both drugs (i.e., Lynparza and abiraterone) is required.
- Based on public list prices, Lynparza, in combination with abiraterone, is estimated to cost the public drug plans approximately $15 million over the next 3 years.

Summary

Additional Information

What Is mCRPC?

mCRPC refers to prostate cancer that has spread to other parts of the body and does not respond to treatment that lowers testosterone levels. It is estimated that 24,600 people would be diagnosed with prostate cancer in 2022, 9% of whom will have metastatic disease. The 5-year survival rate for mCRPC is approximately 26% to 28%.

Unmet Needs in mCRPC

There is no cure for mCRPC with available treatments. For patients with mCRPC, there is a need for effective treatments that can extend survival while improving or maintaining the quality of life of patients.

How Much Does Lynparza Cost?

Treatment with Lynparza is expected to cost approximately $102,194 per patient per year. Combined with abiraterone and prednisone or prednisolone, the cost of the combination regimen is expected to be $140,147 per patient per year.

Recommendation

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 conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, double-blind, placebo-controlled, multicentre trial (PROpel, N = 796) evaluated the efficacy and safety of first-line treatment with olaparib and abiraterone acetate with prednisone or prednisolone (hereafter referred to as olaparib and abiraterone) compared to abiraterone acetate and placebo with prednisone or prednisolone (hereafter referred to as abiraterone) in patients with mCRPC who have not received prior systemic therapy in the mCRPC setting. A subgroup in the PROpel trial (N = 85) aligned with the indication under review: adults with deleterious or suspected deleterious germline and/or somatic BRCA-mutated mCRPC in whom chemotherapy is not clinically indicated. This subgroup analysis demonstrated that treatment with olaparib and abiraterone may result in a clinically important increase in radiographic progression-free survival (rPFS) and overall survival (OS) compared with abiraterone. More specifically, the hazard ratio (HR) for rPFS at the first data cut-off date (DCO1, July 30, 2021) was 0.23 (95% confidence interval [CI], 0.12 to 0.43) favouring olaparib and abiraterone. The median rPFS at DCO1 was not reached in the olaparib and abiraterone group and 8.38 months (95% CI not reported) in the abiraterone group. Regarding OS, the HR reported at the third data cut-off date (DCO3, October 12, 2022) was 0.29 (95% CI, 0.14 to 0.56) favouring olaparib and abiraterone.

Patients identified the need for effective treatments that can extend life, maintain their quality of life, relieve symptoms, have fewer side effects, and are affordable and easily accessed. As described above, pERC concluded that olaparib and abiraterone may meet the need to prolong survival. Although patients expect new treatments for mCRPC to improve health-related quality of life (HRQoL), this was not demonstrated in the PROpel trial due to the very low certainty of HRQoL assessments in this subgroup using the Functional Assessment of Cancer Therapy - Prostate (FACT-P).

The committee considered the cost-effectiveness of olaparib and abiraterone with prednisone or prednisolone relative to abiraterone and enzalutamide based on data from the PROpel trial and a real-world evidence registry study. Based on the sponsor's submitted price for olaparib and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for olaparib and abiraterone was estimated to be $160,535 per quality-adjusted life-year (QALY) gained compared with abiraterone alone. Given the cost of olaparib ($102,000 per patient annually), the Health Canada-indicated requirement to be taken in combination with abiraterone, and extended duration of treatment, there are no price reductions for olaparib alone where a $50,000 per QALY gained threshold could be achieved for the combination regimen.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
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 positive for a germline and/or somatic BRCA1 or BRCA2 gene alteration 1.2. have not received prior treatment with an ARPi in the mCSPC or nmCRPC setting 1.3. have not received prior treatment with a PARP inhibitor for mCRPC 1.4. have not received CYP-17 inhibitor (e.g., abiraterone) for mCRPC for a prolonged time period (refer to the implementation guidance).	In the PROpel trial, treatment with olaparib and abiraterone demonstrated a clinical benefit in the subgroup of adult patients (≥ 18 years of age) with BRCA mutation who had not received prior treatment with a PARP inhibitor or CYP-17 inhibitor. Although patients who had received prior ARPi in the mCSPC stage were allowed in the PROpel trial, only 1 out of 399 study participants received enzalutamide at the mCSPC stage. This patient's BRCA mutation status was not reported. In addition, there is a lack of evidence for using sequencing ARPIs in patients with mCRPC. Therefore, pERC suggests excluding patients who have received prior ARPIs in the mCSPC setting from treatment with olaparib and abiraterone.	Patients must have confirmed BRCA mutation status before treatment with olaparib is initiated. Patients with mCRPC treated with abiraterone for a maximum of 4 months should be eligible for treatment with olaparib and abiraterone as timely access to BRCA testing should not preclude a patient from treatment with the combination therapy.
2. Patients should have good performance status.	Patients with an ECOG performance status of 0 or 1 were included in the PROpel trial.	Treating patients with ECOG performance status of greater than 1 may be at the treating clinician's discretion.
Discontinuation		
3. Reimbursement of olaparib and abiraterone should continue until disease progression or unacceptable toxicity.	Patients from the PROpel trial discontinued treatment upon disease progression or unacceptable toxicities.	—
Prescribing		
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.	To ensure that olaparib and abiraterone is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
5. Olaparib and abiraterone should not be reimbursed when administered in combination with other anticancer drugs.	There is no data supporting the efficacy and safety of olaparib and abiraterone when used in combination with additional anticancer drugs.	—
Pricing		
6. A reduction in price	The ICER for olaparib and abiraterone is $160,535 when compared with abiraterone. Based on the cost of olaparib ($102,000 per patient annually) and the Health Canada-indicated requirement	—

Reimbursement condition	Reason	Implementation guidance
	that it be taken in combination with abiraterone, there are no price reductions for olaparib where the olaparib and abiraterone regimen would achieve an ICER of $50,000 per QALY gained. If a price reduction is applied to both drugs within the regimen, a 79% price reduction (i.e., 79% price reduction for olaparib and 79% price reduction for abiraterone) would be required to achieve an ICER of $50,000 per QALY gained compared to abiraterone alone.	
Feasibility of adoption		
7. The feasibility of the adoption of olaparib and abiraterone must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

ARPi = androgen receptor pathway inhibitors; BRCA = breast cancer gene; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; nmCRPC = nonmetastatic castration-sensitive prostate cancer; PARP = poly-(ADP ribose) polymerase; PSA = prostate-specific antigen; QALY = quality-adjusted life-year.

