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 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 Reimbursement Request: 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 who are in response (complete response or partial response) to first-line platinum-based chemotherapy, until disease progression or up to two years if no evidence of disease. Patients must have confirmation of BRCA mutation (identified by either germline or tumour testing) before Lynparza treatment is initiated.

Submitted By: AstraZeneca Canada	**Manufactured By:** AstraZeneca Canada
NOC Date: May 6, 2019	**Submission Date:** April 18, 2019
Initial Recommendation: October 3, 2019	**Final Recommendation:** December 5, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Olaparib costs $65.89 per 150 mg or 100 mg tablet. At the recommended dose of 600 mg daily, olaparib costs $263.57 per day (two 150 mg tablets, taken twice daily) and $7,188.08 per month (30.44 days, assumed a relative dose intensity of 89.6%).

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC recommends the reimbursement of olaparib (Lynparza) monotherapy if the following conditions are met:

- cost-effectiveness is improved to an acceptable level through a reduction in price.

Reimbursement should be for the maintenance treatment of adult patients with newly diagnosed, advanced, BRCA-mutated (germline or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy, as per SOLO-1 trial.

Patients must have received at least four cycles of platinum-based chemotherapy before starting treatment with olaparib. Maintenance therapy with olaparib should begin within eight weeks of the last dose of platinum-based chemotherapy. Treatment should continue until unacceptable toxicity, disease progression, or completion of two years of therapy, whichever comes first. Reimbursement should be for patients who have a good performance status.

pERC made this recommendation because the Committee was satisfied that there is a net clinical benefit of olaparib maintenance treatment compared with placebo, based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS), no appreciable detrimental effect on quality of life (QoL), and a manageable toxicity profile. pERC agreed that olaparib aligns with patient values because it is an oral treatment

	that delays disease progression, has no detriment to QoL, and has manageable toxicities. Despite the submitted and pCODR Economic Guidance Panel (EGP)'s point estimate of the incremental cost-utility ratio (ICUR) being low, pERC was concerned with the impact of the uncertainty of the clinical effect estimates on the ICUR. Given that the EGP was unable to explore all the uncertainty in long-term extrapolation of overall survival (OS), the Committee agreed that the ICUR is likely underestimated. Overall, the Committee could not confidently draw a conclusion on the cost-effectiveness of olaparib at the submitted price and given the high level of uncertainty in the magnitude of long-term OS benefit compared with routine surveillance care.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit with olaparib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of olaparib given the uncertainty around the long-term benefits. pERC further agreed that until more robust evidence is available to determine the long-term impact of olaparib on OS, a price reduction may be required to manage the uncertainty in the cost-effectiveness of olaparib. **Accessibility to Olaparib for Patients on Non-Platinum Chemotherapy on a Case-by-Case Basis** pERC recognizes that there will be a small number of patients who may have had an allergic reaction or unable to tolerate platinum-based chemotherapy, who would therefore have non-platinum chemotherapy substituted for up to four cycles. pERC noted that patients who had a response on a non-platinum chemotherapy (and otherwise met the criteria for maintenance olaparib) should be candidates for olaparib. Given the difference in the mechanism of action of olaparib and both types of chemotherapy agents, a difference in response is not anticipated. **Re-Treatment After Planned Treatment Interruption** pERC noted that if treatment with olaparib was temporarily stopped, the treating oncologist would need to confirm no evidence of progression before restarting treatment with olaparib. The Committee noted that if there is evidence of progression, treatment with olaparib should be permanently discontinued. **Time-Limited Need for Olaparib in Patients Currently Being Monitored or on Bevacizumab Treatment** At the time of implementing a reimbursement recommendation for olaparib, jurisdictions may consider addressing the short-term, time-limited need to offer to switch to olaparib for patients currently being monitored or who are on maintenance bevacizumab after first-line platinum-based chemotherapy provided there is no evidence of disease progression. However, pERC recognized that the use of maintenance bevacizumab in this setting is infrequent in the Canadian setting. **Timing of Maintenance Treatment After Completion of Platinum-Based Chemotherapy** pERC noted that multiple factors, such as chemotherapy side effects and treatment logistics, can prevent some eligible patients from starting olaparib within eight weeks as mandated in SOLO-1. pERC therefore agreed that olaparib should be offered to all patients eligible for first-line maintenance olaparib as long as treatment can be started within 12 weeks of the last chemotherapy treatment. If more than eight weeks had elapsed from last chemotherapy treatment, patients should be re-staged and those with disease progression should not be treated with olaparib.

Accessibility to Reflex Testing for BRCA-Mutation Status at Diagnosis
pERC agreed that timely BRCA-mutation status (germline or somatic, as detected by approved testing) is required prior to initiating treatment with olaparib. The Committee noted that it would be ideal for jurisdictions to have BRCA-mutation reflex testing at the time of diagnosis to manage both the patient population and the budget impact of a reimbursement recommendation.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

