pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Olaparib (Lynparza)	
Submitted Funding Request: As monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy	
Submitted By: AstraZeneca Canada Inc.	**Manufactured By:** AstraZeneca Canada Inc.
NOC Date: April 29, 2016	**Submission Date:** April 1, 2016
Initial Recommendation: August 5, 2016	**Final Recommendation:** September 29, 2016

pERC RECOMMENDATION	pERC does not recommend reimbursement of olaparib as monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy. pERC made this recommendation because the Committee was not confident that there is a net clinical benefit of olaparib maintenance treatment compared with placebo, due to limitations in the evidence from the available subgroup analysis of the phase 2 clinical trial. While pERC noted that there is a need for treatment in this setting and that olaparib produces some anti-tumour activity, the Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit of olaparib compared with placebo in regard to outcomes important to decision-making, such as overall survival (OS), progression-free survival (PFS), and quality of life. pERC also noted that treatment with olaparib was associated with moderate toxicities requiring additional monitoring compared with placebo. pERC concluded that olaparib partially aligned with patient values based on its anti-tumour activity and therapeutic intent. The Committee noted that, based on the high level of uncertainty in the available clinical data, olaparib could not be considered cost-effective in this population, compared with best supportive care (BSC).
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC acknowledged that a phase 3 randomized controlled trial (RCT), SOLO 2, comparing olaparib maintenance monotherapy with placebo in patients with platinum-sensitive relapsed BRCA-mutated ovarian cancer with a complete or partial response following platinum-based chemotherapy and who have documented BRCA 1 or 2 mutation, is currently ongoing. The estimated primary completion date is September 2016. pERC noted that results from this trial could form the basis of a resubmission to pCODR when the full data are available.

SUMMARY OF pERC DELIBERATIONS

In 2015, an estimated 2,800 new cases of ovarian cancer were diagnosed in Canada, with 1,750 deaths directly attributable to the disease. Serous epithelial ovarian cancer is the most commonly encountered histology in advanced ovarian cancers, and 20% to 30% of high-grade serous ovarian cancers have the breast cancer 1 or 2 gene mutation (BRCAm). Standard treatment for ovarian, fallopian tube, or primary peritoneal cancer — hereafter collectively referred to as ovarian cancer — includes surgery and platinum/taxane combination chemotherapy. Despite expected response rates of 75% to 85%, recurrence is likely in most women. If this recurrence is six months or more after the last platinum-based chemotherapy, patients are classified as platinum-sensitive. After a response is observed following a fixed number of cycles of platinum-based therapy, the current standard treatment strategy is "watch and wait" until further disease progression occurs. All patients will eventually develop platinum resistance with shortened PFS intervals during subsequent lines of chemotherapy. pERC therefore agreed that prolonging PFS is a meaningful outcome in this group of patients. Furthermore, pERC recognized the potential for olaparib, a PARP inhibitor, to fill this need, particularly in BRCA-mutated patients, due to the mechanism of action of the drug.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one randomized, double-blind, phase 2, placebo-controlled trial (Study 19), comparing olaparib monotherapy with placebo in patients with relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer with disease in response to platinum-based chemotherapy. pERC specifically deliberated on the results of a subgroup analysis within Study 19 in patients with BRCAm ovarian cancer and concluded that there may be a net clinical benefit of olaparib compared with placebo. The sample size of Study 19 was small and was designed with PFS (an uncertain surrogate for OS) as the primary outcome in the full intention-to-treat (ITT) population. pERC expressed concern about drawing conclusions using pre-specified exploratory end points in the subgroup of patients with BRCAm. pERC acknowledged that the improvements in PFS within the BRCAm subgroup of patients were consistent with the overall trial results and may be meaningful in this population; however, pERC noted that a high degree of uncertainty in the subgroup results for PFS remained, due to the small sample size of the study (and the subgroups). pERC also noted that the use of a one-sided alpha level of 0.2 in the ITT analysis and the exploratory nature of the subgroup analyses contributed to the high degree of uncertainty. OS was also a pre-specified exploratory secondary end point in the BRCAm subgroup of patients. Upon reconsideration of the Initial Recommendation, pERC reiterated that all secondary end points in the BRCAm population were pre-specified exploratory end points. Multiple interim analyses were conducted and significance was not demonstrated at any analysis point. Additionally, in the overall ITT analysis of OS, where adjustments were made for multiple testing, significance was not demonstrated at any analysis. Therefore, the Committee was unable to draw any conclusions on the OS results within the subgroup of patients with BRCAm, and concluded that the results were, at most, hypothesis-generating. In discussing the trial results, pERC acknowledged that olaparib has some anti-tumour activity, but considerable uncertainty remains as to the magnitude of benefit with respect to outcomes important to decision-making, such as OS and PFS. The Committee agreed that the currently available results are exploratory and further studies are required to confirm these results in order to validate the true benefit of olaparib. Patient-reported outcomes (PROs) were measured in the trial using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) scale, FACT-O Symptom Index (FOSI), and Trial Outcome Index (TOI). In the majority of patients with BRCAm, differences were not observed between baseline and six months after treatment with olaparib or placebo for all three scales. pERC agreed that olaparib maintained quality of life (QoL) in the majority of patients. Among patients with BRCAm experiencing a decline in PROs, more patients in the placebo arm experienced a worsening in FACT-O and TOI scales compared with patients in the olaparib arm. Results were consistent with those seen in the overall ITT analysis for PROs.