Discussion Points

- pERC acknowledged the magnitude of benefit observed for rPFS and OS in a subgroup of patients with BRCA mutations despite the limitations of subgroup analysis and considered the poor prognosis of patients with mCRPC. As part of the discussion of the subgroup analysis, pERC noted that the clinical benefit that was observed in overall population (rPFS) strengthened the certainty of the subgroup analysis. In summary, given the totality of the evidence, pERC concluded that olaparib and abiraterone may offer a clinical benefit for patients with mCRPC in the first-line setting, in particular in the subgroup of those with positive BRCA1 or BRCA2 gene alteration.
- pERC noted that patients with mCRPC identified a need for alternative treatment options with fewer side effects. In the PROpel trial, the proportion of patients in the BRCA subgroup who received treatment with olaparib and abiraterone that experienced adverse events (AEs), serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), and notable harms was similar to those who received abiraterone alone. Despite the uncertainty of the safety evidence, pERC considered that some patients may value the delay of disease progression over the reduction of side effects. The clinical experts considered the harms manageable and in line with clinical expectations. pERC noted that the decision to receive treatment and adopt the risks of side effects can be made by patients who are fully informed of those risks.
- pERC noted that HRQoL was identified as an important patient outcome in the study population; however, the certainty that the effect of olaparib and abiraterone on HRQoL was low due to small

sample size, imbalanced patient baseline characteristics between treatment groups and insufficiently reported HRQoL data.

- CADTH's estimate of the 3-year budget impact was sensitive to assumptions regarding the proportion of patients who would not be clinically indicated for chemotherapy. pERC noted that in clinical practice, no consistent criteria are used to identify patients for whom chemotherapy is not clinically indicated. However, there is consensus that identifying these patients would be mainly based on the clinical judgment of the treating physician informed by multiple factors, including patient characteristics and preferences regarding treatment choice. Because this criterion does not have a consistent clinical definition, CADTH chose a conservative definition of clinical indication for chemotherapy that reflected patients who had not received abiraterone or enzalutamide during either the castration-sensitive or castration-resistant phase of treatment based on input from clinical experts. If a broader definition is adopted, the budget impact will change accordingly.
- pERC noted the importance of timely genetic testing for BRCA mutations, which is required before initiating treatment with olaparib and abiraterone as per the indication approved by Health Canada. It was noted that the availability of genetic testing at diagnosis varies across Canada, as genetic testing before first-line treatment for mCRPC is not a standard practice across CADTH-participating jurisdictions. As one of the first-line therapies for mCRPC that is dependent on genetic testing results, it is anticipated that there will be an increase in the overall number of genetic tests among patients with prostate cancer, which represents added costs to the health care system and may impact timely access to testing.

Background

Prostate cancer is the most common cancer among men living in Canada, affecting 1 in 8 men during their lifetime. It was estimated that in 2022, 24,600 men in Canada would be diagnosed with prostate cancer. Previous research demonstrated that 10% to 20% of patients with prostate cancer would develop castration-resistant prostate cancer (CRPC) within 5 years of follow-up. Among these patients, approximately 90% will have metastatic disease. When the disease progresses to the metastatic CRPC (mCRPC) stage, the 5-year survival rate reduces to approximately 26% to 28%. Metastatic disease is also debilitating and detrimental to patient HRQoL, with symptoms including pain, sexual dysfunction, discomfort, skeletal-related events, anxiety, depression, fatigue, cognitive impairment, urinary and bowel incontinence, nausea, and diarrhea. Certain gene mutations (e.g., BRCA mutation) in patients with prostate cancer are associated with poor prognosis. Patients with BRCA1 or 2 gene mutations have been considered more vulnerable to the effects of an existing treatment for mCRPC, poly-(ADP ribose) polymerase (PARP) inhibitors. Therefore, these patients may benefit from treatment with PARP inhibitors, and testing for genetic alterations can inform about prognosis and assist in the selection of optimal therapies.

The main treatment goals for patients with mCRPC are to prolong their survival, to delay disease progression and to improve their HRQoL. Currently, treatments available for patients with mCRPC usually include new hormone agents (NHAs) (i.e., abiraterone or enzalutamide), taxane-based chemotherapies (i.e., docetaxel

or cabazitaxel), and other therapies such as bone-targeted drug (radium-223), olaparib monotherapy, and lutetium vipivotide tetraxetan. Olaparib is a selective inhibitor of human PARP enzymes. Olaparib alone has been approved by Health Canada for the treatment of adult patients with deleterious germline and/or somatic BRCA or ATM mutated mCRPC who have progressed following prior treatment with an NHA. A combined antitumour effect with administration of PARP inhibitors and NHAs (such as olaparib and abiraterone, respectively) has been reported in preclinical studies in prostate cancer models. On July 11, 2023, olaparib in combination with abiraterone and prednisone or prednisolone (hereafter referred to as olaparib and abiraterone) was approved by Health Canada for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic BRCA-mutated mCRPC in whom chemotherapy is not clinically indicated. BRCA mutation must be confirmed before the combination regimen is initiated. The sponsor's reimbursement request aligns with the Health Canada indication. Olaparib is administered orally and it is available as 100 mg and 150 mg tablets. The recommended total daily dose of olaparib tablets is 600 mg. In the combination regimen, the dose of abiraterone is 1,000 mg orally once daily. Abiraterone should be given with prednisone or prednisolone 5 mg orally twice daily. It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

Sources of Information Used by the Committee

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

- a review of a phase III, randomized, double-blind, placebo-controlled trial (PROpel) in adults with mCRPC. This CADTH reimbursement review focuses on the evidence in the subgroup of patients with BRCA mutation
- patients' perspectives gathered by 2 patient groups: the Canadian Cancer Society (CCS) and the Canadian Cancer Survivor Network (CCSN)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise in diagnosing and treating patients with prostate cancer
- input from 2 clinician groups, including Ontario Health (Cancer Care Ontario) (OH-CCO) Genitourinary Cancer Drug Advisory Committee (GU DAC) and clinicians in Canada with expertise in managing advanced prostate cancer
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Two patient groups, the CCS and the CCSN, provided input to the review of olaparib used in combination with abiraterone for mCRPC. The CCS is a national charitable organization that collected input from patients and caregivers through a survey from an unknown start date to April 27, 2023. In total, 23 respondents provided

input, none of whom had been treated with olaparib. The CCSN is a national network involving patients, families and friends, community partners, funders and sponsors that aims to promote the best standard of care for cancer patients. The CCSN gathered patient input through an online survey from May 10 to 19, 2023. Among the 7 respondents to this survey, 1 patient had experience with olaparib monotherapy.