In 2017, an estimated 2,800 new cases of ovarian cancer were diagnosed in Canada, with 1,800 deaths directly attributable to the disease. Serous epithelial ovarian cancer is the most commonly encountered histology in advanced ovarian cancers, and 25% to 30% of patients with ovarian cancer have either a pathogenic germline (inherited) or somatic (limited to the tumour) mutation in BRCA1 or BRCA2 irrespective of family history. Due to delayed presentation and diagnosis, almost 70% of women with ovarian cancer are diagnosed in the later stage of disease (stages III or IV), and these women have particularly poor outcomes. Standard treatment for ovarian, fallopian tube, or primary peritoneal cancer — hereinafter referred to collectively as ovarian cancer — involves cytoreductive surgery and platinum-based systemic therapy. After first-line chemotherapy with or without surgery, patients are followed up with monitoring. Despite best efforts, more than 80% of patients with stage III and IV ovarian cancer, and almost all of those who have suboptimal debulking or no debulking, relapse with incurable cancer. No major practice changing developments and no significant improvement in survival had been observed in this setting over the past few decades. Therefore, there is an unmet need for a new, effective therapeutic option in ovarian cancer, particularly to extend remission.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated the results of one randomized controlled trial, SOLO-1, that compared olaparib maintenance with placebo. pERC noted that bevacizumab maintenance may also be used for the intended patient population, however based on the Clinical Guidance Panel (CGP) report and registered clinicians' submissions, it is infrequently prescribed in Canada. Therefore, pERC considered placebo to be a reasonable comparator in this setting. The SOLO-1 trial reported a statistically significant improvement in PFS, the primary outcome of the trial, in favour of olaparib compared with placebo. All exploratory subgroup analyses demonstrated a statistically and clinically significant benefit in favour of olaparib compared with placebo. pERC also discussed the lack of mature OS data available at the interim analysis from the SOLO-1 trial. In the absence of mature OS data, pERC discussed the clinical meaningfulness of PFS in relapsed ovarian cancer given the symptomatic nature of ovarian cancer. Given the magnitude of the PFS benefit observed in SOLO-1 the Committee concluded that PFS was statistically significant and clinically meaningful in this setting. Upon reconsideration of the Initial Recommendation, pERC considered feedback from the sponsor providing references that support the surrogacy of PFS for OS in ovarian cancer. pERC further noted input from the CGP that indicated that although the references provided supported surrogacy, it was in the context of having no maintenance treatment. pERC, therefore, agreed that additional evidence would be required to determine the surrogacy of PFS and OS in patients who are treated in the maintenance setting. In response to feedback from registered clinicians on newly available evidence supporting the use of combination olaparib and bevacizumab, pERC noted that the current submission only supports the use of olaparib monotherapy. Any new evidence supporting combination treatment is out of the scope of this review and would need to be submitted for a full CADTH review. pERC discussed the available patient-reported outcomes data from the SOLO-1 trial. Although the trial outcome index (TOI) scores demonstrated statistically significant improvements from baseline scores between treatment groups, the difference did not reach clinical significance. pERC agreed that based on the available QoL measure, olaparib did not have a detrimental impact on patients' QoL compared with placebo. pERC also agreed that in a setting where patients are in complete or stable response to first-line treatment, the ability to administer a maintenance treatment that does not impact QoL is important. pERC deliberated on the toxicity profile of olaparib and noted that there were more serious adverse events (SAEs), grade 3 or higher adverse events (AEs), and withdrawals due to AEs with olaparib compared with placebo. In particular, severe anemia and pneumonitis occurred more often in the olaparib group than the placebo group. Acute myeloid leukemia also developed in three patients on olaparib and none in the placebo group. Overall, pERC agreed that the toxicity profile of olaparib is manageable. pERC therefore concluded that there is a net clinical benefit of olaparib compared with placebo, based on the clinically meaningful results in PFS, no observed detriment in QoL, and a manageable toxicity profile. In

making this conclusion, the Committee acknowledged the unavailability and uncertainty of evidence of olaparib demonstrating a confirmed improvement in OS.

pERC deliberated input from one patient advocacy group (Ovarian Cancer Canada) regarding ovarian cancer and noted that patients value having a treatment that prolongs survival, reduces recurrence, improves QoL, and reduces visits to cancer centres. Respondents indicated that their lives were profoundly affected by ovarian cancer. The following key areas of concern were identified as being negatively affected: work life, sexual relationships, physical activity, level of well-being, relationships with family and friends, and sleep pattern. Although respondents continued to experience fear and anxiety with recurrence, the majority of respondents reported that treatments were able to manage the ovarian cancer. Although most patients were referred for genetic testing by a physician, six patients were recommended for genetic testing of the BRCA mutation by family members or sought out testing individually, with three of these individuals paying for the test out of pocket. Based on this, Ovarian Cancer Canada suggested that there may be more people who can benefit from olaparib than are being identified currently. Patients with experience with olaparib reported that olaparib prolonged survival, lengthened time to recurrence, reduced visits to cancer centres, decreased tumour size, and improved QoL. Based on the evidence in the SOLO-1 trial and input from patients, pERC agreed that olaparib aligns with patient values as it delays disease progression, has no detriment to QoL, and has manageable toxicities. pERC further acknowledged need and availability for both germline and somatic testing for the BRCA mutation across jurisdictions.