pERC deliberated on the toxicity of olaparib compared with placebo and noted that more patients in the olaparib group experienced grade 3 or higher toxicities. Dose reductions and interruptions were also more frequent in the olaparib group, with vomiting, nausea, and fatigue the most common reasons.

Overall, pERC concluded that there may be a net clinical benefit with olaparib compared with placebo, but the results are uncertain, due to the limitations in the evidence from Study 19. pERC discussed one ongoing phase 3 RCT, SOLO 2, with an estimated primary completion date in September 2016. pERC anticipates the phase 3 RCT SOLO 2 will provide data on PFS, OS, and PROs, and clarity on the comparative effectiveness of olaparib versus placebo in the patient population with BRCAm disease. pERC noted that results from this trial could form the basis of a resubmission to pCODR when the full data are available.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from the submitter and from a registered clinician group on the statistical concerns raised by pERC regarding Study 19. pERC further noted additional details provided by the pCODR Clinical Guidance Panel (CGP) and agreed that the limitations identified with Study 19 remain. The Committee acknowledged that the concerns about the limitations of the trial design were appropriate, given the objective of Study 19 and the intent of phase 2 trials. In general, and for Study 19 in particular, phase 2 trials are mainly hypothesis-generating and their intent is to determine whether or not there is sufficient promise to proceed to a phase 3 confirmatory trial. Therefore, the alpha level used in Study 19 which allowed for a greater chance (20%) of detecting a false-positive (type I error rate of 20%) is considered appropriate when keeping the objective in mind, while a more stringent design would be required for confirmatory trials (i.e., a two-sided alpha level of 0.05). The Committee acknowledged the small *P* value achieved with olaparib for PFS both in the overall and BRCAm population indicating that olaparib has activity in this patient population. However, given the limitations of the trial design (including, but not limited to, the small overall sample size [with a type I error rate of 20%], the even smaller size of the BRCAm subgroup, and the lack of stratification at randomization by BRCAm status), pERC concluded that there is a large amount of uncertainty in the trial results. pERC considered that there have been many examples of promising phase 2 trials that have failed to demonstrate benefit in subsequent phase 3 trials and, therefore, the Committee concluded that the results from Study 19 require confirmation through a phase 3 trial. pERC agreed that the *P* value for OS in the overall and BRCAm subgroup was not statistically significant, as defined in the trial, and statistical significance was not met at any interim analysis, including the updated analysis at 70% maturity. pERC noted that similar concerns were raised by other regulatory agencies, including the US FDA and the UK National Institute for Health and Care Excellence (NICE), which have subsequently approved olaparib for indication different from the one currently under review. Additionally, while Health Canada's role in providing regulatory approval is limited to assessing the safety and activity of an agent, pERC stressed that its role as a health technology assessment (HTA) body is to determine the net clinical benefit of an agent relative to comparators and with consideration of other factors, including cost-effectiveness, patient perspectives and clinical evidence, a decision that is greatly influenced by the robustness of the clinical evidence provided. Although pERC did not undertake a formal review or comparison of olaparib with other similar agents, the Committee is aware that various PARP inhibitors are currently being investigated and that, similarly to Study 19, promising phase 2 trial results have been reported. The Committee also understood that the landscape for treatment in this patient population may likely change once robust Phase 3 data are available on PARP inhibitors, noting that the results of the phase 3 RCT SOLO 2 may be a few years away. In light of this, pERC recognizes that the Committee's decisions must be equitable, transparent, timely and accountable to patients, health care funders, and the public to ensure that effective treatment option are considered for public funding. Conversely, pERC also recognizes that these decisions must be rigorous, consistent, and evidence-based. pERC considers the evidence-generation process as outlined in the hierarchy of clinical trial design a benchmark and expressed dismay at receiving data that are promising yet lack the level of rigour expected by international regulatory and HTA agencies. pERC noted that the phase 3 RCT SOLO 2 trial is still ongoing and has not been closed early for ethical reasons, in order to make olaparib available to both treatment arms indicating that clinical equipoise still remains. Having reconsidered all these factors, pERC reiterated that it was unable to conclude that olaparib demonstrates a net clinical benefit compared with placebo and anticipates that the results from the phase 3 RCT SOLO 2 will aid in determining the true benefit of using olaparib in this setting.