Based on the patient input, the majority of the patients had received multiple lines of treatment. None of the patient input specified whether these treatments were received at the mCRPC stage or received since the patients' initial diagnosis of prostate cancer. The disease of mCRPC and the currently available treatments have significant negative impact on patient's physical and psychosocial well-being, affecting their everyday life, work and family. Financial stress is 1 of the key barriers for patients who are receiving treatments for mCRPC.

Patients from both groups indicated that there is a need for new treatments that can improve HRQoL, relieve symptoms, prolong survival, have fewer side effects, as well as being affordable and easily accessed.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts indicated that for patients with mCRPC, the most important goals of treatment are to prolong survival, relieve symptoms, and improve the patient's quality of life. The experts identified these unmet needs associated with the current treatments for mCRPC: 1) therapies that are curative; 2) therapies that improve survival outcomes better than the current treatments; and 3) better targeted therapies based on specific gene mutations.

The clinical experts indicated that among the current treatment options for adult patients with mCRPC, ARPIs (e.g., abiraterone or enzalutamide) or docetaxel can be used as first-line therapy, while ARPIs, docetaxel or radium-223 may be considered as the second-line therapies, depending on what the first-line therapy is. Lutetium vipivotide tetraxetan, radium-223 or cabazitaxel can be used as later lines of treatment thereafter. The experts also noted that in select patients, the combination of docetaxel and ARPI can be used as first-line treatment. Lastly, olaparib monotherapy can be used at any line in patients with a BRCA/ATM mutation who have progressed following prior treatment with an NHA.

With the emergence of the combination regimen of olaparib and abiraterone and based on the study findings from the clinical trials (such as the PROpel trial), the experts expected that there would be a shift in the current treatment paradigm. The experts anticipated that the combination regimen should be considered a first-line therapy option in patients with mCRPC, particularly for patients with BRCA mutations.

The clinical experts indicated that patients with BRCA mutations would be best suited for treatment with the combination of olaparib and abiraterone, based on findings from the clinical trials. The experts noted that patients for whom chemotherapy is not clinically indicated include those who are deemed physically unfit (such as poor renal function or poor performance status), or who have received prior docetaxel treatment in the metastatic castration-sensitive prostate cancer (mCSPC) phase. They also considered patients who refuse chemotherapy as potentially falling under this indication. The clinical experts noted

that the proportion of patients in the first-line mCRPC setting who are likely to be clinically indicated to receive chemotherapy was no more than 10% to 15%. The experts also indicated that for patients who may be clinically indicated to receive taxane-based chemotherapy but who are unwilling to receive docetaxel or cabazitaxel, the combination of olaparib and abiraterone would only be considered as a treatment option if the patients have BRCA mutation. The experts noted that there is a lack of evidence to support the treatment of olaparib and ARPIs in patients with non-HRR mutated cancers.

The clinical experts noted that in clinical practice, the criteria used to determine whether a patient with mCRPC is responding to treatment include prolonged survival, symptom relief (e.g., pain), improved HRQoL, improved prostate-specific antigen (PSA) response and imaging response. Typically, these assessments are reviewed once a month after initiating a new therapy.

According to the clinical experts, treatment with the combination of olaparib and abiraterone will be discontinued if disease progression is detected, based on the results of an imaging scan, PSA response or worsening of symptoms, and any intolerable adverse effects of the treatment.

The clinical experts noted that all centres that can prescribe ARPIs are generally appropriate for providing treatment with the combination of olaparib and abiraterone. Germline testing and/or somatic testing must be accessible in these centres to assist in selecting the suitable patients for this treatment. In addition, due to the high rate of anemia and possible need of blood transfusions in patients receiving combination therapy, the centres should be able to transfuse the patients when transfusion is required quickly and efficiently.

Clinician Group Input

Two clinician groups provided input for the review of olaparib and abiraterone combination therapy: Ontario Health (Cancer Care Ontario) (OH-CCO) Genitourinary Cancer Drug Advisory Committee (GU DAC) and clinicians in Canada with expertise in managing advanced prostate cancer.

In general, the clinician group input was consistent with the input provided by the experts consulted by CADTH for this review. They indicated that mCRPC is an incurable disease. The quick progression of the disease at this stage prohibits the patients from being eligible for second-line therapies and beyond. Effective treatments that are available early in the metastatic stage are lacking, and no effective combination therapy to date has been approved. Therefore, a new early treatment option that could also prolong the treatment duration of available therapies, delay disease progression, and improve long-term outcomes is warranted and critically needed. Both clinician groups stated that olaparib with abiraterone fulfills this unmet need for an effective and tolerable first-line combination, and that all patients with mCRPC would benefit from this combination therapy. One clinician group added that this treatment also suits patients for whom docetaxel is not yet clinically indicated or who were previously treated with docetaxel in the mCSPC setting.

The clinician groups noted that assessing response to treatment should be based on outcomes such as rPFS, PSA response, symptom improvement, as well as improvement in HRQoL.

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	
In the pivotal trial PROpel, treatment effect of combination of olaparib and abiraterone was compared to abiraterone. How does olaparib and abiraterone compare to olaparib monotherapy? Enzalutamide is another comparator for the combination of olaparib and abiraterone in the first-line setting of patients with mCRPC. How does olaparib and abiraterone compare to enzalutamide?	The clinical experts indicated that currently, olaparib monotherapy is not a standard of care for patients with mCRPC in the first-line setting. There is a lack of direct evidence to explore the relative efficacy of olaparib and abiraterone vs. olaparib monotherapy in the first-line setting. Also, there is no evidence to compare treatment of olaparib and abiraterone with enzalutamide in the first-line setting of patients with mCRPC. pERC agreed with the clinical experts.
Considerations for initiation of therapy	
In PROpel, eligible patients were with ECOG performance status of 0 or 1. Should the use of olaparib and abiraterone be extended to patients with ECOG performance status > 1?	The clinical experts suggested that generalizing the study findings of patients with ECOG performance status of 0 or 1 to those with performance status of 2 should be done very cautiously. pERC agreed with the clinical experts and indicated that whether or not to treat patients with ECOG performance status of 2 with the combination of olaparib and abiraterone should be determined by the treating physician.
Should patients who received abiraterone acetate-prednisone in the mCSPC setting be eligible for olaparib and abiraterone acetate with prednisone in the mCRPC setting?	Based on feedback from the clinical experts consulted by CADTH, pERC concluded that if patients have progressed from mCSPC to mCRPC while on abiraterone, they should not be eligible for olaparib and abiraterone in the mCRPC setting. However, pERC also noted that it would be reasonable to consider olaparib and abiraterone for patients being treated with abiraterone alone in the mCRPC setting for less than 4 months if their BRCA mutation status has not been obtained yet and the patient fulfills the remaining eligibility criteria for treatment with olaparib and abiraterone.
Considerations for discontinuation of therapy	
In the PROpel trial, the study drug could be continued even after objective disease progression if the investigator thought that there is continuous clinical benefit, no serious toxicity, and no better alternative treatment was available. What objective parameters should be used to determine when the patient should no longer be eligible for further treatment with olaparib and abiraterone?	The clinical experts noted that in clinical practice, there is no single objective parameter to consider for treatment discontinuation. This treatment may be discontinued if the disease or symptoms cannot be adequately controlled or if there are intolerable toxicities. However, if the patient can tolerate it, the treatment may continue even if the patient's PSA level rises slightly. If the patient plans to switch to a different therapy, the combination treatment of olaparib and abiraterone should be stopped. pERC agreed with the clinical experts.

