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CADTH Reimbursement Recommendation

Olaparib (Lynparza)

Indication: For the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated, human epidermal growth factor receptor 2-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Patients must have confirmation of germline *BRCA* mutation before Lynparza treatment is initiated.

Sponsor: AstraZeneca Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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

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

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Lynparza?

CADTH recommends that Lynparza be reimbursed by public drug plans for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), human epidermal growth factor receptor 2 (HER2)-negative high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Lynparza should only be covered in patients with a confirmed type of inherited (germline) abnormal *BRCA* gene, whose early-stage breast cancer tests negative for the HER2 protein, who are at high risk for breast cancer recurrence, and who have received chemotherapy before or after surgery.

What Are the Conditions for Reimbursement?

Lynparza should only be reimbursed if prescribed by clinicians with expertise and experience in treating breast cancer, and if the cost is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a phase III clinical trial demonstrated that treatment with Lynparza delays breast cancer recurrence and allows patients to live longer.
- Lynparza meets patients' needs for effective treatments that reduce the chance of their breast cancer coming back, have manageable side effects, and are more accessible (as Lynparza is a pill).
- Based on CADTH's assessment of the evidence, Lynparza does not represent good value to the health care system at the public list price and a price reduction is required.
- Based on public list prices, Lynparza will cost the public drug plans approximately $44 million over the next 3 years.

Additional Information

What Is Breast Cancer?

Invasive early breast cancer without metastases is cancer that has spread from the cells of the breasts into the surrounding breast tissue but has not spread to different body parts. Some patients with breast cancers have a certain type of inherited (germline) abnormal *BRCA* gene; some breast cancers do not have much HER2. The 5-year net survival for breast cancer is more than 85% among women diagnosed before age 85, after which it drops to about 73%.

Unmet Needs in Breast Cancer

Surgery along with chemotherapy treatment before or after surgery is meant to cure patients with early-stage breast cancer. However, cancer may come back or worsen for some patients who are at high risk for breast cancer recurrence; therefore, there is a need for treatment options that prevent or delay the cancer's return, prolong survival with an acceptable toxicity profile, and maintain quality of life.

How Much Does Lynparza Cost?

Treatment with Lynparza is expected to cost approximately $7,461 per patient per 28-day cycle.

Recommendation

The CADTH Expert Review Committee (pERC) recommends that olaparib be reimbursed for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), human epidermal growth factor receptor 2 (HER2)-negative high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing, multicentre, randomized, double-blind, placebo-controlled, phase III study (OlympiA; N = 1,836) demonstrated that adjuvant treatment with olaparib, when compared with placebo, resulted in added clinical benefit for adults with germline *BRCA*-mutated, HER2-negative, high-risk early breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. The OlympiA trial showed that, compared with placebo, adjuvant treatment with olaparib demonstrated statistically significant and clinically meaningful improvement in invasive disease-free survival (IDFS) (hazard ratio at the primary interim analysis = 0.58; 99.5% confidence interval [CI], 0.41 to 0.82; P = 0.0000073; hazard ratio at the secondary interim analysis = 0.63; 95% CI = 0.50 to 0.78). Olaparib compared with placebo was associated with statistically significant and clinically meaningful improvement in overall survival (OS) at 3.5 years median follow-up time (hazard ratio at the second interim analysis = 0.68; 98.5% CI = 0.47 to 0.97; P = 0.0091). As well, adjuvant treatment with olaparib demonstrated statistically significant and clinically meaningful improvement in distant disease-free survival (DDFS) (hazard ratio at the primary interim analysis = 0.57; 99.5% CI = 0.39 to 0.83; P = 0.0000257; hazard ratio at the secondary interim analysis = 0.61, 95% CI = 0.48 to 0.77) compared with placebo. Olaparib was associated with a manageable toxicity profile.

Patients identified a need for effective treatments that reduce the risk of recurrence, maintain quality of life, prolong life, have manageable side effects, and are affordable and accessible. pERC concluded that olaparib met some of the needs identified by patients as it reduces the risk of recurrence, improves survival, may be more accessible due to the oral route of administration, and has manageable side effects.

Using the sponsor-submitted price for olaparib, the incremental cost-effectiveness ratio was $43,599 per quality-adjusted life-year (QALY) gained compared with watch and wait for the triple-negative breast cancer (TNBC) population and $157,407 per QALY gained compared with watch and wait for the HER2-negative, hormone receptor (HR)–positive population. While no price reduction is required for olaparib in the TNBC population, a reduction in price is required for olaparib to be considered cost-effective at a $50,000 per QALY gained willingness-to-pay threshold for the HER2-negative and HR-positive population. When considering the combined target population, a price reduction is required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with olaparib should be initiated in patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative high-risk early breast cancer if 1 the following criteria is met: 1.1. For patients who underwent initial surgery and received adjuvant chemotherapy: 1.1.1. those with TNBC must have axillary node-positive or axillary node-negative disease with pT ≥ 2 cm, OR 1.1.2. those with HR-positive, HER2- negative disease must have ≥ 4 involved pathologically confirmed positive lymph nodes. OR 1.2. For patients who underwent neoadjuvant chemotherapy followed by surgery: 1.2.1. those with TNBC must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pCR), OR 1.2.2. those with HR-positive, HER2- negative disease must have residual invasive cancer in the breast and/or the resected lymph nodes (non-pCR) and a CPS + EG[a] score ≥ 3.	Evidence from the OlympiA study demonstrated that adjuvant treatment with olaparib when compared with placebo resulted in added clinical benefit for adults with germline *BRCA*-mutated, HER2-negative, high-risk early breast cancer who have completed definitive local treatment, and neoadjuvant or adjuvant chemotherapy. The population outlined reflects the patient population of the OlympiA study, and this aligns with clinical expert opinion.	pERC noted that CPS + EG[a] score is not a commonly used risk-assessment tool and clinicians may use other assessment tools for high-risk disease.
2. Patients must have confirmation of a germline *BRCA* mutation before olaparib treatment is initiated.	Confirmation of a germline *BRCA* mutation before initiating olaparib was required in the OlympiA study, and this aligns with the Health Canada indication.	Germline *BRCA* testing should be available for all patients who are eligible for treatment with olaparib.
3. Patients are not eligible if they have HER2-positive or metastatic breast cancer.	Patients who have HER2-positive or metastatic breast cancer were excluded from the OlympiA study, and this aligns with the Health Canada indication.	—