pERC acknowledged registered clinician input regarding the value of delaying symptomatic progression and lengthening the time to the next treatment. While olaparib demonstrates activity, pERC was greatly limited in drawing any conclusions on the magnitude of PFS and OS benefit, given the considerable limitations in the trial design. pERC anticipates that the ongoing phase 3 RCT, SOLO 2, may answer these questions. Input from clinicians also indicated that olaparib has improved toxicity compared with chemotherapy; however, the Committee was unable to comment on this comparison, as the evidence presented in Study 19 was in a setting where the clinical alternative is "watch and wait". pERC acknowledged input provided by registered clinicians and noted that the current review addressed only

patients who are relapsed and in response to a second platinum-based treatment and, therefore, data were unavailable to make any statement on the use of olaparib as maintenance treatment following first-line treatment. Upon reconsideration of the pERC initial recommendation, pERC acknowledged feedback from registered clinicians noting that their original input was misunderstood by pERC and clarifying that they are in alignment with the funding request and the population approved by Health Canada (i.e., patients who have had at least two prior lines of platinum based chemotherapy and who are in response to their last round of platinum based chemotherapy and remain platinum sensitive). pERC also acknowledged the importance of PFS and QoL to patients in the maintenance setting. pERC also considered the importance of an improved toxicity profile as detailed in the clinician feedback and by the CGP. In the absence of robust comparative evidence, pERC was, however, unable to make conclusions about the net clinical benefit of olaparib and the comparative impact it has on safety and efficacy.

pERC deliberated upon input from one patient advocacy group concerning ovarian cancer and noted that patients value having treatment options that help manage disease-related symptoms, prolong survival, prolong time until recurrence, improve QoL, and reduce the visits to the cancer centre. Patients show willingness to tolerate side effects with new therapies, even if the benefit of treatment is short-term. Patients were, however, least willing to tolerate blood cancer and inflammation of the lungs as drug-related side effects. The majority of patients also expressed a desire to control fatigue. pERC agreed that results from Study 19 suggest olaparib showed no decrement in QoL, which pERC considered to be reasonable in the setting of maintenance treatment. Overall, pERC concluded that the oral route of administration, anti-tumour activity, and therapeutic intent of olaparib aligned with patient values. pERC was, however, limited by the quality of clinical evidence provided and unable to conclude that olaparib provided a net clinical benefit compared with "watch and wait". pERC also applauded the quality of the patient input provided and the methodology used to collect information on patients specific to the population under consideration. pERC stated that the input was very useful in understanding whether olaparib aligned with patient values.

pERC deliberated on the cost-effectiveness of olaparib compared with BSC and concluded that, at the submitted price, olaparib is not cost-effective. pERC made this conclusion noting the significant uncertainty regarding the incremental cost-effectiveness ratio (ICER), due to the uncertainty in the clinical effectiveness of olaparib compared with BSC, based on the available clinical data. Given the limitations in the design of the clinical trial, pERC noted that the uncertainty in the ICER is greatly impacted by the uncertain magnitude of the OS benefit, if any, with olaparib. pERC also discussed a number of other inputs explored by the pCODR Economic Guidance Panel (EGP), and which the Committee considered to have a secondary impact on the ICER compared with the uncertainty in the OS benefit. pERC also noted that, although already high, the submitted ICER was substantially lower than the EGP's lower estimate of the ICER. Additionally, pERC considered the difficulty in quantifying the uncertainty in the OS benefit given the limitations in the clinical data and agreed that the uncertainty in the ICER is appropriately captured by the EGP's decision to not provide an upper estimate. pERC noted that robust clinical inputs would be needed to better estimate the true ICER. Overall, pERC concluded that olaparib could not be considered cost-effective.

pERC discussed the feasibility of implementing a reimbursement recommendation for olaparib for the treatment of patients with relapsed BRCAm-positive ovarian cancer who are in response to platinum-based chemotherapy. pERC echoed the pCODR Provincial Advisory Group's (PAG's) concern regarding the uncertainty of the OS benefit from Study 19 and noted the ongoing phase 3 RCT, SOLO 2 (with an estimated primary completion date in September 2016, as mentioned above), which will provide data on PFS, OS, and PROs. pERC noted that results from this trial could form the basis of a resubmission and encouraged a resubmission to pCODR when the full data are available. pERC also considered the significant capsule burden with olaparib in Study 19. pERC noted that different formulations of olaparib are being explored in ongoing trials and, therefore, a lower pill burden may be available in the future. pERC acknowledged, in accordance with the EGP analysis, that the number of eligible patients, the inclusion of BRCAm testing, and the drug cost have the largest impact on the budget impact analysis. Given that the number of eligible patients is expected to increase, if testing for *de novo* tumoral mutations becomes available, pERC considered that the submitter's estimates and the reanalysis estimates provided by the EGP likely underestimate the budget impact analysis as related to BRCAm testing.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the *Clinical Guidance Report* that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from one patient advocacy group, Ovarian Cancer Canada (OCC)
- Input from one clinician group, the Society of Gynecologic Oncology of Canada (GOC), and one individual clinician
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, OCC
- One clinician group, GOC
- The PAG
- The submitter (AstraZeneca Inc.).