Implementation issues	Response
Considerations for prescribing of therapy	
In the PROpel trial, patients could continue on olaparib if abiraterone was discontinued (and vice-versa). Is this consistent with practice in Canada? Is evidence available to support this treatment regimen? Should this approach be allowed in public listing?	The clinical experts indicated that the main reason for treatment discontinuation is likely related to disease progression or intolerable toxicity. In this case, usually, both drugs would be discontinued in practice unless there is a clear signal that intolerable toxicity is linked to one of the drugs, then the drug causing the toxicity should be stopped. pERC agreed with the clinical experts.
Generalizability	
For patients with mCRPC who are currently receiving first-line abiraterone treatment, can olaparib be added?	The experts noted that there is no evidence to support adding olaparib for patients who are already on first-line abiraterone treatment. However, the experts suggested that olaparib may be added if the patient has only been on abiraterone for a short period of time, i.e., within 4 months. pERC agreed with the clinical experts.
Funding algorithm (oncology only)	
In the PROpel trial, patients might have prior docetaxel treatment in the localized or mCSPC setting. Under what circumstances would first-line olaparib and abiraterone be preferred over other available systemic treatment options? Is there evidence to support the treatment 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.
Care provision issues	
Companion diagnostics: Does BRCA mutation need to be confirmed before olaparib therapy is initiated to align with Health Canada NOC? Are there instances where dual therapy is preferred over triplet therapy?	As per the indication, BRCA mutation must be confirmed before olaparib treatment is initiated. The clinical experts agreed that BRCA testing will likely become mandatory for the treatment for mCRPC. The experts noted that the availability of testing for BRCA mutations varies widely between jurisdictions in Canada, and they anticipated that germline testing will be widespread much sooner as it is easy to use, while widespread implementation of somatic testing may take more time. The experts also indicated that for patients with mCRPC in the first-line setting, it is unlikely that a triplet therapy would be given to the patients. pERC agreed with the clinical experts and noted the challenges in practice related to lab capacity that must be considered, such as wait time for testing for BRCA status and obtaining results, funds available for testing, and the subsequent impact on the patients in receiving treatments in time.

Implementation issues	Response
System and economic issues	
PAG has concerns about the budget impact of this combination regimen.	Comment from the drug programs to inform pERC deliberations.
Generic abiraterone is available	Comment from the drug programs to inform pERC deliberations.

BRCA = breast cancer susceptibility gene; ECOG = Eastern Cooperative Oncology Group; HRRm = homologous recombination repair gene mutation; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; NOC = notice of compliance; PAG = Provincial Advisory Group; PSA = prostate-specific antigen.

Clinical Evidence

Description of Studies

One phase III, randomized, double-blind, placebo-controlled, multicentre trial, PROpel (N = 796) met the inclusion criteria for the systematic review conducted by the sponsor, and a subgroup of patients who had a BRCA mutation (N = 85) was enrolled into the study. Even though the purpose of the PROpel trial was to evaluate the efficacy and safety of the combination of olaparib and abiraterone versus abiraterone and placebo with prednisone or prednisolone (hereafter referred to as abiraterone) in all patients with mCRPC who had received no prior cytotoxic chemotherapy or NHAs at the mCRPC stage, to align with the Health Canada–approved indication, evidence in the subgroup of patients with a BRCA mutation was the focus of this review.

In the PROpel trial, patients were randomized to either a combination of olaparib (300 mg twice daily) and abiraterone (1,000 mg once daily) and prednisolone/prednisone (5 mg twice daily) (n = 399, BRCA mutated n = 47) or placebo (matched to olaparib; twice daily) and abiraterone (1,000 mg once daily) prednisolone/prednisone 5 mg twice daily (n = 397, BRCA mutated n = 38). The primary efficacy end point in the PROpel trial was rPFS by investigator assessment. Other outcomes in this study included OS, time to first subsequent therapy (TFST), HRQoL measured by the FACT-P questionnaire, overall response rate (ORR), PSA response and safety. In the subgroup population of patients with BRCA mutation, all outcomes analyzed (rPFS, OS, TFST, ORR, PSA response rate, FACT-P total score and safety) were exploratory.

Among patients in the olaparib and abiraterone treatment group (n = 47) of the subgroup of patients with BRCAm, the median age at baseline was 67.0 years (range = 43 to 83), 30 (63.8%) patients were over age 65 years, 34 (72.4%) had a Gleason score of 8 to 10, 8 (17.0%) had previously been treated with docetaxel at the mCSPC stage, 36 (76.6%) had an ECOG performance status of 0, 31 (66.0%) had no or mild or no pain, and the median PSA level was 29.0 (range not reported). Among patients in the abiraterone treatment group (n = 38) of the subgroup of patients with BRCAm, the median age at baseline was 70.0 years (range = 46 to 85), 27 (71.1%) were over age 65 years, 25 (65.8%) had a Gleason score of 8 to 10, 10 (26.3%) had previously been treated with docetaxel at the mCSPC stage, 20 (52.6%) had an ECOG performance status of 0, 26 (68.4%) had no or mild or no pain, and the median PSA level was 22.5 (range not reported). Other important baseline characteristics, e.g., TNM classification (a standard for cancer staging that includes the extent of

the tumour [T], extent of spread to the lymph nodes [N], and presence of metastasis[M]) and prior treatments, were not reported.