Reimbursement condition	Reason	Implementation guidance
4. Patients must have completed neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or the combination of both.	Patients who have completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes, or the combination of both were included in the OlympiA study.	pERC acknowledged that there may be situations where chemotherapy was stopped early (e.g., due to toxicity), and these patients may still be offered olaparib.
5. Olaparib should be initiated within up to 12 weeks of completion of the last treatment, including surgery, chemotherapy, or radiation therapy.	Based on the OlympiA study eligibility criteria, patients should ideally be randomized to the study within a maximum of 8 weeks after the completion of the last treatment, including surgery, chemotherapy, or radiation therapy, but in no case for more than 12 weeks.	The clinical experts noted that there may be situations where some patients with high-risk breast cancer will start treatment beyond the 12-week window used in the trial.
Discontinuation		
6. Treatment with olaparib should be discontinued upon the occurrence of any of the following, whichever occurs first: 6.1. disease recurrence 6.2. unacceptable toxicity 6.3. completion of a total of 1 year of treatment.	Treatment with olaparib in the OlympiA study was given for up to 12 months, or until disease recurrence or unacceptable toxicity, whichever occurred first. This also aligns with the Health Canada product monograph.	—
Prescribing		
7. Olaparib should be prescribed by clinicians with expertise and experience in treating breast cancer.	This helps ensure that olaparib is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
8. A reduction in price	The ICER for olaparib is $43,599 per QALY gained compared to watch and wait for the TNBC population and $157,407 per QALY gained compared to watch and wait for the HER2-negative, HR-positive population. When considering the combined target population, a price reduction of 3% would be required for olaparib to be able to achieve an ICER of $50,000 per QALY compared to watch and wait.	—

g*BRCA*m = germline *BRCA* mutation; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; pCR = pathological complete response; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; pT = pathological tumour; QALY = quality-adjusted life-year; TNBC = triple-negative breast cancer.

[a]The CPS + EG is a disease scoring system that includes clinical stage, estrogen receptor status, nuclear grade, and posttreatment pathologic stage.

Discussion Points

- pERC noted that confirmation of a germline *BRCA* mutation before initiating olaparib was required in the OlympiA study, and this also aligned with the Health Canada indication and requested reimbursement criteria. Input from the clinical experts and clinical groups highlighted that *BRCA* testing is perceived as a barrier as not all patients qualify for genetic testing based on provincial guidelines, and as a result, patients who may carry a *BRCA* mutation may not receive the testing and thereby lose the opportunity to receive olaparib. Therefore, germline *BRCA* testing should be available for all patients who are eligible for treatment with olaparib.
- pERC discussed the health-related quality of life (HRQoL) results observed in the OlympiA study and concluded that no strong conclusions could be drawn about the effect of olaparib compared with placebo on HRQoL due to lack of multiplicity adjustments and a high risk of attrition bias, especially at longer follow-up.
- pERC also discussed the sponsor-submitted indirect treatment comparison (ITC) that compared olaparib to capecitabine for the adjuvant treatment of adult patients with high-risk, early-stage TNBC. pERC acknowledged that no conclusions could be drawn from the ITC about the effect of olaparib relative to capecitabine on IDFS or disease-free survival (DFS), or OS due to methodological limitations and imprecision in the effect estimates.
- pERC acknowledged that the input from clinical experts that clinicians would likely prefer olaparib to capecitabine for the treatment of patients with TNBC who have residual disease. pERC discussed that abemaciclib with endocrine therapy is currently available for the treatment of patients with HR-positive, HER2-negative breast cancer, and olaparib can be another option for these patients if they have a *BRCA* mutation. Due to the absence of direct clinical evidence comparing olaparib to relevant comparators (i.e., improvement in IDFS and other end points compared to capecitabine, pembrolizumab, and abemaciclib, and lack of safety data for combination with pembrolizumab or abemaciclib) in this setting, and based on the input from clinical experts, pERC concluded that it remains unclear how olaparib will be integrated into the current treatment paradigm.
- pERC noted that the data in the OlympiA study are immature (OS, IDFS, and DDFS results were from interim analyses) as the trial is ongoing; therefore, the long-term impact of adjuvant olaparib on OS, IDFS, and DDFS is uncertain.
- pERC noted that the most common treatment-related adverse events (TRAEs) were anemia, diarrhea, decreased neutrophil count, and decreased white blood cell count, all of which were higher with olaparib than with placebo. pERC acknowledged that the majority of TRAEs were manageable with supportive care and/or dose modifications.
- The estimated proportion of patients who had TNBC (82.3%) and whose disease was HER2 negative and HR positive (17.7%) in the OlympiA trial was used to estimate the overall price reduction for the full patient population. However, pERC noted that the price reduction needed for olaparib may vary based on the distribution of HER2-negative, HR-positive disease and TNBC observed in clinical practice.

Background

Breast cancer is the most commonly diagnosed cancer among women in Canada, and the second most common cancer in men and women combined. In 2020, 27,700 women were

diagnosed with breast cancer, representing about 25% of new cancer cases in Canada. Breast cancer is the second leading cause of cancer deaths among women, accounting for 14% of all cancer deaths. The 5-year net survival for breast cancer is more than 85% among women diagnosed before 85 years of age, after which it drops to about 73%. In men, the incidence of breast cancer is less than 1% per year, with 260 new cases diagnosed in 2021 in Canada. Breast cancer susceptibility genes (*BRCA1* and *BRCA*2) are human genes that produce proteins responsible for repairing damaged DNA, and play an important role in maintaining the genetic stability of cells. Mutations in 1 or both *BRCA* genes reduce gene expression, which can lead to uncontrolled cell growth, and are associated with an increased risk of cancer, including breast cancer.

Hereditary, deleterious mutations account for 5% to 10% of all breast cancers, and 60% to 68% of these hereditary cancers occur in individuals with germline *BRCA* mutations. In women harbouring a *BRCA1* gene mutation, the estimated lifetime risk of developing breast cancer by the age 80 years is 65% to 80%, and the 10-year actuarial risk of developing contralateral breast cancer is 25% to 31%. The estimated lifetime risk of developing breast cancer is approximately 76% among women with a *BRCA2* mutation, while among men with *BRCA1* or *BRCA2* mutations it ranges from 3% to 8%. The *BRCA* mutations occur in those with all subtypes of breast cancer, but more commonly in those with early onset or family history. Approximately 75% of patients with breast cancer who have a mutation in the *BRCA1* gene are classified as having TNBC. In contrast, patients with breast cancer carrying mutations in the *BRCA*2 gene are more likely to be positive for expression of the HR (HR positive), and only approximately 20% have TNBC.

Olaparib is a selective inhibitor of human poly (adenosine diphosphate ribose) polymerase (PARP) enzymes (PARP1, PARP2, and PARP3) involved in normal cellular functions, such as DNA transcription and DNA repair. Olaparib is approved by Health Canada for the adjuvant treatment of adult patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. The recommended total daily dose of olaparib is 600 mg, taken as two 150 mg tablets twice daily for a total of 1 year, or until disease recurrence or unacceptable toxicity, whichever occurs first. Olaparib is available as a 150 mg or 100 mg tablet. Olaparib has been previously reviewed by CADTH for other indications, including as monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease is responding (complete or partial) to first-line platinum-based chemotherapy, until disease progression or up to 2 years if no evidence of disease; and also as monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease is responding to platinum-based chemotherapy.