The pERC Initial Recommendation was to not recommend reimbursement of olaparib as monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy. Feedback on the pERC Initial Recommendation indicated that the manufacturer, patient advocacy group, and registered clinician group disagreed with the Initial Recommendation, while the PAG agreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of olaparib monotherapy, compared with an appropriate comparator, on patient outcomes in the treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) epithelial ovarian, fallopian tube, or primary peritoneal cancer — hereafter collectively referred to as ovarian cancer — who are in response to platinum-based chemotherapy.

Studies included: One randomized controlled trial

The pCODR systematic review included one randomized, double-blind, phase 2, placebo-controlled trial, comparing olaparib as monotherapy to placebo in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer with high-grade (2 or 3) serous features who have completed at least two courses of platinum-based chemotherapy, of which their most recent regimen included an objective response.

A key inclusion criterion was that patients had to have been initiated on the study within eight weeks of completing their final dose of a platinum-containing regimen. BRCA mutation (BRCAm) status was not required at trial entry; however, testing was done in the post-study period and retrospective pre-planned subgroup analysis was performed in patients with the BRCAm.

The pCODR review also provided contextual information on Study 41, a small phase 2, open-label, double-blind, randomized study that compared olaparib in combination with paclitaxel and carboplatin to paclitaxel and carboplatin dual therapy for the treatment of patients with platinum-sensitive ovarian cancer who have received no more than three previous platinum-containing regimens. The study reported on a subgroup of patients with BRCAm (n = 41). pERC noted that Study 41 provided some supportive information, but was prone to the same limitations described for Study 19.

Patient populations: Subgroup analysis in BRCA mutation-positive patients

Patients in Study 19 were randomized 1:1 to receive olaparib at 400 mg (eight 50 mg capsules) twice daily oral dose continually throughout a 28-day cycle or placebo capsules. Among 265 enrolled patients (136

and 129 in the olaparib and placebo arms, respectively), 136/265 (51.3%) had the BRCAm status (74 and 62 in the olaparib and placebo arms, respectively).

Baseline characteristics were mostly balanced between treatment groups for the overall trial population and within the BRCAm subgroup of patients. Fewer patients in the olaparib arm had Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 (15% versus 24% in the placebo arm), while more patients in the olaparib arm had ECOG PS 0 (84% versus 73% in the placebo arm). Similarly, in the BRCAm subgroup, fewer patients in the olaparib arm had a complete response to their most recent platinum-based regimen (49% versus 55% in the placebo arm), while more patients in the olaparib arm had a partial response (51% versus 45% in the placebo arm). Given that data were reported on the subgroup of patients with BRCAm, a Cox proportional hazards model was used to adjust the progression-free survival (PFS) and overall survival (OS) data for baseline covariates that were considered to be important prognostic factors. These included ethnic descent (Jewish versus non-Jewish), time to progression on penultimate platinum therapy (six to 12 months versus more than 12 months), and response to platinum therapy before randomization (complete response versus partial response).

Treatment with olaparib continued until objective disease progression, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, or until any grade 3 or 4 adverse event that did not resolve completely or to grade 1 within 28 days after onset, according to the Common Terminology Criteria for Adverse Events (CTCAE).

Key efficacy results: Pre-planned retrospective exploratory end points

The key efficacy outcome deliberated on by pERC was PFS, the primary outcome in the trial. Subgroup analysis for PFS in the BRCAm population was a pre-planned exploratory end point. Upon reconsideration of the Initial Recommendation, pERC reiterated that all secondary end points in the BRCAm population were pre-specified exploratory end points. In the BRCAm subgroup of patients, median PFS was 11.2 versus 4.3 months (hazard ratio [HR] = 0.18; 95% confidence interval [CI], 0.10 to 0.31; $P < 0.0001$) in the olaparib compared with placebo groups. This translated into a 6.9-month gain in PFS in the BRCAm-positive subgroup. pERC acknowledged that improvement in PFS within the BRCAm subgroup of patients was consistent with the overall trial results and would be meaningful in this population; however, uncertainty remained, due to the small sample size of the study, the exploratory nature of the subgroup analysis, and the use of a one-sided alpha level of 0.2 in the intention-to-treat (ITT) analysis, which allowed a 20% risk for concluding a statistical difference in PFS in favour of olaparib when there is no difference. Upon reconsideration of the Initial Recommendation, pERC noted that while the 2012 *New England Journal of Medicine* publication of Study 19 indicated a trial design to report a statistical difference, the trial protocol and confirmation from the manufacturer through feedback indicated that the design of the trial was to detect a promising difference (e.g., 80% power to demonstrate a promising difference in favour of olaparib [$P < 0.2$, one-sided] and statistical significance is not referred to using this sample size calculation). The protocol also indicated that results would be deemed to have statistical significance if they had a $P < 0.025$. pERC reiterated that the reported P value for the ITT and BRCAm subgroup of patients for PFS was far below the set threshold for statistical difference. However, this does not negate the uncertainty introduced due to the trial design, which allowed for a greater chance (20%) of detecting a false- positive. pERC acknowledged that the low P values demonstrate a promising difference, requiring confirmation through a phase 3 study with a more stringent trial design.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from the submitter addressing a group of patients who had long-term PFS: 16% and 15% in the BRCAm group having PFS over four and five years, respectively. pERC noted the pCODR Clinical Guidance Panel (CGP) input on this, indicating that this long-term PFS is meaningful; however, the CGP noted that patients under consideration are among those with the best prognostic subgroup in this disease (e.g., platinum-sensitive, responded to second-line platinum therapy, BRCA-positive), and therefore it is unclear whether or not such a response would be expected in all patients with disease recurrence.