Efficacy Results

The investigator-assessed rPFS was the primary outcome in the PROpel trial. rPFS had an HR of 0.23 (95% CI, 0.12 to 0.43). The median rPFS was not reached in the olaparib and abiraterone group and was 8.4 months in the abiraterone group. According to the clinical expert consulted by CADTH, the survival benefit gained from the treatment may be considered moderate and clinically important. However, a median rPFS has yet to reach the data cut-off date. Results of the blinded independent central review (BICR)-assessed rPFS were consistent with those from the primary analysis.

Treatment with olaparib and abiraterone may be associated with prolonged OS. Results from the OS analyses in the BRCAm subgroup showed that the HR of OS was 0.29 (95% CI, 0.14 to 0.56). Due to the immature data at the final OS analysis, the median OS was not reached in the olaparib and abiraterone group and was 23.0 months in the abiraterone group. The clinical experts considered the improvement in OS to be clinically important. Overall, treatment with olaparib and abiraterone was associated with prolonged OS. However, the benefit gained in these patients was considered small compared to the abiraterone group, given the limitations of the available data. A longer follow-up time for the survival outcomes is desired.

The HR for TFST was 0.35 (95% CI, 0.21 to 0.61). The median TFST was 37.39 months in the olaparib and abiraterone group compared to 14.75 months in the abiraterone group. The clinical experts considered the benefit from TFST clinically important and consistent with the primary outcome, rPFS. Given the available evidence, treatment with olaparib and abiraterone was associated with a longer time required for the first subsequent anticancer treatment than abiraterone.

HRQoL was assessed based on the least squares (LS) mean change from baseline in FACT-P total score. The change from baseline in the total score was 2.43 in the olaparib and abiraterone group and −1.21 in the abiraterone group. The between-group difference in the mean change from baseline with 95% CI was not reported. Based on the data on FACT-P total score, the treatment effect of olaparib and abiraterone on improving patients' HRQoL compared to abiraterone remains uncertain.

Two exploratory outcomes, ORR and PSA response, were also measured in PROpel to provide evidence on treatment response. The proportion of patients who achieved complete response or partial response was 50.0% in the olaparib and abiraterone group and 26.7% in the abiraterone group. The proportion of patients with a PSA response was 85.1% in the olaparib and abiraterone group and 51.4% in the abiraterone group. Results of ORR and PSA response suggested that patients treated with olaparib and abiraterone were associated with a higher response rate and a higher PSA response rate, compared to those treated with abiraterone. However, definite conclusions on response rate related to the treatment with the combination of olaparib and abiraterone cannot be made, due to the concerns about the risk of bias related to baseline imbalances in patient characteristics and the high proportion of patients who were not evaluable, imprecision related to the small sample size of the subgroup, and lack of details in data reporting.

Harms Results

Limited results were reported for harms in the subgroup of patients with BRCA mutation.

The overall frequency of AEs was similar between olaparib and abiraterone and abiraterone in the PROpel trial, 100% versus 89.5% experienced at least 1 AE in the 2 treatment groups, respectively, with the most frequently reported AEs being anemia, fatigue, nausea, back pain and arthralgia. The proportion of experiencing at least 1 SAE was similar between the olaparib and abiraterone and abiraterone treatment groups (29.8% versus 31.6%, respectively). The proportion of patients who withdrew from olaparib (or placebo) treatment due to AEs was 12.8% in the olaparib and abiraterone group and 10.5% in the abiraterone group. The proportion of AEs leading to death was 2.1% in the olaparib and abiraterone group and 5.3% in the abiraterone group. Reasons for the deaths were not provided in this subgroup. In this subgroup, 5 (10.6%) patients in the olaparib and abiraterone group reported pulmonary embolism; there were no pulmonary embolisms reported in the abiraterone group. Other notable harms were not reported in this subgroup. The small sample size and low number of events in the subgroup of patients with a BRCA mutation resulted in an assessment of certainty rated low to very low; however, the proportion of patients reported as having experienced SAEs, WDAEs, and notable harms (pulmonary embolisms) were aligned with expectations from the clinical experts consulted by CADTH based on their experience treating patients with mCRPC and did not raise significant safety concerns.

Critical Appraisal

The current CADTH review focused on the subgroup of patients with BRCA mutation in the PROpel trial (which aligned with Health Canada–approved indication) but not the overall population. One of the key limitations of this study was the small sample size. Although the sample size of the full population in PROpel was approximately 800 patients, there were only 85 patients with a BRCA mutation, 47 in the olaparib and abiraterone group and 38 in the abiraterone group.

Prognostic balance cannot be ensured across the treatment groups in this subgroup of patients as the randomization was not stratified by BRCA mutation status. There was an imbalance between the treatment groups based on several patient baseline characteristics (e.g., age, baseline pain scores, baseline Gleason score and body location of metastases), and several important patient characteristics (e.g., TNM classification, prior treatments for mCRPC) were not reported. Patients in the olaparib treatment group tended to be younger, had more severe pain, slightly higher PSA level at baseline and better performance status. It is unclear how these factors, in combination, may have biased the study results. Small sample size resulted in imprecision in many of the effect estimates. Further, between-group differences (relative or absolute) were not provided for some outcomes (such as HRQoL and ORR) precluding the comprehensive appraisal of comparative efficacy.

In the PROpel trial, all subgroup analyses were considered exploratory and were not adjusted for multiple comparisons, so there is an increased risk of type I error (i.e., a false-positive result) for statistically significant findings.

In the subgroup of patients with BRCA mutation, efficacy and safety outcomes were not reported in sufficient detail. As a result, these outcomes were mostly affected by concerns for imprecision, uncertainties and study limitation (e.g., imbalanced baseline characteristics between the 2 treatment groups). This often precludes a robust critical appraisal, for example, reasons for censoring patients were not provided, information about the proportion of patients who completed HRQoL assessments in each group was not reported, and baseline values for HRQoL outcomes were not reported. Therefore, it is difficult to fully explore the magnitude of treatment effect on these outcomes. The sponsor noted that according to an FDA briefing document[17], adjustment by a known prognostic model in mCRPC did not produce overall divergent results from the unadjusted results. However, CADTH review team did not have access to the adjusted model. Without any knowledge of the model and the variables within it, the team cannot fully interpret the results of the adjusted analysis. Furthermore, longer follow-ups are needed to examine the long-term clinical benefits or risks of this combination regimen, given the immature survival data at the third data cut-off date.