Sources of Information Used by the Committee

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

- a review of 1 phase III, randomized, multicentre, double-blind, placebo-controlled trial in patients with deleterious or suspicious deleterious g*BRCA*m, HER2-negative high-risk,

early-stage breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy

- patient perspectives gathered by 2 patient groups, Rethink Breast Cancer (Rethink) and the Canadian Breast Cancer Network (CBCN)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with breast cancer
- input from 2 clinician groups, including the Ontario Health (OH-CCO) Breast Cancer Drug Advisory Committee and a group of medical oncologists from across Canada
- a review of 1 sponsor-submitted ITC
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient and clinician input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups, CBCN and Rethink, provided input for this review. CBCN is a national health charity that aims to ensure the best quality of care for all people living in Canada who are affected by breast cancer. The CBCN patient input was based on an online survey in 6 patients with germline *BRCA*-mutated early breast cancer, and a literature review of current studies and grey literature. Rethink is a Canadian charity with a focus on improving the experience and outcomes of patients with breast cancer. Rethink gathered information for this review from general observations and insights through various ongoing initiatives (including stories shared by patients, virtual support groups, working groups, and patient advisory boards), in-depth telephone interviews with 3 patients with a *BRCA*-mutated breast cancer who participated in the OlympiA study, as well as responses from people in the Rethink Instagram community with high-risk early breast cancer.

According to the patient input received, *BRCA*-mutated breast cancer is more likely to be detected in young people. These young patients would face several age-specific issues such as fertility or family-planning challenges; diagnosis during pregnancy; childcare concerns; impact on relationships, body image, dating, and sexuality; feeling isolated from peers who do not have cancer; career hiatuses; and financial insecurity. The main factors influencing patients' decision about currently available treatment options included effectiveness of the treatment (i.e., how well the treatment could help stabilize disease and delay recurrence), prolonging life without sacrificing quality of life (i.e., how well the treatment could help maintain productive, active lives with minimal disruption to daily routines), risk of side effects, as well as cost and accessibility of treatments. The Rethink input revealed that patient respondents, especially those with stage iii breast cancer, tended to endure side effects as well as its impacts on quality of life to achieve satisfied effectiveness. In terms of experience with olaparib, none of the 3 patients from the Rethink group who had participated in the OlympiA study and did not experience a recurrence mentioned unendurable side effects.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH noted that current systemic treatment of patients with early breast cancer is based on the receptor status and pathological findings and does not consider patients' *BRCA* mutation status as there is no treatment specific for mutation status. Therefore, there is a need for new therapeutic options to improve survival outcomes and increase the overall cure rate in this subgroup of patients. The clinical experts noted that patients who meet the inclusion criteria outlined in the OlympiA trial will be best suited for treatment with olaparib. According to the clinical experts, by improving survival and reducing disease recurrence, patients whose disease is cured will have a higher quality of life and longer life. The goal of treating *BRCA*-mutated early breast cancer is to eradicate disease and prevent metastatic spread, resulting in cure. It was further noted by the clinical experts that it remains unclear how to integrate olaparib within the current treatment paradigm with other drugs, such as capecitabine, pembrolizumab, abemaciclib, or a combination of drugs in the treatment of early breast cancer. The clinical experts consulted mentioned that companion diagnostic testing is perceived as a barrier, given that not all patients qualify for genetic testing based on provincial guidelines (i.e., these patients have a low likelihood of hereditary syndromes). The clinical experts indicated that current genetic testing guidelines vary by province, and *BRCA* mutations are underdiagnosed based on most provincial testing criteria. According to the clinical experts, toxicities and disease recurrence will be the main factors to consider when deciding to discontinue treatment with olaparib.

Clinician Group Input

The clinician group input was obtained from 2 clinician groups, the OH-CCO Breast Cancer Drug Advisory Committee (1 clinician provided input) and a group of medical oncologists from across Canada (4 clinicians provided input). Both clinician groups identified that the important goal of treatment for early breast cancer, including germline *BRCA*-mutated early breast cancer, is to decrease recurrence of cancer and improve survival. One potential barrier, which was mentioned by the OH-CCO Breast Cancer Drug Advisory Committee, is that the current guidelines for *BRCA* mutation testing are restrictive in terms of eligibility criteria because many patients may carry a *BRCA* mutation but may not receive the testing and thereby will lose the opportunity to receive olaparib. Both clinician groups noted the following reasons that may lead to the discontinuation of olaparib: recurrence or progression of disease, intolerant toxicity or severe side effects, and patient or physician preference.

Drug Program Input

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	
No issues were identified as the OlympiA study was a placebo-controlled trial.	This was a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
Considerations for initiation of therapy	
Disease diagnosis, scoring, or staging for eligibility: What are the criteria for defining "high risk" for eligibility (e.g., clinical stage, pathologic stage, receptor status, nuclear grade)?	Most clinicians would use the criteria used to define high-risk groups in the OlympiA trial: • Node-positive disease or pT ≥ 2 cm for TNBC with upfront surgery • Non-pCR for TNBC treated with neoadjuvant chemotherapy • ≥ 4 involved lymph nodes for HR-positive, HER2-negative breast cancer with upfront surgery • CPS + EG[a] score ≥ 3 for HR-positive, HER2-negative breast cancer treated with neoadjuvant chemotherapy (optional, as per clinician adoption); pERC noted that CPS + EG[a] score is not a commonly used risk-assessment tool and clinicians may use other assessment tools for high-risk disease According to the OlympiA trial, those who have HER2-positive disease would not be offered olaparib.
Prior therapies required for eligibility: Is there a minimum number of chemotherapy cycles that should be completed for eligibility?	pERC acknowledged that while at least 6 cycles of chemotherapy had to be used in the trial, in real practice, there might be situations where chemotherapy is stopped early (e.g., due to toxicity), and these patients may still be offered olaparib.
Considerations for discontinuation of therapy	
Treatment interruptions: Should olaparib be restarted if there was a prolonged treatment break?	Olaparib could be restarted if the prolonged break was not related to olaparib-induced toxicity or disease recurrence.
Considerations for prescribing of therapy	
The recommended dose is 600 mg daily, taken as two 150 mg tablets twice daily. There are 100 mg tablets for dose reductions if needed. This is for 1 year or until disease recurrence, whichever occurs first. The tablets are administered orally.	This was a comment from the drug programs to inform pERC deliberations.
Concerns related to combination usage: Would olaparib ever be prescribed in combination with capecitabine and/or pembrolizumab for triple-negative high-risk breast cancer?	While the clinical experts stated that there are safety data on olaparib in combination with pembrolizumab, and in combination with capecitabine in other disease sites, these safety data were not reviewed in this submission. As well, there are no efficacy data to support the use of these combinations in early breast cancer.
Generalizability	
Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review: Is there a time-limited need to add olaparib for up to 1 year for any patient who otherwise meets listing and reimbursement criteria and who has not progressed on treated with neoadjuvant or adjuvant chemotherapy?	pERC noted that in the OlympiA study eligibility criteria, patients should ideally be randomized to the study within a maximum of 8 weeks after the completion of their last treatment, including surgery, chemotherapy, or radiation therapy, but in no case for more than 12 weeks. According to the clinical experts, there may be situations where some high-risk patients will start treatment beyond the 12-week window used in the trial. As a result, olaparib should be initiated within up to 12 weeks of completion of the last treatment, including surgery, chemotherapy, or radiation therapy. pERC agreed with the clinical experts that there may be situations where some high-risk patients will start treatment beyond the 12-week window used in the trial; these patients would include legacy patients.