pERC deliberated the cost-effectiveness of olaparib compared with routine surveillance. pERC noted the significant uncertainty in the incremental cost-effectiveness ratio (ICER) due to the uncertainty in the clinical effectiveness of olaparib compared with routine surveillance, due to limitations in the available clinical data. pERC noted that the SOLO-1 trial did not report mature OS results, which resulted in 99% of the quality-adjusted life-year (QALY) gains being derived through extrapolation in the economic model. pERC further noted concerns expressed by the EGP regarding the sponsor's approach in deriving OS for patients on routine surveillance (concern that the OS data might be confounded by the nearly 40% of patients on routine surveillance who crossed over to receive a PARP inhibitor upon disease progression). The EGP further noted that the hazard for death appears different between the olaparib and routine surveillance groups as the survival curves cross in the trial (proportional hazard assumption might be violated). The EGP thus agreed that it is inappropriate to derive OS for routine surveillance by applying a treatment effect of routine surveillance to the OS olaparib curve. The EGP assessed the impact of this OS assumption by conducting several exploratory analyses, all of which showed that the ICER is highly sensitive to this parameter. Other drivers of the model included time horizon, utilities, and use of the full trial data for modelling PFS and OS. pERC agreed that the EGP's pessimistic analysis (by reducing the time horizon to the trial period) is an unlikely scenario as the treatment effect of olaparib is unlikely to drop off at the end of the trial period. Based on the uncertainty in the long-term survival benefit and the large impact OS has on the ICER, pERC agreed that it could not draw a conclusion on the cost-effectiveness of olaparib. pERC further agreed that until more robust evidence is available to determine the long-term impact of olaparib on patients' survival, a price reduction is required to manage the uncertainty in the cost-effectiveness.

Upon reconsideration of the Initial Recommendation pERC considered feedback from stakeholders regarding the long-term OS benefit predicted in the submitted and EGP's best estimates. pERC re-iterated that a pessimistic scenario where the time horizon is truncated to the trial period (4.17 years) is not representative of the clinical course of this disease and did not inform pERC's decision on cost-effectiveness. pERC further re-iterated that the Committee's inability to draw a conclusion on cost-effectiveness was driven by limitations in the submitted model which did not allow the EGP to fully explore all the uncertainty in the long-term OS. While the EGP conducted a number of analyses to explore uncertainty in the OS benefit, methodological uncertainties associated with the true long-term OS benefit of olaparib was not explored through alternative modelling strategies (e.g., statistical approaches to adjust for treatment switching and the use of non-proportional hazard models to predict long-term OS data). Overall, given that the majority of benefit informing the model is being derived through extrapolation, pERC reiterated its concern that the ICUR presented in the submitted and EGP's best-case reanalysis is likely underestimated.

pERC discussed the feasibility of implementing a reimbursement recommendation for olaparib in patients with newly diagnosed, advanced, BRCA-mutated (germline or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy. pERC noted that the budget impact analysis was sensitive to the market

share of olaparib, the extent to which the use of olaparib in the front-line setting would replace use of second-line olaparib or bevacizumab, the inclusion of drug wastage, and the inclusion of mark-up and dispensing fees. The budget impact increased with the greater market share of olaparib and when drug wastage, mark-up and dispensing fees, and the cost of BRCA testing were considered.

pERC addressed a number of implementation questions from PAG as outlined in the Appendix.

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 the pCODR clinical and economic review panels
- input from one patient advocacy group (Ovarian Cancer Canada)
- input from registered clinicians
- input from PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group (Ovarian Cancer Canada)
- one clinician group (Cancer Care Ontario Gynecology DAC)
- PAG
- the submitter (AstraZeneca Canada).

The pERC Initial Recommendation was to recommend the reimbursement of olaparib (Lynparza). Feedback on the pERC Initial Recommendation indicated that the manufacturer, patient advocacy group, and registered clinician group agreed in part while PAG agreed fully with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of olaparib (Lynparza) as a maintenance treatment for adult patients with platinum-sensitive (complete or partial response to first-line platinum-based chemotherapy) advanced-stage ovarian, primary peritoneal, and/or fallopian tube cancer with somatic or germline BRCA mutations that were deleterious or suspected to be deleterious.

Studies included: One randomized controlled trial

The pCODR systematic review included one double-blinded, placebo-controlled, phase III, superiority randomized controlled trial, the SOLO1 trial (N=391), which compared olaparib with placebo in the maintenance setting of platinum-sensitive (complete or partial response to first-line platinum-based chemotherapy), advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III and IV) stage ovarian, primary peritoneal, and/or fallopian tube cancer patients with somatic or germline BRCA mutations that were deleterious or suspected to be deleterious. Randomization was in a 2:1 ratio with 260 patients in the olaparib group and 131 patients (and 130 treated) in the placebo group. pERC noted that bevacizumab maintenance may also be used in patients; however according to input from the CGP and registered clinicians, it is infrequently prescribed in Canada. Therefore, pERC considered placebo to be a reasonable comparator in this setting.

Patients continued treatment until investigator-assessed progressive disease (PD) as per Response Evaluation Criteria in Solid Tumors version 1.1 (unless in the investigator's opinion there was clinical benefit to continue treatment), patient decision, unacceptable toxicity due to AEs, bone marrow findings consistent with myelodysplastic syndrome or acute myeloid leukemia (AML), or if at completion of two years of treatment there was no evidence of disease.

Patient populations: Reflective of clinical population

Key eligibility criteria required that patients have BRCA1 or BRCA2 mutation predicted or known to be deleterious, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1, and last dose of chemotherapy was 8 weeks or less prior to randomization with completion of a minimum of six cycles and a maximum of nine cycles of first-line platinum chemotherapy (unless discontinued due to toxicity, then four cycles minimum).