OS, a pre-specified exploratory secondary end point in the subgroup analysis, was analyzed at multiple time points without adjustments for multiplicity. Significance was not demonstrated at any of the interim analyses. At the latest OS analysis, in patients with the BRCAm and with 70% maturity, the median OS was 34.9 compared with 30.2 months in the olaparib and placebo arms, respectively (HR = 0.62; 95% CI, 0.41 to 0.94; $P = 0.02480$, not adjusted for multiple testing). The final analysis is expected at 80% maturity. Adjustments were made for multiple testing in the ITT OS analysis and statistical significance was not demonstrated at any interim analysis. The Committee therefore agreed that considerable uncertainty

remains regarding the conclusions that could be drawn from the OS results. Based on objective response rates of 16% and 5% in the olaparib and placebo arms, respectively, pERC agreed that olaparib demonstrates anti-tumour activity. Overall, due to the type I error rate, the sample size of the trial, analysis of results based on a small subgroup of patients, and multiple testing for outcomes, pERC agreed that considerable uncertainty remained regarding the magnitude of benefit associated with olaparib. The Committee therefore agreed that the current data are exploratory and confirmatory results would be needed to validate the true clinical benefit of olaparib.

pERC further discussed one ongoing phase 3 randomized controlled trial (RCT), SOLO 2, with an estimated primary completion date in September 2016. pERC anticipates that the phase 3 RCT SOLO 2 will provide data on PFS, OS, and patient-reported outcomes (PROs), and further clarity on the comparative effectiveness of olaparib versus placebo in patients with BRCAm-positive disease. pERC noted that results from this trial could form the basis of a resubmission and encouraged a resubmission when the full data are available.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the PAG commenting on the consistency of decisions pERC made in reviews where data were presented from a subgroup analysis. pERC noted that as a principle, the Committee considers a review based on its own merits and the evidence presented for the agent under consideration. Furthermore, in this instance, pERC briefly considered the strength of the evidence provided for the review identified by the PAG feedback (bevacizumab for front-line therapy in patients with advanced stage ovarian cancer at high risk of progression) as compared with the evidence presented for olaparib. pERC noted that unlike Study 19, the bevacizumab review included two large Phase III RCTs, which presented analyses from two large subgroups of patients: 406 and 502 patients from the two studies, respectively. Additionally, both studies were stratified based on the subgroups of interest, and statistically significant and clinically meaningful results were measured and consistent across these two large subgroups of patients. A statistical test for interactions in one trial supported that a treatment effect was indeed present for bevacizumab in that setting. In Study 19, pERC reiterated that improvement in PFS within the BRCAm subgroup of patients was consistent with the overall trial results and represents a promising benefit in this population; however, uncertainty remained, due to the small sample size of the study, the exploratory nature of the subgroup analysis, and the use of a one-sided alpha level of 0.2 in the ITT analysis, which allowed for a 20% risk for detecting a difference for PFS in favour of olaparib when there is no difference. Furthermore, the study was not stratified based on the subgroup of interest, and tests for interaction for PFS were negative. Overall, pERC agreed that based on the merits of the data presented, a conclusion could not be made supporting net clinical benefit in favour of olaparib.

Patient-reported outcomes: No decrement in PROs for most patients

PROs were measured using the Total Functional Assessment of Cancer Therapy–Ovarian (FACT-O), FACT-O Symptom Index (FOSI), and Trial Outcome Index (TOI). TOI captures a patient's ability to lead a normal, fulfilling life and is derived from the physical and functional well-being and ovarian cancer subscales of the FACT-O questionnaire. In the overall population, compliance rates were high, at approximately 85% at baseline, were approximately 80% across all time points, and notably fell after six months in the placebo group.

In the majority of patients, differences were not observed between baseline and six months after treatment with olaparib or placebo for all three scales. Among those experiencing a worsening in PROs, a greater portion of the patients experienced worsening as per the FACT-O and TOI scales in the placebo arm compared with the olaparib arm of the BRCAm population. pERC agreed that results from Study 19 suggest olaparib showed no decrement in quality of life (QoL), which pERC considered to be reasonable in the setting of maintenance treatment. Although patient input indicated value in treatment that increased QoL, pERC agreed that results observed with olaparib in terms of PROs are in alignment with the values expressed by patients.