Updated analyses at the third data cut-off were not provided for all outcomes (e.g., rPFS, FACT-P total score and PSA response). Missing data in the subgroup of patients with BRCA mutation concerns the potential for bias in the study results.

External Validity

The clinical experts consulted by CADTH considered the eligibility criteria and baseline characteristics of the PROpel trial, and suggested that the study population is reflective of a typical patient population in Canada (although could be somewhat healthier; for example, patients in the PROpel trial had better performance status and less pain) that would receive combination therapy of olaparib and abiraterone, except that patients in the PROpel trial were not allowed to receive prior abiraterone therapy before study entry. However, in clinical practice, patients at the mCRPC stage usually would have been treated with other active treatments including abiraterone. Therefore, the study findings may only be generalized to patients who haven't received abiraterone before. The experts indicated that the outcome measures in the PROpel trial are appropriate and clinically relevant in clinical trials of metastatic prostate cancer. However, some important outcomes were not reported for the BRCA-mutated subgroup (such as pain symptoms and symptomatic skeletal-related events [SSRE]). Results for certain AEs were not reported in this subgroup.

The combination therapy under review is indicated for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic BRCA-mutated mCRPC in whom chemotherapy is not clinically indicated. The drug is intended to be used in the first-line setting at mCRPC. According to the clinical experts consulted by CADTH, there are no consistent criteria used in clinical practice to identify patients for whom chemotherapy are not clinically indicated. This patient group may include those who are deemed physically unfit (such as poor renal function or poor performance status), those refuse chemotherapy, or who have received prior docetaxel treatment. The clinical experts noted that the proportion of patients in the first-line mCRPC setting who are likely to be clinically indicated to receive chemotherapy was no more than 10% to 15%, implying that 85% to 90% of these patients would be eligible for the treatment with olaparib and abiraterone. In the PROpel trial, the combination of olaparib and abiraterone was compared

to abiraterone, which was a relevant comparator. Evidence for the comparisons between olaparib and abiraterone and other comparators is lacking.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials (RCTs) identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group:

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The reference points for the certainty of evidence assessment for OS and rPFS were set to null since there were no absolute effects for these outcomes. The reference point for the certainty of the evidence assessment for FACT-P total score was set according to the presence or absence of an important effect based on thresholds identified in the literature. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for the TFST due to the lack of a formal minimal important difference (MID) estimate and for harm events due to the unavailability of the absolute difference in effects, the certainty of the evidence was summarized narratively.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Survival outcomes (rPFS, OS, TSFT, SSRE)
- Response (ORR, PSA response)
- HRQoL (FACT-P, BPI-SF)
- Harms (any AEs, any SAEs, WADEs, notable harms)

Results of GRADE Assessment

Table 3 presents the GRADE summary of findings for olaparib and abiraterone versus abiraterone.

Table 3: Summary of Findings for Olaparib and Abiraterone Versus Abiraterone for Patients with mCRPC having BRCA mutation

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
rPFS				
rPFS at DCO1 (July 30, 2021) Median follow-up: • 16.5 months for olaparib and abiraterone group • 14.0 months for abiraterone group	1 RCT, 85 BRCAm patients	Events at DCO1: • Olaparib and abiraterone: 298 per 1,000 (95% CI not reported) • Abiraterone: 737 per 1,000 • HR = 0.23 (95% CI 0.12 to 0.43) Median (95% CI) rPFS at DCO1, months: • Olaparib and abiraterone: not reached (95% CI not reported) • Abiraterone: 8.38 (95% CI not reported) Survival probability (95% CI): not reported at 1 or 2 years	Low[a]	Olaparib and abiraterone may result in a clinically important increase in rPFS when compared with abiraterone.
OS				
OS at DCO3 (October 12, 2022) Median follow-up: • 18.5 months for olaparib and abiraterone group • 14.3 months for abiraterone group	1 RCT, 85 BRCAm patients	Deaths at DCO3: • Olaparib and abiraterone: 277 per 1,000 (95% CI not reported) • Abiraterone: 658 per 1,000 • HR = 0.29 (95% CI 0.14 to 0.56) Median (95% CI) OS at DCO3, months: • Olaparib and abiraterone: not reached (95% CI not reported) • Abiraterone: 22.97 (95% CI not reported) Survival probability (95% CI): not reported at 1 or 2 years	Low[b]	Olaparib and abiraterone may result in a clinically important increase in OS when compared with abiraterone.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
TFST				
Time to first subsequent anticancer therapy at DCO3 (October 12, 2022) Median follow-up: • 18.5 months for olaparib and abiraterone group • 14.3 months for abiraterone group	1 RCT, 85 BRCAm patients	Events at DCO3: • Olaparib and abiraterone: 511 per 1,000 (95% CI not reported) • Abiraterone: 789 per 1,000 • HR = 0.35 (95% CI 0.21 to 0.61) Median (95% CI) rPFS at DCO1, months: • Olaparib and abiraterone: 37.39 • Abiraterone: 14.75 (95% CI not reported) Survival probability (95% CI): not reported at 1 or 2 years	Low[c]	Olaparib and abiraterone may result in a clinically important increase in the time to the first subsequent anticancer therapy when compared with abiraterone.
SSRE				
NR	—	NA	NA	There was no evidence for the effect of olaparib and abiraterone on SSRE when compared with abiraterone
ORR				
ORR at DCO1 (July 30, 2021) Median follow-up: • 16.5 months for olaparib and abiraterone group • 14.0 months for abiraterone group	1 RCT, 35 BRCAm patients	Response at DCO1: • Olaparib and abiraterone: 500 per 1,000 (95% CI not reported) • Abiraterone: 267 per 1,000 • OR (95% CI) not reported	Very low[d]	The evidence is very uncertain about the effect of olaparib and abiraterone on ORR when compared to abiraterone
FACT-P				
LS mean change from baseline in FACT-P total score at DCO3 (October 12, 2022) (range of scores: 0 to [worst] to 156 [best]) Median follow-up:	1 RCT, N not reported	Baseline, mean (SD): • Olaparib and abiraterone: not reported • Abiraterone: not reported At DCO3, mean change from baseline	Very low[e]	The evidence is very uncertain about the effect of olaparib and abiraterone on HRQoL measured with a disease-specific questionnaire when compared to abiraterone.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
• 18.5 months for olaparib and abiraterone group • 14.3 months for abiraterone group		(95% CI): • Olaparib and abiraterone: 2.43 (95% CI not reported) • Abiraterone: −1.21 • Mean difference (95% CI): not reported		
BPI-SF				
NR	—	NA	NA	There was no evidence for the effect of olaparib and abiraterone on BPI-SF score when compared with abiraterone.
PSA Response				
PSA_{50} response at DCO1 (July 30, 2021) Median follow-up: • 16.5 months for olaparib and abiraterone group • 14.0 months for abiraterone group	1 RCT, 85 BRCAm patients	Response at DCO1: • Olaparib and abiraterone: 851 per 1,000 • Abiraterone: 514 per 1,000 • OR (95% CI) not reported	Very low[f]	The evidence is very uncertain about the effect of olaparib and abiraterone on PSA response when compared to abiraterone.
Harms				
Any AEs at DCO3 (October 12, 2022) Median follow-up: • 18.5 months for olaparib and abiraterone group • 14.3 months for abiraterone group	1 RCT, 85 BRCAm patients	In the subgroup of patients with BRCA mutation, the proportion of AEs was 100% in the olaparib and abiraterone group and 89.5% in the abiraterone group	Low[g]	Olaparib and abiraterone may result in little to no difference in the number of patients experiencing one or more AEs when compared to abiraterone.
Any SAEs at DCO3 (October 12, 2022) Median follow-up: • 18.5 months for olaparib and abiraterone group • 14.3 months for abiraterone group	1 RCT, 85 BRCAm patients	In the subgroup of patients with BRCA mutation, the proportion of SAEs was 29.8% in the olaparib and abiraterone group and 31.6% in the abiraterone group	Very low[h]	The evidence is very uncertain about the effect of olaparib and abiraterone on the number of patients experiencing one or more SAEs when compared to abiraterone.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
WDAEs at DCO3 (October 12, 2022) Median follow-up: • 18.5 months for olaparib and abiraterone group • 14.3 months for abiraterone group	1 RCT, 85 BRCAm patients	In the subgroup of patients with BRCA mutation, the proportion of WDAEs was 12.8% in the olaparib and abiraterone group and 10.5% in the abiraterone group	Very low[h]	The evidence is very uncertain about the effect of olaparib and abiraterone on the number of patients withdrawing from treatment due to AEs when compared to abiraterone.
Pulmonary embolisms at DCO3 (October 12, 2022) Median follow-up: • 18.5 months for olaparib and abiraterone group • 14.3 months for abiraterone group	1 RCT, 85 BRCAm patients	In the subgroup of patients with BRCA mutation, 5 patients (10.6%) in the olaparib and abiraterone group reported pulmonary embolism, compared to no patient in the abiraterone group.	Very low[h]	The evidence is very uncertain about the effect of olaparib and abiraterone on the number of patients who experience a pulmonary embolism when compared to abiraterone.