Patient disease characteristics were generally well balanced with respect to ECOG PS, primary tumour location, cancer antigen 125 (CA 125) level, and histologic type. The median age of patients enrolled on the trial was 53.0 years of age in both treatment groups and most patients were white (81.8%). In both

treatment groups, 82% of patients experienced a complete response following first-line platinum therapy and 18% experienced a partial response. Overall, the majority of patients had an ECOG PS of 0 (78%); a primary tumour location in the ovary (85%); a CA 125 level of less than or equal to the upper limit of normal (94.6%); fewer patients in the olaparib treatment group reported six cycles of treatment (76%) compared to the placebo (81%). More patients in the olaparib group had FIGO stage III (85%) compared to the placebo (80%), with FIGO stage IIIC being the most common in both treatment groups (68.5% and 69.5% in the olaparib and placebo groups, respectively), and more patients in the olaparib group with FIGO stage IIIB compared to the placebo (10.4% compared to 5.3%, respectively). Fewer patients in the olaparib group compared with the placebo group had stage IV disease (15.4% and 19.8%, respectively). Approximately, 25.4% of patients in the olaparib group had a BRCA2 mutation, which was approximately 5% less patients compared to the placebo group (30.5%). There were more patients in the olaparib group with a BRCA1 mutation (73.5%) compared with the placebo group (69.5%).

Key efficacy results: Statistically significant and clinically meaningful progression-free survival improvement, immature overall survival

The key efficacy outcome deliberated by pERC included PFS, the primary end point of the SOLO-1 trial. After a median follow-up of 40.7 months, there was a 70% reduction in the risk of PD or death in the olaparib group compared with the placebo (hazard ratio, 0.30; 95% confidence interval [CI], 0.23 to 0.41; $P < 0.001$). The median PFS in the olaparib group was not reached and was 13.8 months in the placebo group. All exploratory subgroup analyses demonstrated a statistically and clinically significant benefit in favour of olaparib compared with placebo. Sensitivity analyses evaluating potential biases and using centrally confirmed germline and somatic BRCA-mutated subsets of the study population were consistent with the primary analysis of PFS. Key secondary end points deliberated by pERC included OS. At the time of the analysis, the interim OS data were immature (approximately 21% maturity). There was no difference in the risk of death between the olaparib and placebo group (hazard ratio, 0.95; 95% CI, 0.60 to 1.53) with a total of 82 deaths having occurred (21.2% and 20.6% in the olaparib and placebo groups, respectively).

pERC noted the lack of mature OS data available at this time from the SOLO-1 trial. In the absence of mature OS data, pERC discussed the clinical meaningfulness of PFS in relapsed ovarian cancer. Given the magnitude of the PFS benefit observed in SOLO-1, the Committee concluded that PFS was statistically significant and clinically meaningful.

Patient-reported outcomes: No detriment in quality of life

Health-related QoL was assessed using the TOI score from the Functional Assessment of Cancer Therapy-Ovarian Cancer questionnaire. A difference of 10 points is considered clinically relevant (i.e., minimally important difference). QoL measured through the EuroQoL 5-Dimensions 5-Levels was an exploratory end point in the trial.

Study compliance was high (more than 80%) from baseline to week 97. Mean baseline TOI scores were similar between treatment groups. The adjusted mean change from baseline to 24 months was 0.3 (95% CI, -0.72 to 1.32) in the olaparib group and 3.3 (95% CI, 1.84 to 4.76) in the placebo group. The estimated difference between the treatment groups in mean change from baseline to 24 months was -3.00 (95% CI, -4.78 to -1.22), which was statistically, but not be clinically, significant. There was no worsening or deterioration of patients in the olaparib group relative to patients in the placebo group as measured by the weighted health index score or by the Visual Analogue Scale to week 97.

pERC discussed the available patient-reported outcomes and noted that although the TOI scores showed significant improvement in change from baseline scores between treatment groups, the difference did not reach clinical significance. pERC therefore agreed that based on the available QoL measure, olaparib did not have a detrimental impact on patients' QoL. pERC agreed that in a setting where patients are in complete or partial response to first-line treatment, the ability to administer a maintenance treatment that does not impact QoL is important.

Safety: Manageable toxicity profile

pERC deliberated the safety data of the SOLO-1 trial and agreed that the toxicity profile of olaparib is manageable. More grade 3 or higher AEs (39.2% and 18.5%) occurred in the olaparib group than the placebo group. Anemia and neutropenia were the most common grade 3 or 4 AEs in the olaparib group, which occurred in 22% and 9% of patients, respectively. In the placebo group, neutropenia was the most

common grade 3 or 4 AE, which occurred in 5% of patients. The frequency of any grade of AEs was similar in the two treatment groups (98.5% and 92.3% in the olaparib and placebo groups, respectively).

More SAEs (20.8% and 12.3%) also occurred in the olaparib group compared with the placebo group. Anemia was the most common SAE in the olaparib group, which occurred in 6.5% of patients, compared with no patients in the placebo group. Breast cancer was the most common SAE in the placebo group and occurred in 2.3% of patients compared with 0.4% (n = 1) of patients in the olaparib group. AML occurred in 1% patients in the olaparib group and no AML occurred in the placebo group.