Safety: More frequent grade 3 or 4 toxicities

pERC discussed the toxicity profile of olaparib in the trial. In the BRCAm population, adverse events (AEs) of all grades occurred in 97% and 94% of the patients in the olaparib and placebo arms, respectively. AEs of grade 3 or higher occurred more frequently in the olaparib arm than in the placebo arm (38% and 18%, respectively). pERC agreed that this increased incidence in grade 3 or higher AEs with olaparib is meaningful. Specifically, the incidences of grade 3 or higher fatigue (7% versus 2%), anemia (5% versus 2%), and neutropenia (4% versus 2%) were higher in the olaparib arm of the BRCAm population than the

placebo arm. pERC considered the fact that control of fatigue was valued by the majority of patients providing input, and noted that fatigue was experienced by a greater proportion of patients in the olaparib group, which then resulted in dose reductions. Fatigue, vomiting, and nausea were the most frequent reason for dose reduction and interruptions in the olaparib group.

pERC noted that blood disorders or blood cancer were the side effect patients were least willing to tolerate. Myelodysplastic syndrome (MDS) occurred in two patients, one each in patients with BRCAm receiving olaparib and placebo. At this time, the risk of MDS and leukemia appears low and difficult to attribute solely to olaparib in this population of patients pre-treated with chemotherapy.

Need: Active maintenance treatment to prolong progression-free survival and time to next treatment

In 2015, an estimated 2,800 new cases of ovarian cancer were diagnosed, and 1,750 deaths were attributed directly to the disease. Standard therapy includes surgery and platinum/taxane combination chemotherapy. Despite expected response rates of 75% to 85%, recurrence is unfortunately likely in most women. If this recurrence is six months or more after the platinum chemotherapy, patients are classified as platinum-sensitive. Serous epithelial ovarian cancer is the most commonly encountered histology in advanced ovarian cancers, and 20% to 30% of high-grade serous ovarian cancers have BRCA mutations. Although all patients will eventually develop platinum resistance with shortened PFS intervals during subsequent lines of chemotherapy, there is currently no standard maintenance therapy given to patients. The standard practice after response is observed in patients following a fixed number of cycles of platinum-based regimen is to keep patients in "watch and wait" until further disease progression occurs. Furthermore, pERC acknowledged registered clinician input that stressed the value of delaying symptomatic progressions and time to the next treatment. pERC, therefore, agreed that prolonging PFS would be meaningful to patients and recognized the potential for olaparib, a PARP inhibitor, to fill this need, particularly in BRCAm patients.

Registered clinician input: Disease burden, delay in progression, and time to next treatment

Based on registered clinician input, patients with BRCAm ovarian cancer who have relapsed and platinum-sensitive disease are not given maintenance therapy; however, previous trials have demonstrated benefits of continuing the initial chemotherapy in terms of PFS, but not QoL or OS, and the utility of this approach is usually limited by cumulative toxicities. Input indicated that olaparib represents a targeted therapy with a specific biomarker for a clearly defined and small population of patients with the BRCAm status. pERC also acknowledged the value of delaying symptomatic progression and lengthening the time to the next treatment in a patient population that experiences significant disease symptom burden. pERC considered registered clinician input and acknowledged that olaparib demonstrates activity, but was greatly limited in drawing any conclusions on the magnitude of PFS and OS benefit, given the considerable limitations in the trial design. pERC anticipates that the ongoing phase 3 RCT, SOLO 2, may answer these questions. Input from clinicians also indicated that olaparib has improved toxicity compared with chemotherapy; however, the Committee was unable to comment on this comparison, as the evidence presented in Study 19 was in a setting where the clinical alternative is "watch and wait". pERC further noted that the current review addressed only patients who are relapsed and in response to a second platinum-based treatment and, therefore, data were unavailable to allow for any statement on the use of olaparib as maintenance treatment following first-line treatment.

PATIENT-BASED VALUES

Values of patients with ovarian cancer: Impact on daily life and quality of life

pERC noted that 39 of 40 patients providing input were Canadian. Among these, the majority (n = 24) had BRCAm ovarian cancer. pERC applauded the quality of the patient input provided and the methodology used to collect information on patients specific to the population under consideration. pERC expressed that the input was very useful in understanding whether olaparib aligned with patient values.