Implementation issues	Response
Funding algorithm	
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products: There is the potential to insert adjuvant olaparib into the treatment algorithm after neoadjuvant or adjuvant chemotherapy for many subpopulations.	This was a comment from the drug programs to inform pERC deliberations.
Care provision issues	
Patients must have confirmation of a germline *BRCA* mutation before Olaparib treatment can start.	This was a comment from the drug programs to inform pERC deliberations.
System and economic issues	
The budget impact is 11.3 million at year 1, 15.8 million at year 2, and 17.3 million at year 3.	This was a comment from the drug programs to inform pERC deliberations.

HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; pCR = pathological complete response; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; pT = pathological tumour; TNBC = triple-negative breast cancer.

[a]The CPS + EG is a disease scoring system that includes clinical stage, estrogen receptor status, nuclear grade, and posttreatment pathologic stage.

Clinical Evidence

Pivotal Study

Description of Study

The OlympiA trial is an ongoing, phase III, randomized, multicentre, double-blind, placebo-controlled trial. The primary objective of the trial is to assess the efficacy and safety of olaparib versus placebo for the adjuvant treatment of patients with deleterious or suspicious deleterious germline *BRCA1* or *BRCA2* mutations, high-risk HER2-negative early-stage breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. A total of 1,836 patients with breast cancer and g*BRCA*m were enrolled across 546 sites in 23 countries in North America (34 patients from Canada), South America, Europe, Asia Pacific, and South Africa. The primary efficacy end point was IDFS, and the key secondary efficacy end points were OS and DDFS. Patient-reported outcomes (PROs) were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Treatment with olaparib was given for up to 12 months, or until disease recurrence or unacceptable toxicity, whichever occurs first.

Overall, baseline characteristics were well-balanced between the treatment groups in the OlympiA trial. The mean age of patients was 43.3 years (standard deviation [SD] = 9.97 years), and about 68.7% of patients were aged between 30 and 49 years. Most patients were female (99.7%), premenopausal (61.3%), white (66.7%), identified as not being Hispanic or Latino (88.1%), and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (88.7%). A total of 26.4% of patients received prior platinum therapy and half of patients (50.1%) received neoadjuvant treatment. A total of 82.3% of the patients had TNBC, while 17.7% had HR-positive, HER2-negative breast cancer. Germline *BRCA1* deleterious or suspected deleterious mutations were identified in 72.2% of patients, germline *BRCA2* mutations in 27.1% of patients, and both germline *BRCA1* and germline *BRCA2* mutations

in 0.4% of patients. The majority of patients with TNBC (60.3%) had a mutation in *BRCA1*, while the majority of patients with HR-positive, HER2-negative breast cancer (51.4%) had a mutation in *BRCA2*. A total of 36.1% of patients had clinical American Joint Committee on Cancer (AJCC) stage IIA, 21.0% had AJCC stage IIB, and 13.0% had AJCC stage IIIA disease.

Efficacy Results

Table 3 and Table 4 present a summary of key results from the OlympiA trial.

Overall Survival

At the first interim analysis (March 27, 2020), the OS data were 7.9% mature. Deaths were reported in 59 (6.4%) patients in the olaparib group and 86 (9.4%) patients in the placebo group. The median OS was not estimable in either treatment group, and the stratified hazard ratio was 0.68 (99% CI, 0.44 to 1.05; P = 0.0236). At the second interim analysis (July 12, 2021), the OS data were 10.0% mature. In the full analysis set, deaths were reported in 75 (8.1%) patients in the olaparib group and 109 (11.9%) patients in the placebo group. The median OS was not estimable, and the stratified hazard ratio was 0.68 (98.5% CI, 0.47 to 0.97; P = 0.0091) in favour of the olaparib group. The proportion of patients who remained alive at 4 years was 89.8% (95% CI, 87.2% to 91.9%) in the olaparib group and 86.4% (95% CI, 83.6% to 88.7%) in the placebo group (difference = 3.4%; 95% CI, −0.1% to 6.8%). The results of prespecified sensitivity and subgroup analyses were consistent with the primary analysis.

Invasive Disease-Free Survival

At the first interim analysis (March 27, 2020), 106 (11.5%) patients in the olaparib group and 178 (19.5%) patients in the placebo group had an IDFS event. The median IDFS was not estimable in either treatment group, and the stratified hazard ratio for invasive disease recurrence or death was 0.58 (99.5% CI, 0.41 to 0.82; P = 0.0000073) in favour of the olaparib group. At the second interim analysis (July 12, 2021), the stratified hazard ratio for invasive disease recurrence or death was 0.63 (95% CI, 0.50 to 0.78). The proportion of patients who remained invasive disease free at 4 years was 82.7% (95% CI, 79.6% to 85.4%) in the olaparib group and 75.4% (95% CI, 72.2% to 78.3%) in the placebo group (difference = 7.3%; 95% CI, 3.0% to 11.5%). The results of prespecified sensitivity and subgroup analyses were consistent with the primary analysis.

Distant Disease-Free Survival

At the first interim analysis (March 27, 2020), 89 (9.7%) patients in the olaparib group and 152 (16.6%) patients in the placebo group had a DDFS event. The median DDFS was not estimable in either treatment group, and the stratified hazard ratio for distant disease recurrence or death was 0.57 (99.5% CI, 0.39 to 0.83; P = 0.0000257) in favour of the olaparib group. At the second interim analysis (July 12, 2021), the stratified hazard ratio for distant disease recurrence or death was 0.61 (95% CI, 0.48 to 0.77). The proportion of patients who remained distant disease free at 4 years was 86.5% (95% CI, 83.8% to 88.8%) in the olaparib group and 79.1% (95% CI, 76.0% to 81.8%) in the placebo group (difference = 7.4%; 95% CI, 3.6% to 11.3%). The results of prespecified sensitivity and subgroup analyses were consistent with the primary analysis.

Health-Related Quality of Life

HRQoL data were assessed only in the PRO analysis set using the FACIT-Fatigue or EORTC QLQ-C30 questionnaires. No strong conclusions could be drawn about the effect of olaparib

compared with placebo on HRQoL due to an increased risk of type I error and a high risk of attrition bias.

FACIT-Fatigue

No clinically meaningful differences were found between treatment groups in mean change in FACIT-Fatigue score at follow-up (minimally important difference of fewer than 3 points). For the subgroup of patients who had previously received neoadjuvant chemotherapy (N = 727), the adjusted least squares (LS) mean difference for olaparib versus placebo was −1.3 (95% CI, −2.4 to −0.2; P = 0.024) at 6 months, and −1.5 (95% CI, −2.8 to −0.2; P = 0.025) at 12 months. For the subgroup of patients who had previously received adjuvant chemotherapy (N = 778), the adjusted LS mean difference for olaparib versus placebo was −1.3 (95% CI, −2.3 to −0.2; P = 0.017) at 6 months, and −1.3 (95% CI, −2.4 to 0.1; P = 0.027) at 12 months.