There were no AEs with an outcome of death on study treatment during the 30-day follow-up period. Two patients in the olaparib group had developed AML and deaths occurred after the 30-day follow-up period. Both were considered to be related to olaparib treatment. The proportion of patients with dose interruptions (61.2% versus 30.8%) and at least one dose reduction (36.2% versus 8.5%) was higher in the olaparib group compared with the placebo group, respectively. Withdrawals from treatment were also more common in the study arm as compared to the control arm (11.5% versus 2.3%).

Need and burden of illness: Unmet need for a new therapeutic option in ovarian cancer
Despite best efforts, more than 80% of patients with stage III or IV ovarian cancer, and almost everyone who has suboptimal debulking or no debulking, relapse, or progress with incurable cancer. Since the addition of paclitaxel to standard therapy in the early 1990s and use of bevacizumab in a selected group of high-risk patients in the 2000s, there have been no major practice changing developments in ovarian cancer therapeutics and no significant improvement in survival had been observed over the past few decades. Therefore, there is an unmet need for a new therapeutic option in ovarian cancer, particularly to prevent relapse and death.

Registered clinician input: Preferred maintenance treatment after first-line treatment
pERC considered input provided from five registered individual clinicians or groups. Clinicians highlighted the unmet need for treatment in this setting, as women with ovarian cancer who complete initial treatment do not have other treatment options available to them. Clinician input stated that oncologists do an excellent job at reducing disease burden during the initial treatment phase; however, more than 80% of patients' cancer will recur. All clinicians agreed that the patient population in the reimbursement request and the inclusion and exclusion criteria of the trial, were applicable to clinical practice.

Generally, registered clinicians agreed that observation is the standard of care for patients after first-line platinum chemotherapy. Clinicians stated that bevacizumab is either not readily used in jurisdictions or has conflicting efficacy and a dissatisfying tolerability profile. One clinician described the results of the SOLO-1 trial as being the most significant finding in the management of ovarian cancer since the discovery of platinum-based treatments and that it is practice changing. Regarding the safety profile of olaparib, registered clinicians noted that it is consistent with that seen in patients with relapsed disease. Other benefits of olaparib among high-risk patients were stated to be the ease of use, the superior safety profile, and tolerability compared with bevacizumab. All clinicians agreed that olaparib would be used upon completion of first-line therapy in patients with a clinical response. All clinicians also identified that patients will need to be tested for BRCA status, and germline and/or somatic BRCA testing was available at their centres.

A number of implementation questions were addressed by registered clinicians, most of which were in alignment with conclusions made by the CGP. Regarding the sequencing of available agents, clinicians from multiple inputs, suggested the use of chemotherapy, and, in some cases, surgery depending on the nature and location of the tumours. Patients may be candidates for platinum-based regimens, paclitaxel alone, or other therapy if toxicity is a concern. Patients may also be eligible for clinical trials. Although patients may be treated with olaparib in the second-line setting (if olaparib naive), clinicians acknowledged that olaparib is much more effective if given in the first-line setting.

PATIENT-BASED VALUES

Values of patients with ovarian cancer: Improve quality of life and reduced recurrence
pERC deliberated input from Ovarian Cancer Canada. Respondents indicated that their lives were profoundly affected by ovarian cancer. Key areas that were negatively affected were work life, sexual

relationship, physical activity, level of well-being, relationships with family and friends, and sleep patterns. There were also comments about high levels of anxiety about the fear of recurrence and death.

All patients and caregivers reported that the current treatments included chemotherapy and surgery. Although respondents continued to experience fear and anxiety, the majority reported that treatments were able to manage the ovarian cancer. On a scale 1 (no effect) to 5 (extremely negative effect), respondents noted that very negative or extremely negative side effects of current treatments included fatigue, hair loss, neuropathy, ascites, and blood problems. Side effects rated as minimal or no effect included loss of fertility, skin irritation, nausea and vomiting, ascites, and bowel problems. The most significant barriers to treatment were travel issues, financial issues, and that treatment was not available. Caregivers noted that their family relationships and ability to care for their family was most negatively impacted by ovarian cancer.

Of the 28 respondents (25 patients and three caregivers), most were recommended for genetic testing by a physician while six were recommended by family members or sought out testing individually, with three of these individuals paying for the test out of pocket. Based on this input on the availability of testing, Ovarian Cancer Canada suggested that there may be more people who can benefit from olaparib than are being identified currently. Respondents described the importance of genetic testing for their own benefit and also to explain some family history and to inform other family members who could then take protective measures for their own health.

Patient values on treatment: Prolong survival, delay recurrence, improve quality of life, and reduce cancer centre visits

Patients expectations for new treatments included prolonged survival, lengthened time until recurrence, improved QoL, and reduced visits to cancer centres. When asked specifically about how much improvement patients would expect with olaparib, more than half of the sixteen respondents indicated that they would be willing to take olaparib if there was no improvement, or mild or moderate improvement (score of 1 to 3 out of 5) in their ovarian cancer. Many of these patients would also be willing to tolerate many side effects if olaparib were to improve their overall daily functioning or prognosis. Patients were most willing to tolerate tiredness, taste changes, nausea, bruising and bleeding easily, and headaches. Blood disorders or blood cancer and inflammation of lungs were those side effects least willing to be tolerated. Some patients also indicated a willingness to tolerate side effects for prolonged survival.