Patients providing input ranked sleep, sexual relationship, work life, physical activity, and well-being as the most negatively affected issues with ovarian cancer. Patients' experiences with current therapy for ovarian cancer indicated that the following areas were least effectively managed by current therapies: fatigue, hair loss, bowel problems, blood problems, nausea and/or vomiting, aching joints, neuropathy,

skin irritations, loss of fertility, and ascites. The majority of respondents (80%) specifically noted fatigue as having a large effect on their QoL. Travel, financial issues, and lack of available treatment were the most frequently cited significant barriers to accessing treatment.

pERC discussed patient and caregiver experience with ovarian cancer and acknowledged the significant impact on day-to-day life and QoL. pERC agreed that results from Study 19 suggest olaparib showed no decrement in QoL and that this aligned with patient values. pERC also considered patients' willingness to tolerate additional drug-related toxicities as a trade-off for clinical benefit in light of the increased grade 3 or 4 AEs with olaparib compared with placebo. pERC acknowledged that olaparib demonstrates anti-tumour activity but was unable to reconcile the limitations associated with the use of pre-specified exploratory end points from Study 19, which introduced considerable uncertainty in the reported results for clinical efficacy and safety. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the patient advocacy group. Patients highlighted the need that exists in this "watch and wait" stage of their disease, where shorter and shorter periods of progression-free intervals are expected with each progression. Therefore, pERC agreed with the CGP that PFS and QoL are important outcomes if they are achieved with a low toxicity profile. However, pERC reiterated its concern with the results of Study 19, given the limitations in the phase 2 design of the trial. Notably, the Phase 3 RCT, SOLO 2, is still ongoing and has not been closed for ethical considerations to make olaparib available to both treatment arms indicating that clinical equipoise still remains. pERC considered the promising data available through Study 19 and that the results of the Phase 3 RCT SOLO 2 may be two years away. In light of this, pERC recognizes that the Committee's decisions must be equitable, transparent, timely and accountable to patients, health care funders, and the public to ensure that effective treatment option are considered for public funding. pERC also recognizes that these decisions must be rigorous, consistent and evidence-based. pERC considers the evidence-generation process as outlined in the hierarchy of clinical trial design a benchmark and expressed dismay at receiving data that are promising yet lack the level of rigour expected by international regulatory and HTA agencies. Having re-considered all these factors, pERC re-iterated that it was unable to conclude that olaparib demonstrates net clinical benefit and anticipates that the results from the Phase 3 RCT SOLO 2 will aid in determining the true benefit of using olaparib in this setting.

Patient experience with olaparib: Prolonging survival and recurrence, and improving quality of life

Patients stated that they place a high value on whether this new treatment will be able to prolong survival, prolong the time until recurrence, improve QoL, and reduce visits to the cancer centre. Patients indicated a willingness to take olaparib even if there was only some or little improvement in their ovarian cancer. Side effects such as tiredness, nausea, taste changes, blood problems (e.g., anemia), bruising and bleeding easily, dizziness, headaches, and pain under the ribs were considered tolerable if the treatment could improve overall daily functioning and prognosis. Side effects that patients were least willing to tolerate were blood cancer and inflammation of the lungs.

pERC noted that 10 of 40 patients providing input had experience with olaparib. Olaparib was noted to prolong recurrence, shrink tumour size, prolong survival, and improve QoL compared with previous treatments. Patients providing input experienced tiredness and/or weakness, nausea, taste changes, diarrhea, blood disorder or blood cancer, headaches, blood problems (e.g., anemia), pain under the ribs, dizziness, infections, and sore mouth with olaparib. Side effects considered to be least tolerable with olaparib were tiredness, hair loss, nausea, bowel issues, and blood disorders. The majority of respondents believed the benefits of olaparib outweighed the risks. pERC acknowledged patients' willingness to tolerate additional side effects of a treatment even if the benefits were short-term; however, given the considerable uncertainty in the clinical evidence, pERC expressed uncertainty in the trade-off of efficacy compared with side effects of olaparib and indicated that information provided may not capture experience from patients with a poor outcome from olaparib.

Overall, pERC concluded that the oral route of administration, anti-tumour activity, and therapeutic intent of olaparib aligned with patient values. pERC was, however, limited by the quality of clinical evidence provided and unable to conclude that olaparib provided a net clinical benefit.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed cost-effectiveness and cost-utility analyses comparing olaparib monotherapy as maintenance treatment in patients with platinum-sensitive recurrent BRCAm-positive ovarian cancer.

Basis of the economic model: Study 19 data

Costs included were cost of the drugs, follow-up costs, costs of treating AEs, costs of subsequent treatments, and end-of-life care costs. pERC noted that the factor most significantly affecting cost was the drug cost. Key clinical effects considered in the analysis were obtained from Study 19. pERC noted that the uncertainty in the OS data had the largest impact on the incremental cost-effectiveness ratio (ICER). Other uncertainties in the clinical effect estimates included the use of time to discontinuation of therapy as a proxy for PFS and the method of extrapolation of OS data.

Drug costs: High drug cost

Olaparib costs $16.74 per 50 mg capsule. At the recommended dose of eight capsules twice per day, this amounts to $267.84 per day and $7,499.52 per 28-day course. Given the high dose intensity observed in the trial and the 50 mg capsule size, pERC does not anticipate that olaparib would be associated with significant wastage.