AE = adverse event; BRCAm = BRCA mutated; EFR = evaluable for response analysis set; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HR = hazard ratio; HRQoL = health-related quality of life; mCRPC = metastatic castration-resistant prostate cancer; NA = not applicable; NR = not reported; ORR = overall response rate; OS = overall survival; RCT = randomized controlled trial; rPFS = radiographic progression-free survival; SAE = serious adverse event; SSRE = symptomatic skeletal-related event; TFST = time to first subsequent anticancer therapy; WDAE = withdrawal due to adverse event.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes. All analyses for the BRCAm subgroup presented within this report were exploratory; as such, there were no adjustments for multiple comparisons and statistically significant results are at increased risk of type I error.

[a]Rated down 1 level for serious risk of bias. Randomization was not stratified by BRCA mutation status and there were baseline imbalances in important patient characteristics. Rated down 1 level for serious imprecision. In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of precision is based on the 95% CI for the HR using the null as the threshold, and the number of events at the DCO. The clinical importance of the between-group difference was judged based on the difference in median event rates and the input of the clinical experts consulted by CADTH for the review. Although the null was not crossed by the 95% CI, the small sample size (n = 85) and number of events (n = 42) raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance. The clinical experts indicated that the improvement in rPFS was clinically meaningful.

[b]Rated down 1 level for serious risk of bias. Randomization was not stratified by BRCA mutation status and there were baseline imbalances in important patient characteristics. Rated down 1 level for serious imprecision. In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of precision is based on the 95% CI for the HR using the null as the threshold, and the number of events at the DCO. The clinical importance of the between-group difference was judged based on the difference in median event rates and the input of the clinical experts consulted by CADTH for the review. Although the null was not crossed by the 95% CI, the small sample size (n = 85) and number of events (n = 38) raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance. The clinical experts indicated that the improvement in OS was clinically meaningful.

[c]Rated down 1 level for serious risk of bias. Randomization was not stratified by BRCA mutation status and there were baseline imbalances in important patient characteristics. Rated down 1 level for serious imprecision. In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of precision is based on the 95% CI for the HR using the null as the threshold, and the number of events at the DCO. The clinical importance of the between-group difference was judged based on the difference in median event rates and the input of the clinical experts consulted by CADTH for the review. Although the null was not crossed by the 95% CI, the small sample size (n = 85) and number of events (n = 54) raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance. The clinical experts indicated that the improvement in TFST was clinically meaningful.

[d]Rated down 2 levels for very serious risk of bias. Randomization was not stratified by BRCA mutation status and there were baseline imbalances in important patient characteristics. A large proportion of patients were not included in the EFR (57.4% and 60.5% of patients were not evaluable in the olaparib and abiraterone and abiraterone groups, respectively). Rated down 2 levels for serious imprecision. There was no point estimate and 95% CI for the assessment of between-group difference. The small sample size (n = 35) is small and there were few events (n = 14).

[e]Rated down 2 levels for very serious risk of bias. Randomization was not stratified by BRCA mutation status and there were baseline imbalances in important patient characteristics. It is unknown how many patients with mCRPC with BRCA mutation completed this assessment; however, in the overall population the completion rates for FACT-P were 67.6% in the olaparib and abiraterone group and 66.3% in the abiraterone group. Rated down 1 level for

serious imprecision. There was no point estimate and 95% CI for the assessment of between-group difference. MID of FACT-P total score ranged from 6 to 10, however, the between-group difference appeared smaller than MID. The sample size is small (n = 85 or less [total analyzed not reported]) and there is evidence of prognostic imbalance.

[f]Rated down 1 level for serious risk of bias. Randomization was not stratified by BRCA mutation status and there were baseline imbalances in important patient characteristics. Rated down 1 level for serious imprecision. There was no point estimate and 95% CI for the assessment of between-group difference. The small sample size (n = 85) and number of events (n = 59) raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance. Rated down 1 level for serious indirectness. There is a lack of consistent evidence to inform whether this surrogate outcome correlates with OS.