Among the seven patients and three caregivers with direct experience using olaparib, prolonged survival and lengthened time to recurrence were the top two patient concerns managed by treatment. This was followed closely by reduced visits to cancer centres, shrinking tumour size, and improved QoL. Nine respondents agreed or strongly agreed that olaparib improved their QoL compared with previous treatments used. Nine respondents reported side effects from olaparib, which included tiredness and weakness, blood problems, and dry mouth. Three respondents reported they had no side effects. Two respondents listed blood problems as an unacceptable side effect. Almost all respondents believed olaparib should be available as a treatment option after first-line chemotherapy for women with BRCA mutation and ovarian cancer.

ECONOMIC EVALUATION

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

The EGP assessed cost-effectiveness and cost-utility analyses comparing olaparib with routine surveillance for patients with advanced BRCA-mutated ovarian cancer in complete or partial response to platinum-based chemotherapy.

Basis of the economic model: SOLO-1 trial data and long-term extrapolation of overall survival

Key cost inputs included drug acquisition costs, costs associated with health care use, AEs costs, end-of-life care costs, and BRCA testing costs. Key clinical effects considered in the analysis including OS, PFS, and utilities that were obtained from the SOLO-1 trial. pERC noted that the majority of resulting life-year or QALY gains derived from the model were from the post-trial extrapolated period. Given that the OS

data are not mature, pERC agreed that the long-term clinical effect estimates with olaparib are very uncertain.

Drug costs: No cost for routine surveillance

Olaparib costs $65.89 per 150 mg or 100 mg tablet. At the recommended dose of 600 mg daily, olaparib costs $263.57 per day (two 150 mg tablets, taken twice daily) and $7,188.08 per month (based on 30.44 days, assuming a relative dose intensity of 89.6%). There was no cost assumed for routine surveillance.

Cost-effectiveness estimates: Considerable uncertainty in long-term benefit

pERC deliberated on the cost-effectiveness of olaparib compared with routine surveillance for patients with advanced BRCA-mutated ovarian cancer in complete or partial response to platinum-based chemotherapy. The sponsor's best estimate of the ICER was $21,517 per QALY. Upon reconsideration of the Initial Recommendation, pERC noted feedback from PAG and the sponsor requesting clarity on the EGP's reanalysis estimate. pERC acknowledged clarification from the EGP indicating that the best estimate was $57,784 per QALY, with sensitivity analyses ranging from $15,721 to $648,080 per QALY. The EGP further clarified that the pessimistic scenario where the time horizon is truncated to 4.17 years ($648,080 per QALY) was not part of the EGP's best estimate.

pERC noted the significant uncertainty in the ICER due to the uncertainty in the clinical effectiveness of olaparib compared with routine surveillance, given the limitations in the available clinical data. pERC noted that the SOLO-1 trial did not report mature OS results, which resulted in 99% of the QALY gains in the economic model being derived through extrapolation. pERC further noted concerns expressed by the EGP regarding the sponsor's approach in deriving OS for patients on routine surveillance (as there was concern the OS data might be confounded by the nearly 40% of patients on routine surveillance who crossed over to receive a PARP inhibitor upon disease progression). The EGP noted that the hazard for death appears different between the olaparib and routine surveillance survival groups as the survival curves cross in the trial (proportional hazard assumption violated). Based on this, the EGP agreed that it is inappropriate to derive OS for routine surveillance by applying a treatment effect of routine surveillance to the OS olaparib curve. In addition, the derived OS curve for routine surveillance did not have face validity as it did not reflect the data in the trial and the EGP was unable to apply any statistical approaches to adjust for crossover. The EGP assessed the impact of these OS assumptions by conducting several exploratory analyses, all of which showed that the ICER is highly sensitive to the estimate of OS. Other drivers of the model included time horizon, utilities, and use of the full trial data for modelling PFS and OS. The EGP explored reducing the time horizon to the trial period as a pessimistic and unrealistic analysis resulting in the higher range of its reanalysis estimate. pERC agreed that it is unlikely the treatment effect will drop off at the end of the trial period; however, the Committee agreed that there is considerable uncertainty in the long-term benefit to be derived from the use of olaparib as maintenance therapy.

Overall, pERC discussed these factors and agreed that the uncertainty in the long-term OS and PFS benefit and the large impact OS has on the ICER made it difficult to draw a conclusion on the cost-effectiveness of olaparib, at the submitted price, compared with routine surveillance. pERC further agreed that until more robust evidence is available to determine the long-term incremental effect of olaparib on patients' OS, a price reduction is required to manage the uncertainty in the cost-effectiveness.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from stakeholders regarding the long-term OS benefit predicted in the submitted and EGP's best estimates. pERC reiterated that a pessimistic scenario where the time horizon is truncated to the trial period (4.17 years) is not representative of the clinical course of this disease and did not inform pERC's decision on cost-effectiveness. pERC further reiterated that the Committee's inability to draw a conclusion on cost-effectiveness was driven by the limitations in the submitted model to allow the EGP to fully explore all of the uncertainty in the long-term OS. Overall, given that the majority of benefit of olaparib in the model is being derived through extrapolation, pERC reiterated its concern that the ICUR presented in the EGP's reanalysis is likely underestimated. pERC also noted feedback from the sponsor speaking to the surrogacy of PFS for OS in ovarian cancer and accepted statements from the CGP indicating that surrogacy of PFS for OS has not been validated in a setting where maintenance treatment is introduced.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Eligibility for treatment to mostly follow SOLO-1 trial