EORTC QLQ-C30

The adjusted LS mean difference for olaparib versus placebo in the global health status score was [redacted] at 6 months, [redacted] at 12 months, [redacted] at 18 months, and [redacted] at 24 months. The adjusted LS mean difference between treatment groups in the nausea and vomiting symptom scale was 6.0 (95% CI, 4.0 to 8.0; [redacted]) at 6 months, 6.3 (95% CI, 4.4 to 8.2; [redacted]) at 12 months, 0.4 (95% CI, −1.2 to 1.9; [redacted]) at 18 months, and 1.4 (95% CI, −0.4 to 3.3; P [redacted]) at 24 months. The adjusted LS mean difference between treatment groups in the diarrhea symptom scale was 0.3 (95% CI, −2.0 to 2.7; [redacted]) at 6 months, 2.0 (95% CI, −1.0 to 4.9; [redacted]) at 12 months, 1.1 (95% CI, −2.0 to 4.3; [redacted]) at 18 months, and 1.8 (95% CI, −1.5 to 5.0; P = [redacted]) at 24 months.

Patients Who Had Previously Received Adjuvant Chemotherapy

The adjusted LS mean difference for olaparib versus placebo in the global health status score was [redacted] at 6 months, [redacted] at 12 months, [redacted] at 18 months, and [redacted] at 24 months. The adjusted LS mean difference between treatment groups in the nausea and vomiting symptom scale was 5.3 (95% CI, 3.4 to 7.2; [redacted]) at 6 months, 4.5 (95% CI, 2.8 to 6.2 [redacted]) at 12 months, −0.3 (95% CI, −1.9 to 1.3 [redacted]) at 18 months, and −0.6 (95% CI, −2.5 to 1.2; [redacted]) at 24 months. The adjusted LS mean difference between treatment groups in the diarrhea symptom scale was −1.7 (95% CI, −4.1 to 0.7 [redacted] at 6 months, 0.1 (95% CI, −2.2 to 2.4; [redacted]) at 12 months, 0.4 (95% CI, −1.9 to 2.7; [redacted]) at 18 months, and −1.0 (95% CI, −3.4 to 1.4; P = [redacted]) at 24 months.

Harms Results

A total of 836 (91.8%) patients in the olaparib group and 758 (83.8%) patients in the placebo group experienced more than 1 adverse event (AE). Common Terminology Criteria for Adverse Events (CTCAE) grade 3 to 5 AEs occurred in 24.5% of patients in the olaparib group and 11.3% of patients in the placebo group. A total of 736 (80.8%) patients in the olaparib group and 480 (53.1%) patients in the placebo group experienced more than 1 TRAE. The most common TRAEs occurring in the olaparib or placebo groups were anemia (20.6% and 1.7%, respectively), diarrhea (12.0% and 7.5%, respectively), decreased neutrophil count (14.9% and 4.6%, respectively), and decreased white blood cell count (14.1% and 4.5%, respectively). A total of 33 (33.6%) patients in the olaparib group and 6 (0.7%) patients in the placebo group experienced at least 1 serious TRAE. The majority of TRAEs were manageable with supportive care and/or dose modifications and consistent with the known safety profile of olaparib. There were 2 fatal AEs in the placebo group and 1 fatal AE in the olaparib group during the treatment period or within the 30-day follow-up period, as well as 2 fatal AEs in the placebo group and 1 fatal AE in the olaparib group 30 days after discontinuation.

The frequency of notable harms identified in the protocol were comparable between the treatment groups. The most commonly reported notable AE was new primary cancer (2.3% and 4.0% in the olaparib and placebo groups, respectively), followed by pneumonitis (1.0% and 1.3% in the olaparib and placebo groups, respectively), and myelodysplastic syndrome or acute myeloid leukemia (0.2% and 0.3% in the olaparib and placebo groups, respectively). No new safety concerns have been identified compared to previous trials in patients with metastatic breast cancer.

Table 3: Summary of Key Results From Pivotal Study

Characteristic	Olaparib (N = 921)	Placebo (N = 915)
IDFS at interim analysis 1[a]		
Patients with events, n (%)	106 (11.5)	178 (19.5)
Stratified hazard ratio (99.5% CI[b])	0.58 (0.41 to 0.82[c])	
Log-rank test: P value[d]	0.0000073	Reference
Median follow-up[e] (range), years	2.3 (0 to 5.5)	2.5 (0 to 5.5)
Number of patients censored,[f] n (%)	815 (88.5)	737 (80.5)
DDFS at interim analysis 1[a]		
Patients with events, n (%)	89 (9.7)	152 (16.6)
Stratified hazard ratio (99.5% CI[c])	0.57 (0.39 to 0.83[c])	
Log-rank test: P value[d]	0.0000257	Reference
Median follow-up[e] (range), years	2.3 (0 to 5.5)	2.5 (0 to 5.5)
Number of patients censored,[f] n (%)	832 (90.3)	763 (83.4)
OS at interim analysis 2[g]		
Patients with events, n (%)	75 (8.1)	109 (11.9)
Stratified hazard ratio (98.5% CI[c])	0.68 (0.47 to 0.97[c])	
Log-rank test: P value[d]	0.0091	Reference
Median follow-up[e] (range), years	3.5 (0 to 6.8)	3.6 (0 to 6.7)
Number of patients censored,[f] n (%)	846 (91.9)	806 (88.1)
FACIT-Fatigue		
Patients who had completed neoadjuvant chemotherapy		
6 months, n[h]	371	356
LS mean (95% CI)	−1.5 (−2.2 to −0.7)	−0.2 (−1.0 to 0.6)
LS mean difference[i]	−1.3 (−2.4 to −0.2)	
P value[j]	0.024	Reference
12 months, n[h]	371	356
LS mean (95% CI)	−1.5 (−2.4 to −0.6)	−0.0 (−0.9 to 0.9)

Characteristic	Olaparib (N = 921)	Placebo (N = 915)
LS mean difference (95% CI)[i]	−1.5 (−2.8 to −0.2)	
P value[j]	0.025	Reference
Patients who had completed adjuvant chemotherapy		
6 months, n[h]	375	403
LS mean (95% CI)	−0.7 (−1.4 to 0.1)	0.6 (−0.1 to 1.3)
LS mean difference (95% CI)[i]	−1.3 (−2.3 to −0.2)	
P value[j]	0.017	Reference
12 months, n[h]	375	403
LS mean (95% CI)	−0.8 (−1.6 to 0.0)	0.5 (−0.3 to 1.2)
LS mean difference (95% CI)[i]	−1.3 (−2.4 to 0.1)	
P value[j]	0.027	Reference
Harms		
Patients with ≥ 1 AE, n (%)	836 (91.8)	758 (83.8)
Patients with ≥ 1 TRAE, n (%)	736 (80.8)	480 (53.1)
Patients with ≥ 1 AE of CTCAE Grade ≥ 3, n (%)	223 (24.5)	102 (11.3)
Patients who died due to AE, n (%)	2 (2.7)	4 (3.7)
Patients with ≥ 1 SAE, n (%)	79 (8.7)	78 (8.6)
Patients who discontinued study treatment due to AE, n (%)	98 (10.8)	42 (4.6)
Patients with ≥ 1 AE leading to dose reduction, n (%)	213 (23.4)	33 (3.7)
Patients with ≥ 1 AE leading to dose interruption, n (%)	286 (31.4)	99 (11.0)
Notable harms, n (%)		
Myelodysplastic syndrome or acute myeloid leukemia	2 (0.2)	3 (0.3)
Pneumonitis	9 (1.0)	12 (1.3)
New primary cancer	21 (2.3)	36 (4.0)

AE = adverse event; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; DDFS = distant disease-free survival; FACIT = Functional Assessment of Chronic Illness Therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IDFS = invasive disease-free survival; LS = least squares; MMRM = mixed model for repeated measures; OS = overall survival; SAE = serious adverse event; TNBC = triple-negative breast cancer; TRAE = treatment-related adverse event; vs. = versus.