[g]Rated down 1 level for serious risk of bias. Randomization was not stratified by BRCA mutation status and there were baseline imbalances in important patient characteristics. Rated down 1 level for serious imprecision. The sample size (n = 85) and total number of events is small and there is evidence of prognostic imbalance.

[h]Rated down 1 level for serious risk of bias. Randomization was not stratified by BRCA mutation status and there were baseline imbalances in important patient characteristics. Rated down 2 levels for very serious imprecision. The sample size is small (n = 85) and there were very few or no events in either group.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	BRCA 1/2-mutated adult patients with first-line mCRPC who are NHA-naive and are not clinically indicated for chemotherapy in Canada. Note: The target population is not aligned with the Health Canada-indicated population, which is line-agnostic and NHA-agnostic. It is also narrower than the reimbursement request population, which is NHA-agnostic.
Treatment	Olaparib, in combination with abiraterone and prednisone or prednisolone (olaparib + abiraterone).
Dose regimen	The recommended total daily dose of olaparib tablets is 600 mg, taken as two 150 mg tablets twice daily, in combination with abiraterone (1,000 mg once daily) and supportive prednisone or prednisolone (5 mg twice daily).
Submitted price	Olaparib, 100 mg or 150 mg: $69.95 per tablet.
Treatment cost	The annual per-patient cost of olaparib is $102,194. In combination with abiraterone and prednisone or prednisolone, the annual per-patient cost of the combination regimen is $140,147.
Comparators	Abiraterone (with supportive prednisone or prednisolone) Enzalutamide
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	20 years
Key data sources	Olaparib + abiraterone vs. abiraterone: PROpel trial (Data cut-off date: October 12, 2022) Enzalutamide vs. abiraterone: Prospective real-world evidence registry study
Key limitations	• The population included in the economic model reflected the PROpel trial and was restricted to patients who are NHA-naive. However, the indicated population is NHA-agnostic, and thus broader than the modelled population. The cost-effectiveness of olaparib + abiraterone in patients with mCRPC who have failed prior treatment with an NHA is unknown. • There is uncertainty regarding how the clinical indication for chemotherapy would be defined in clinical practice given that it is based on the judgment of the treating physician rather than consistent clinical criteria. This leads to uncertainty in the cost-effectiveness in the patient population that is likely to receive olaparib + abiraterone in Canada. • Despite data immaturity, the parametric distribution selected by the sponsor to model long-term OS for olaparib + abiraterone assumed the risk of death would remain stable during the majority of the extrapolated period which was not considered plausible by clinical experts consulted by CADTH. • The sponsor's modelling approach predicts a 23% survival benefit in the postprogression period for olaparib + abiraterone compared to abiraterone, which does not align with clinical expectations or available clinical evidence. • The TTD and TTDA distributions selected by the sponsor lacked face validity and suggested that 12% of patients receiving olaparib + abiraterone continued to experience rPFS benefit despite treatment discontinuation (i.e., accruing health outcomes in the rPFS state with no treatment cost). • The sponsor's use of trial-based utility values lacks face validity, as the modelled cohort was suggested to have better quality of life in preprogression ([redacted]) than the reported general age-adjusted male

Component	Description
	population in Canada (0.842). • The use of RDI estimates to calculate drug costs may underestimate the total treatment costs that would be observed in real-world clinical practice. • Clinical experts noted that radium-223 is indicated for patients who are NHA-experienced, therefore, the sponsor omitted a relevant comparator for the indicated population.
CADTH reanalysis results	• CADTH base case was derived by making changes to the following model parameters: using the gamma distribution to extrapolate OS for olaparib + abiraterone; using the log-normal parametric distribution to extrapolate TTD and TTDA; sourcing utilities from alternative sources; and assuming 100% RDI for all therapies considered. • In the CADTH base case, olaparib + abiraterone was associated with an ICER of $160,535 per QALY gained compared to abiraterone (incremental costs: $508,237; incremental QALYs: 3.17).

ICER = incremental cost-effectiveness ratio; LY = life-year; mCRPC = metastatic castration-resistant prostate cancer; NHA = new hormonal agent; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; RDI = relative dose intensity; rPFS = radiological progression-free survival; TTD = time to treatment discontinuation of olaparib; TTDA = time to treatment discontinuation of abiraterone.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the modelled population does not align with the indicated population, the definition of the clinical indication for chemotherapy in clinical practice is uncertain, the projected market share of olaparib + abiraterone is underestimated, the use of relative dose intensity underestimated drug acquisition costs, the prevalence of clinically confirmed BRCA 1/2 mutation is uncertain, and the proportion of patients pre-tested for mutation status is uncertain.

CADTH conducted re-analyses of the budget impact analysis (BIA) by adjusting the projected market share of olaparib + abiraterone in line with clinical expert input and assuming 100% relative dose intensity across all therapies considered. Based on the CADTH base case, the estimated budget impact associated with the reimbursement of olaparib + abiraterone for the first-line treatment of BRCA1/2-mutated patients with mCRPC who are NHA-naive, and for whom chemotherapy is not clinically indicated, as per its reimbursement request, is expected to be $3,191,277 in Year 1, $6,208,353 in Year 2, and $5,434,236 in Year 3, for a three-year budgetary impact of $14,833,866, under the drug plan perspective. When considering the broader health care system perspective, CADTH estimated a budgetary impact of $4,337,451 in Year 1, $7,198,128 in Year 2, and $6,220,287 in Year 3, for a three-year cumulative total of $17,755,867.

Under the drug plan perspective, a scenario analysis that assumed 20% of patients would not be considered clinically indicated to receive chemotherapy resulted in a decrease of olaparib + abiraterone's estimated three-year budget impact to $3,087,173. This indicates that the budget impact is highly sensitive to the definition of the clinical indication for chemotherapy. It was assumed that olaparib + abiraterone does not displace docetaxel in these analyses.

Under a health care system perspective, a scenario analysis that assumed 50% of patients with mCRPC would be pre-tested for mutation status resulted in a decrease of olaparib + abiraterone's estimated three-year budget impact to $12,721,936. This indicates that the health care system's budget impact is highly sensitive to the prevalence of confirmed BRCA 1/2 mutations.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, 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: December 5, 2023

Regrets: 1 expert committee member did not attend.

Conflicts of interest: None.

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