pERC discussed the feasibility of implementing a reimbursement recommendation for olaparib in patients with newly diagnosed, advanced, BRCA-mutated (germline or somatic), high-grade, epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy. pERC noted that the budget impact analysis was sensitive to the market share of olaparib, the extent to which use of olaparib in the front-line setting would replace second-line olaparib or bevacizumab, the inclusion of drug wastage, and the inclusion of mark-up and dispensing fees. The budget impact increased with the greater market share of olaparib and when drug wastage, mark-up and dispensing fees, and the cost of BRCA testing were considered. However, the budget impact decreased if the use of olaparib in the front-line setting displaced the use of bevacizumab in the front-line setting or olaparib in the platinum-sensitive relapse setting.

pERC addressed a number of implementation questions from PAG as outlined in the Appendix.

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:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)	Dr. Leela John, Pharmacist
Dr. Catherine Moltzan, Oncologist (Vice-Chair)	Dr. Anil Abraham Joy, Oncologist
Daryl Bell, Patient Member Alternate	Dr. Christine Kennedy, Family Physician
Dr. Kelvin Chan, Oncologist	Dr. Christian Kollmannsberger, Oncologist
Lauren Flay Charbonneau, Pharmacist	Dr. Christopher Longo, Health Economist
Dr. Matthew Cheung, Oncologist	Cameron Lane, Patient Member
Dr. Winson Cheung, Oncologist	Valerie McDonald, Patient Member
Dr. Henry Conter, Oncologist	Dr. Marianne Taylor, Oncologist
Dr. Avram Denburg, Pediatric Oncologist	Dr. W. Dominika Wranik, Health Economist

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

- Dr. Matthew Cheung, who was absent from the meeting
- Dr. Anil Abraham Joy who was excluded from voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)	Dr. Leela John, Pharmacist
Dr. Catherine Moltzan, Oncologist (Vice-Chair)	Dr. Anil Abraham Joy, Oncologist
Daryl Bell, Patient Member Alternate	Dr. Christine Kennedy, Family Physician
Dr. Kelvin Chan, Oncologist	Dr. Christian Kollmannsberger, Oncologist
Lauren Flay Charbonneau, Pharmacist	Dr. Christopher Longo, Health Economist
Dr. Michael Crump, Oncologist	Cameron Lane, Patient Member
Dr. Winson Cheung, Oncologist	Valerie McDonald, Patient Member
Dr. Henry Conter, Oncologist	Dr. Marianne Taylor, Oncologist
Dr. Avram Denburg, Pediatric Oncologist	Dr. W. Dominika Wranik, Health Economist

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

- Dr. Anil Abraham Joy, who was excluded from voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee 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 ovarian cancer, through their declarations, four members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, one member was 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 the pCODR Expert Review Committee 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.

Disclaimer

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking comparative data on olaparib compared with bevacizumab for patients who received bevacizumab during their first-line course of treatment, either in combination (with paclitaxel) or as maintenance therapy following combination therapy.	• pERC agreed with the CGP that in patients who have previously been treated with bevacizumab as combination therapy, it would be reasonable to offer patients who have confirmed BRCA germline or somatic mutation olaparib as maintenance therapy. • pERC also agreed jurisdictions may consider addressing the short-term, time-limited need to offer to switch to olaparib for patients currently being monitored or who are on maintenance bevacizumab after first-line platinum-based chemotherapy for those who have confirmed BRCA germline or somatic mutation and no evidence of disease progression. • pERC further agreed that eligibility should be aligned to the SOLO-1 trial, who were mainly pERC further noted that there was no comparative evidence between olaparib and bevacizumab maintenance treatments. pERC, however, acknowledged that bevacizumab is used infrequently as maintenance after first-line treatment in the Canadian setting, that the availability of bevacizumab is variable across jurisdictions, and that the CGP and registered clinicians acknowledged that if both options were available, the preferred option would be olaparib. pERC therefore agreed that the absence of a comparison with bevacizumab should not create an implementation barrier.
Eligibility for treatment with olaparib in the following subgroups: • patients with early stage disease (FIGO stage I, IIA, IIB, or IIC) • patients who have previously received chemotherapy (i.e., adjuvant) for prior diagnosis at an earlier stage for their ovarian, fallopian tube, or primary peritoneal cancer • patients who are not surgical candidates (in the trial patients with stage III disease must have had one attempt at optimal debulking surgery (upfront or interval debulking) and stage IV patients must have had either a biopsy and/or upfront or interval debulking surgery).	• pERC agreed that there is no evidence provided through the SOLO-1 trial to determine the efficacy of olaparib in early stage disease (FIGO stage I, IIA, IIB, or IIC) nor for patients who may have received chemotherapy at an earlier stage of disease (i.e., adjuvant setting). Upon reconsideration of the Initial Recommendation, pERC noted feedback from registered clinicians regarding the eligibility of patients with stage II disease for treatment with olaparib. pERC however agreed with the CGP that there is currently no evidence to extend the results of the SOLO-1 trial to patients with stage II disease. • pERC further agreed that eligibility should be aligned to the SOLO-1 trial, mainly patients with stage III who had an attempt at debulking surgery as well as patients at stage IV with or without surgery. Upon reconsideration of the Initial Recommendation, pERC noted feedback from registered clinicians regarding the eligibility of patients with stage III disease who hadn't undergone attempted debulking surgery. pERC also considered comments from the CGP that noted that the clinical course of patients with and without an attempt at debulking surgery is the same and that there is no clinical rationale to treat these two patient groups differently. pERC, therefore, agreed that it would be reasonable to make olaparib treatment available to patients with stage III disease, regardless of an attempt at debulking surgery.
• PAG is seeking guidance on whether olaparib following first-line non-platinum-based chemotherapy is appropriate in patients who	• pERC agreed that patients with BRCA-positive disease who received platinum therapy but then received non-platinum-based chemotherapy (due to intolerance or