[a]Data cut-off date of March 27, 2020.

[b]Inferential, according to the alpha spending rules for the interim analysis.

[c]Estimate of the treatment hazard ratio was based on the stratified Cox's proportional hazards model. Stratification factors were the same as those used in the stratified log-rank test. The CI for the hazard ratio was estimated using the profile likelihood approach.

[d]P value from a stratified log-rank test. Stratification was by chemotherapy type (2 levels: adjuvant vs. neoadjuvant), HR status (2 levels: HR positive, HER2 negative disease vs. TNBC), and prior platinum therapy (2 levels: yes vs. no). Stratification factors were based on the categories used in the randomization system and were chosen by the pooling strategy. Once the pooling strategy was applied, only the HR status stratification factor was selected.

[e]Median clinical follow-up was calculated using the reverse censoring method.

[f]Patients who had not had a recorded event at the time of the analysis were censored at the date of their last disease evaluation.

[g]Data cut-off date of July 12, 2021.

[h]Only patients with an evaluable baseline form were included.

[i]Adjusted LS mean changes, P values (2-sided), and 95% CI were obtained from an MMRM analysis of the change from baseline. The model included treatment, time and treatment by time interaction, corresponding baseline score, and the baseline score by time interaction. The difference was the values for olaparib minus placebo.

[j]P value was not adjusted for multiple comparisons.

Source: Clinical Study Reports for OlympiA.

Table 4: Change From Baseline for EORTC QLQ- C30 Subscale Scores: PRO

Subscale measure	Patients who had completed neoadjuvant chemotherapy		Patients who had completed adjuvant chemotherapy	
	Olaparib	Placebo	Olaparib	Placebo
EORTC QLQ-C30 global health status QoL				
Baseline, n				
Mean (SD)				
6 months, n				
LS mean (95% CI)				
LS mean difference (95% CI)				
P value[a]				
12 months, n				
LS mean (95% CI)				
LS mean difference (95% CI)				
P value[a]				
18 months, n				
LS mean (95% CI)				
LS mean difference (95% CI)				
P value[a]				
24 months, n				
LS mean (95% CI)				
LS mean difference (95% CI)				
P value[a]				
EORTC QLQ-C30 nausea and vomiting symptom scale				
Baseline, n	440	433	436	440
Mean (SD)	3.2 (9.23)	3.7 (10.82)	3.1 (8.73)	3.4 (9.92)
6 months, n	383	359	385	406
LS mean (95% CI)	7.6 (6.2 to 9.0)	1.6 (0.2 to 3.1)	6.9 (5.5 to 8.2)	1.6 (0.3 to 2.9)
LS mean difference (95% CI)	6.0 (4.0 to 8.0)		5.3 (3.4 to 7.2)	
P value[a]		Reference		Reference
12 months, n	383	359	385	406
LS mean (95% CI)	7.3 (6.0 to 8.7)	1.0 (−0.4 to 2.4)	5.5 (4.2 to 6.7)	1.0 (−0.2 to 2.1)
LS mean difference (95% CI)	6.3 (4.4 to 8.2)		4.5 (2.8 to 6.2)	

Subscale measure	Patients who had completed neoadjuvant chemotherapy		Patients who had completed adjuvant chemotherapy	
	Olaparib	Placebo	Olaparib	Placebo
P value[a]	[redacted]	Reference	[redacted]	Reference
18 months, n	383	359	385	406
LS mean (95% CI)	0.7 (−0.4 to 1.8)	0.4 (−0.8 to 1.5)	0.7 (−0.5 to 1.8)	1.0 (−0.2 to 2.1)
LS mean difference (95% CI)	0.4 (−1.2 to 1.9)		−0.3 (−1.9 to 1.3)	
P value[a]	[redacted]	Reference	[redacted]	Reference
24 months, n	383	359	385	406
LS mean (95% CI)	1.3 (0.0 to 2.6)	−0.1 (−1.5 to 1.2)	−0.0 (−1.3 to 1.3)	0.6 (−0.6 to 1.9)
LS mean difference (95% CI)	1.4 (−0.4 to 3.3)		−0.6 (−2.5 to 1.2)	
P value[a]	[redacted]	Reference	[redacted]	Reference
EORTC QLQ-C30 diarrhea symptom scale				
Baseline, n	438	431	435	440
Mean (SD)	5.9 (15.79)	6.1 (16.59)	5.7 (14.61)	5.9 (14.94)
6 months, n	380	357	384	406
LS mean (95% CI)	1.6 (−0.0 to 3.3)	1.3 (−0.4 to 3.0)	0.0 (−1.7 to 1.8)	1.7 (0.1 to 3.4)
LS mean difference (95% CI)	0.3 (−2.0 to 2.7)		−1.7 (−4.1 to 0.7)	
P value[a]	[redacted]	Reference	[redacted]	Reference
12 months, n	380	357	384	406
LS mean (95% CI)	4.0 (1.9 to 6.2)	2.0 (−0.1 to 4.1)	1.5 (−0.1 to 3.1)	1.4 (−0.2 to 3.0)
LS mean difference (95% CI)	2.0 (−1.0 to 4.9)		0.1 (−2.2 to 2.4)	
P value[a]	[redacted]	Reference	[redacted]	Reference
18 months, n	380	357	384	406
LS mean (95% CI)	2.7 (0.5 to 4.9)	1.5 (−0.7 to 3.8)	−0.2 (−1.8 to 1.4)	−0.6 (−2.2 to 1.0)
LS mean difference (95% CI)	1.1 (−2.0 to 4.3)		0.4 (−1.9 to 2.7)	
P value[a]	[redacted]	Reference	[redacted]	Reference
24 months, n	380	357	384	406
LS mean (95% CI)	1.3 (−1.0 to 3.5)	−0.5 (−2.9 to 1.8)	−1.6 (−3.2 to 0.1)	−0.6 (−2.2 to 1.1)
LS mean difference (95% CI)	1.8 (−1.5 to 5.0)		−1.0 (−3.4 to 1.4)	
P value[a]	[redacted]	Reference	[redacted]	Reference

CI = confidence interval; EORTC QLQ-30 = European Organization for Research and Treatment of Cancer quality of life questionnaire; LS = least square; MMRM = mixed model for repeated measures; PRO = patient-reported outcome; QoL = quality of life; SD = standard deviation.

Notes: Only patients with an evaluable baseline form were included.

Adjusted LS mean changes, P values (2-sided), and 95% CI were obtained from an MMRM analysis of the change from baseline. The model included treatment, time and treatment by time interaction, corresponding baseline score, and the baseline score by time interaction. The difference was the values for olaparib minus placebo.

[a]P value was not adjusted for multiplicity.

Source: Clinical Study Report for OlympiA.