Cost-effectiveness estimates: Uncertainty in OS benefit

pERC deliberated on the cost-effectiveness of olaparib compared with best supportive care (BSC) and accepted the EGP's reanalysis, concluding that, at the submitted price, olaparib is not cost-effective. pERC made this conclusion noting the significant uncertainty in the ICER due to the uncertainty in the clinical effectiveness of olaparib compared with BSC, given the limitations in the design of the clinical trial. pERC discussed the issue that the uncertainty in the ICER is greatly affected by the magnitude of the OS benefit with olaparib. Given that the uncertainty in the clinical data was not quantifiable, the EGP was unable to provide an upper limit to the ICER. pERC accepted this reanalysis and agreed that more robust clinical data are needed to better estimate the true ICER. pERC discussed a number of other inputs explored by the EGP, and which had an impact on the ICER, including changes to the time horizon, the use of alternative extrapolation methods, adjustments made in the data for baseline covariates, the source of PFS data, and the use of equal OS benefit between arms at the end of the trial period. Secondary to the uncertainty in the magnitude of OS benefit, all of these factors had substantial impacts on the ICER. pERC therefore agreed with the EGP's reanalysis estimates and noted that although already high, the submitted ICER was substantially lower than the EGP's lower estimate of the ICER. Overall, pERC concluded that olaparib could not be considered cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Ongoing phase 3 trial, BRCA testing, alternative formulation with lower pill burden

pERC discussed factors affecting the feasibility of implementing a reimbursement recommendation for olaparib for patients with platinum-sensitive BRCAm ovarian cancer. pERC echoed the concerns of the PAG related to the absence of OS data in Study 19. pERC further stressed the considerable uncertainty regarding the clinical evidence from Study 19, due to the design of the study. pERC noted one ongoing phase 3 RCT, SOLO 2, in patients with histologically diagnosed relapsed high-grade serous ovarian cancer (including primary peritoneal and/or fallopian tube cancer) or high-grade endometrioid cancer who have documented BRCA 1 or 2 mutation. The phase 3 RCT SOLO2 has an estimated primary completion date in September 2016 and will provide data on PFS, OS, and PROs. pERC noted that results from this trial could form the basis of a resubmission to pCODR and encouraged a resubmission when the full data are available.

pERC noted that olaparib is an oral drug, which can be administered more easily than an intravenous drug. However, the dose requirement of eight capsules twice per day (a total of 16 capsules per day) is a large pill burden for patients. pERC noted that alternative dose formulations are being explored in ongoing trials, and that tablets with lower pill burden may be available in the future.

With regard to the budget impact, pERC acknowledged, in accordance with the EGP's reanalysis, that the factors that most influenced the budget impact analysis (BIA) included limiting the number of patients to those eligible under the respective jurisdictional drug program. Given that there is a cohort of patients who are not covered within provincial oral drug programs, pERC acknowledged that the BIA underestimates the number of eligible patients. Other factors that influenced the BIA were the inclusion of BRCAm testing, and the drug cost. Input from registered clinicians indicated that although the number of patients eligible for olaparib will be small, if testing for *de novo* tumoral mutations becomes available, the number may be slightly higher. pERC therefore considered that the submitter's analysis, and likely the reanalysis provided by the EGP, underestimated the BIA as related to BRCAm testing. Registered clinician input also noted that both germline and somatic testing would be essential in this setting.

DRUG AND CONDITION INFORMATION

Drug Information	• Olaparib is a PARP inhibitor • Olaparib is available as a 50 mg capsule • The recommended dose is eight 50 mg tablets twice per day
Cancer Treated	• Platinum-sensitive relapsed BRCA mutation-positive (germline or somatic) ovarian cancer in response to platinum-based chemotherapy
Burden of Illness	• 2,800 new cases and 1,750 deaths from ovarian cancer in Canada in 2015 • 75% to 85% of ovarian cancer recurs (high grade) • 20% to 30% of high-grade serous ovarian cancer patients are BRCA mutation-positive • Shortened progression-free survival intervals during subsequent lines of chemotherapy
Current Standard Treatment	• "Watch and wait" after response is observed following a fixed number of cycles of platinum-based regimen until further disease progression occurs
Limitations of Current Therapy	• No maintenance therapy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Carole McMahon, Patient Member Alternate
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Maureen Trudeau, who did not vote
- Paul Hoskins, who did not participate in the information-gathering, deliberations, and voting
- Valerie McDonald, who did not vote due to her role as a patient member alternate
- Allan Grill and Scott Berry, who were not present.

All members participated in deliberations and voting on the Final Recommendation, except:

- Maureen Trudeau, who did not vote
- Paul Hoskins, who did not participate in the information-gathering, deliberations, and voting.

Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of olaparib (Lynparza) for platinum-sensitive relapsed BRCA mutation-positive (germline or somatic) ovarian cancer in response to platinum-based chemotherapy, through their declarations, four members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, two of these members were excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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