are allergic to or unable to tolerate platinum chemotherapy.	drug infusion reaction) and had a response (and otherwise met the criteria for maintenance olaparib) should be candidates for olaparib. Given the difference in the mechanism of action of olaparib and both types of chemotherapy agents, a difference in response is not anticipated.
• PAG is seeking guidance on whether olaparib could be considered for patients who have completed platinum-based chemotherapy more than eight weeks ago and what maximum time between completion of chemotherapy and commencement of olaparib would be.	• pERC noted the CGP's consensus stating that olaparib should be offered to all patients eligible for first-line maintenance olaparib as long as the treatment can be started within 12 weeks of the last chemotherapy treatment, as multiple factors such as chemotherapy side effects and treatment logistics can prevent some eligible patients from starting olaparib within eight weeks as mandated in SOLO-1. If more than eight weeks had elapsed from last chemotherapy treatment, patients should be re-staged and those with disease progression should not be treated with olaparib.
Treatment duration and stopping rules: • PAG is seeking clarity on treatment duration (i.e., two year maximum, if not the criteria to determine if treatment should go beyond) and monitoring of disease. • PAG is seeking clarity on how frequently disease should be assessed on olaparib and what the stopping rules are for olaparib (e.g., rising CA 125 levels or a combination of rising CA 125 levels and radiological progression). • PAG is seeking guidance on re-treatment with olaparib following periods of planned treatment interruption due to patient preference during maintenance treatment.	• pERC agreed that olaparib be administered in the same fashion that was mandated in the SOLO-1 trial. Patients who had no evidence of disease at two years stopped receiving olaparib, but patients who had at least a partial response or stable disease at two years were permitted to continue receiving olaparib at the discretion of the treating oncologist. • pERC cited discussion from the CGP noting that treatment is usually not stopped until CA-125 progression is confirmed by radiographical disease progression. Based on this, the CGP agreed that the trial is consistent with clinical practice. Additionally, scans were conducted more frequently on the trial than in clinical practice. Although it may vary by centre, in clinical practice, regular CA-125 and/or CT scans are recommended to monitor ongoing disease response and stability. CT scans may be typically conducted every three months for the first two years, every four months for the third year, and every six months for the fourth and fifth year, as clinically indicated. • pERC noted that planned periods of dose interruptions due to patient preference should be allowed at the treating physician's discretion, not to exceed one month. A lack of cancer progression should be confirmed prior to restarting olaparib as maintenance therapy if the interruption is greater than 14 days.
Sequencing of agents: • PAG is seeking guidance on the sequencing of subsequent agents after olaparib maintenance treatment and development of metastatic disease (e.g., use of platinum-based chemotherapy)? • For patients who complete two years of olaparib monotherapy maintenance and then progress, would patients be treated with olaparib followed by second-line platinum-based chemotherapy (e.g., as second-line treatment for platinum-sensitive disease, as per the previous pERC recommendation for olaparib as monotherapy maintenance treatment of adult patients with platinum-	• pERC agreed with CGP and clinicians that for patients who progress on olaparib, subsequent treatment will be based on time from last chemotherapy, toxicity to prior therapies, and patient preference (as per usual practice). • pERC noted the registered clinician input that suggested the use of chemotherapy, and, in some cases, surgery depending on the nature and location of the tumours in patients who progress on olaparib. Patients may be candidates for platinum-based regimens, paclitaxel alone, or other therapy if toxicity is a concern. Patients may also be eligible for clinical trials. Upon reconsideration of the Initial Recommendation, pERC noted feedback from PAG related to the sequencing of therapies following progression on olaparib. pERC

sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy)?	acknowledged the lack of clarity on sequencing in this setting, and supported guidance provided by the CGP that outlined that sequencing will likely follow usual treatment practice and be based on platinum sensitivity of the disease.
• PAG is seeking guidance on the definitions of deleterious BRCA mutations as well as whether BRCA testing can be somatic or germline. In the SOLO-1 trial, eligible patients had a deleterious or suspected deleterious germline or somatic BRCA 1/2 mutation.	• pERC noted consensus from the CGP that regardless of germline or somatic mutation, patients with a BRCA-mutation should be eligible for olaparib maintenance therapy. Upon reconsideration of the Initial Recommendation, pERC agreed with the CGP that it is reasonable to adopt the definition of deleterious BRCA mutation used in the American College of Medical Genetics (ACMG) guidelines.

BRCA = breast cancer gene; CA 125 = cancer antigen 125; CGP = Clinical Guidance Panel; CT = computed tomography; FIGO = International Federation of Gynecology and Obstetrics; PAG = Provincial Advisory Group; PD = progressive disease; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.