Critical Appraisal

The OlympiA trial used accepted methods for blinding, allocation concealment, and randomization with stratification. The demographic and baseline patient characteristics were generally balanced between the treatment groups, so randomization was successful. A relatively high proportion of patients prematurely discontinued the trial medication (25.6% and 20.4% in the olaparib and placebo groups, respectively); however, the clinical experts noted that this is reflective of clinical practice. As the OlympiA trial is ongoing, the longer-term efficacy of adjuvant olaparib for IDFS, DDFS, and OS is unknown. Furthermore, as all results are based on interim analyses, there is the potential that the benefit of olaparib relative to placebo is overestimated; however, the presence and extent of any overestimation is uncertain. All interim and subgroup analyses were prespecified in the statistical plan. Multiplicity adjustments for type I error were conducted for IDFS, DDFS, and OS according to a prespecified statistical hierarchy plan. The results were robust to a number of supportive and sensitivity analyses for the primary and key secondary outcomes. Subgroup analyses were prespecified in the OlympiA trial but may not have been powered to detect a treatment difference and there were no adjustments made for multiplicity. While improvement in quality of life was of primary importance of both patients and clinical experts, conclusions for HRQoL were limited as no adjustments for multiplicity were made (so there is an increased risk of type I error). In addition, HRQoL was assessed using FACIT-Fatigue and EORTC QLQ-C30 questionnaires only in the PRO analysis set based on the evaluable baseline data; thus, there is a high risk of bias due to missing data, especially at later follow-up. There was a potential for unblinding of patients and investigators due to differences in the AE profile for olaparib relative to placebo. If unblinding were to occur, there would be a risk of performance and detection bias for self-reported QoL and safety data; however, the direction and extent of any bias is uncertain.

The patient population in the OlympiA trial generally reflects patients in clinical practice in this setting. The majority of the study participants were white and did not identify as Hispanic or Latino. Only 34 patients from Canada were recruited; however, the clinical experts consulted noted that although this may not be representative of the general breast cancer population, it is reflective of the population eligible for olaparib treatment, and the lack of representation of patients from Canada does not reduce the generalizability of results to Canadian clinical practice. To be enrolled in the OlympiA trial, patients were required to complete at least 6 cycles of chemotherapies, and all local therapies at least 2 weeks before randomization. The clinical experts consulted noted that olaparib would probably not be withheld if patients had previously received fewer than 6 cycles of chemotherapy for medical reasons. Patients with HR-positive, HER2-negative breast cancer were underrepresented in the OlympiA trial (17.7% had HR-positive, HER2-negative disease versus 82.3% who had TNBC). The clinical experts consulted noted that these proportions are reflective of the hereditary group with breast cancer with *BRCA* mutations in clinical practice. Health Canada reviewers noted that due to the small number of patients with HR-positive, HER2-negative disease and lack of statistical power, the magnitude of the clinical benefit of olaparib in this subpopulation remains unclear. It was further indicated by the clinical experts that the criteria used in the OlympiA trial to determine high risk of disease recurrence were reasonable, with the exception of a CPS + EG score (CPS + EG is a disease scoring system that includes clinical stage, estrogen receptor status, nuclear grade, and posttreatment pathologic stage) of 3 or higher, which is not commonly used in clinical practice, although it is easily calculated. About 87.2% of patients in the OlympiA trial were screening failures, most commonly because the patients did not have a deleterious or suspected deleterious *BRCA* mutation in part 1 of the screening process. The clinician groups and clinical experts consulted agreed that the companion diagnostic testing

would be a challenge in Canada. They noted that current *BRCA* testing guidelines vary by province, and *BRCA* mutations are underdiagnosed based on most provincial testing criteria because current guidelines are restrictive in terms of eligibility criteria because many patients who may carry a *BRCA* mutation may not receive testing and will lose the opportunity to receive treatment with olaparib under current local or regional guidelines.

Indirect Comparisons

Description of Studies

To date, there have been no clinical trials directly comparing the efficacy of olaparib with other adjuvant treatments in patients diagnosed with HER2-negative, g*BRCA*m, high-risk nonmetastatic breast cancer. The sponsor conducted a Bucher ITC to address this gap.

The sponsor selected studies identified from a systematic literature review (SLR) to ensure that the population (or subpopulation), the control treatment, and the study design were aligned with those from the sponsor-conducted OlympiA trial. Relevant comparator interventions included adjuvant HER2-negative, high-risk breast cancer treatments publicly reimbursed in Canada. A feasibility assessment was then conducted to assess homogeneity between the included studies and to determine the appropriateness of inclusion in an ITC. The sponsor identified 1 randomized controlled trial (RCT), CIBOMA, feasible to be included in the ITC along with the sponsor-conducted OlympiA trial. The OlympiA trial is a phase III, double-blind RCT comparing olaparib with placebo in patients who were diagnosed with HER2-negative, g*BRCA*m, high-risk early breast cancer and received local treatment and neoadjuvant or adjuvant chemotherapy. The CIBOMA trial was a phase III, open-label RCT that compared capecitabine with observation in patients with TNBC who had been treated with neoadjuvant or adjuvant chemotherapy. Unlike the OlympiA trial, the CIBOMA trial did not require participants to have confirmed g*BRCA*m. The median duration of follow-up is 2.5 years for the OlympiA trial and more than 7 years for the CIBOMA trial (interquartile range not reported).

The sponsor adopted the Bucher method to perform the ITC. The clinical end points included 3-year IDFS or DFS and OS. The risk of bias of the included studies was assessed independently by 2 reviewers using the checklist of the National Institute for Health and Care Excellence (NICE) single technology appraisal user guide.

Efficacy Results

The Bucher ITC compared olaparib versus capecitabine via the common comparator, placebo and observation, and estimated the hazard ratios for IDFS or DFS and OS in patients with TNBC from the OlympiA and CIBOMA trials. No conclusions could be drawn about the efficacy of olaparib compared with capecitabine due to imprecision in the effect estimates (i.e., wide 95% CIs, including hazard ratio = 1).

No analysis of harms was reported in the sponsor-submitted ITC report.

Critical Appraisal

The SLR used to identify relevant studies was methodologically sound in terms of the sponsor using a comprehensive literature search strategy as well as performing study selection, data extraction, and risk of bias assessment in duplicate. However, it was unclear in the ITC report whether the feasibility assessment was carried out by a single or multiple assessors. Moreover, although the risk of bias of individual studies were assessed in the

SLR, the assessment results were not incorporated and discussed in the ITC report. The sponsor conducted the ITC, based on the Bucher method, to estimate the relative treatment efficacy of olaparib against capecitabine. The Bucher method assumes that the trials included in the ITC should be sufficiently similar with respect to study population, study design, outcome measurements, and the distribution of treatment effect modifiers. The ITC has some limitations that reduce the CADTH's confidence in the effect estimates. There were notable differences across the 2 trials in patient baseline demographics and disease characteristics (e.g., unknown *BRCA* mutation status in the CIBOMA trial) and trial design (e.g., double blind versus open label; outcome definitions) that might threaten the plausibility of the assumptions of the Bucher method. In addition, safety outcomes were not analyzed in the ITC report and no justification was provided, which precludes a balanced judgment of comparative benefits relative to comparative harms. Other outcomes that are important to patients (e.g., symptoms and HRQoL), were not investigated. Finally, the ITC was performed only for patients with TNBC, which only aligned with a part of the population indicated in the sponsor's application; therefore, the results may not be generalizable to all patients who meet the criteria in the reimbursement request.

Other Relevant Evidence

No other relevant evidence was submitted by the sponsor or identified from the literature.

Conclusions

Based on data from the OlympiA trial, olaparib demonstrated a clinically meaningful and statistically significant benefit compared to placebo in improving IDFS, DDFS, and OS in adult patients with HER2-negative, high-risk early breast cancer. The median IDFS, OS, and DDFS were not estimable in either treatment group because insufficient follow-up time had elapsed for these outcomes; thus, the longer-term efficacy of adjuvant olaparib is unknown. In addition, the estimates of benefit of olaparib may be overestimated because the results are from interim analyses, although the presence and extent of any overestimation is uncertain. However, olaparib could help optimize adjuvant treatment in patients with *BRCA*-mutated early breast cancer to improve outcomes in terms of disease recurrence and survival given its acceptable and manageable safety profile. The safety profile of olaparib was consistent with the known adverse effects profile of olaparib, and no new safety signals were identified. Strong conclusions could not be drawn related to the effect of olaparib on HRQoL due to the high risk of attrition bias and increased risk of type I error in the analyses of these outcomes. The evidence of olaparib was limited to 1 placebo-controlled pivotal trial, and no direct evidence of olaparib versus other comparators was available for this review, most likely because the current systemic treatment of early breast cancer does not consider patients' *BRCA* mutations statuses. Uncertainties remain regarding the availability of *BRCA* mutation testing in Canada for clinical implementation in determining patient eligibility for olaparib treatment. No conclusions could be drawn from the ITC about the effect of olaparib relative to capecitabine on IDFS, DFS, or OS due to methodological limitations and imprecision in the effect estimates (wide 95% CIs, including HR = 1).

Economic Evidence

Table 5: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target population(s)	Adult patients (aged ≥ 18 years) with g*BRCA*m, high-risk HER2-negative early breast cancer who have received prior adjuvant or neoadjuvant chemotherapy. Target population included patients with TNBC or those whose disease is HER2 negative and HR positive.
Treatment	Olaparib, patients with HER2-negative, HR-positive disease may also receive adjuvant endocrine therapy
Submitted price	Olaparib, 100 mg and 150 mg: $66.62 per tablet
Treatment cost	$7,461 per 28-day cycle
Comparators	Watch and wait, patients with HER2-negative, HR-positive disease may also receive adjuvant endocrine therapy. Capecitabine was considered in scenario analyses for patients with TNBC.
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (57 years)
Key data source	OlympiA trial
Submitted results	ICER = $45,237 per QALY (incremental costs = $74,206 and incremental QALYs = 1.64)
Key limitations	• As data in the OlympiA trial were immature, the long-term impact of adjuvant olaparib on IDFS and OS is uncertain. • The inclusion of all patients regardless of HR status in the sponsor's base-case analysis was inappropriate due to anticipated differences in the underlaying survival and cure assumptions for patients with TNBC and those whose disease is HER2 negative and HR positive. These subgroups should be assessed separately in accordance with the CADTH economic guidelines. • The sponsor submitted an ITC informing the comparative clinical efficacy between adjuvant olaparib and capecitabine in patients with TNBC; however, notable differences in patient baseline demographics and disease characteristics (i.e., unknown g*BRCA*m status in the CIBOMA trial) and trial design, as well as other methodological limitations resulted in significant uncertainty in the effect estimates. • The economic model structure does not accurately capture the disease pathway for patients with nonmetastatic breast cancer. These patients are treated with curative intent; however, these patients could not become disease free in the submitted model. • The modelling of subsequent therapies may not be aligned with Canadian clinical practice as paclitaxel may be used in the nonmetastatic setting in patients with TNBC, but was omitted from the sponsor's base case, and fewer patients would receive surgery in the metastatic setting than assumed by the sponsor.
CADTH reanalysis results	• CADTH undertook reanalyses that assessed the TNBC and HER2-negative, HR-positive subgroups separately and used subgroup specific data to inform IDFS to address 1 of the identified key limitations. • In the CADTH reanalysis: ◦ For the TNBC subgroup population, the ICER for adjuvant olaparib was $43,599 per QALY (incremental costs = $74,660; incremental QALYs = 1.71) compared to watch and wait. ◦ For the HER2-negative, HR-positive subgroup, the ICER was $157,407 per QALY (incremental costs = $84,098; incremental QALYs = 0.53) compared to watch and wait. ◦ A price reduction of 67% is required for olaparib to be cost-effective compared to watch and wait in the

Component	Description
	HER2-negative, HR-positive subgroup at a WTP threshold of $50,000 per QALY. When considering the population regardless of HR status (calculated using a weighted average ICER for the TNBC and HER2-negative, HR-positive subgroups informed by the distribution of patients present in the OlympiA trial), a price reduction of approximately 3% would be required for adjuvant olaparib to be cost-effectiveness at a WTP threshold of $50,000 per QALY. • There remains uncertainty in the long-term treatment effect of adjuvant olaparib in both subgroups of interest and the comparative efficacy of olaparib vs. capecitabine for patients with TNBC. Additionally, there is uncertainty with the results of the HER2-negative, HR-positive subgroup analysis, due to the small sample size of patients whose disease was HER2 negative and HR positive within the OlympiA trial. • The treatment landscape for g*BRCA*m, HER2-negative high-risk early breast cancer is changing as CADTH recently published reimburse with conditions recommendations for abemaciclib and pembrolizumab for the treatment of early HER2-negative, HR-positive disease and TNBC, respectively. The cost-effectiveness of adjuvant olaparib compared to these treatments is unknown.

g*BRCA*m = germline *BRCA* mutation; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ICER = incremental cost-effectiveness ratio; IDFS = invasive disease-free survival; ITC = indirect treatment comparison; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year; TNBC = triple-negative breast cancer; WTP = willingness to pay.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: g*BRCA*m prevalence estimates were not specific to the Canadian population; g*BRCA*m testing rates were not aligned with current or anticipated clinical practice; and there were concerns with respect to market uptake assumptions for olaparib, including the availability of new alternatives that were not considered in the budget impact analysis. Each limitation affected the size of the estimated target population and the subset treated with olaparib. In the absence of more reliable estimates of g*BRCA*m prevalence and testing rates, the sponsor's base case was maintained. The net budget impact of olaparib was estimated to be $11,305,410 in year 1, $15,812,426 in year 2, and $17,274,463 in year 3. The net budget impact over the 3-year time horizon was estimated to be $44,392,299. The budget impact in the context of the availability of abemaciclib and pembrolizumab for HER2-negative high-risk early breast cancer is unknown. In the secondary budget impact analysis, the net budget impact of expanding access to genetic testing was estimated to be $832,352 in year 1, $1,266,688 in year 2, and $1,499,322 in year 3. The 3-year net budget impact of expanded genetic testing was $3,598,362.

pERC Information

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

Meeting date: January 11, 2023

Regrets: Two of expert committee members did not attend.

Conflicts of interest: None