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: Niraparib (Zejula)

Submitted Reimbursement Request: As maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Submitted By: GlaxoSmithKline Inc.	**Manufactured By:** GlaxoSmithKline Inc.
NOC Date: October 2, 2020	**Submission Date:** September 21, 2020
Initial Recommendation: March 4, 2021	**Final Recommendation:** April 29, 2021

Approximate per Patient Drug Costs, per Month (28 Days)	Niraparib costs $131.79 per 100 mg capsule. At the recommended dose of 200 mg (two 100 mg capsules), or 300 mg (three 100-mg capsules; for patients who weigh greater than or equal to 77 kg and have baseline platelet count greater than or equal to 150,000/µL) taken orally once daily, niraparib costs $7,380 to $11,070 per 28-day course.

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 conditionally recommends the reimbursement of niraparib as maintenance treatment of adult patients with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy if the following condition is met:

- cost-effectiveness improved to an acceptable level.

Eligible patients should have high-grade serous or endometrioid tumours classified as stage III or IV according to the International Federation of Gynecology and Obstetrics (FIGO) criteria. Patients should have completed between 6 and 9 cycles of first-line platinum-based chemotherapy and be in complete or partial response. Maintenance therapy with niraparib should start within 12 weeks of the last dose of platinum-based chemotherapy and continue until unacceptable toxicity, disease progression, or completion of 3 years of therapy, whichever occurs first. Reimbursement should be for patients who have good performance status.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of niraparib maintenance treatment compared with placebo (i.e., active surveillance) based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS), which was observed regardless of breast cancer susceptibility gene (BRCA) mutation status, a manageable but not insignificant toxicity profile, and no apparent detriment in quality of life (QoL).

	pERC also concluded that niraparib aligns with the following patient values: delays disease recurrence, maintains QoL, delays future chemotherapy, offers convenient oral administration, and fulfills an unmet need for a treatment option in patients who are BRCA-wild type (BRCA-wt). pERC concluded that, based on the sponsor's submitted price, niraparib is unlikely to be cost-effective when compared to active surveillance in the overall trial population (i.e., intent to treat [ITT] population studied in the PRIMA trial). In the BRCA-mutation subgroup where equivalent comparative efficacy was assumed between niraparib and olaparib, niraparib is more costly but equally effective than olaparib and is thus dominated. pERC noted that, given methodological limitations with the sponsor's model which excluded a relevant treatment comparator (i.e., olaparib) in the analysis of the overall trial population, the incremental cost-effectiveness ratio estimates for this population are likely underestimated. pERC was further unable to determine the cost-effectiveness of niraparib in the Health Canada indicated population given the lack of comparative clinical evidence on patients with stage III ovarian cancer with no visible residual disease (NVRD) after surgery.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit with niraparib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of niraparib to an acceptable level given the uncertainty around comparative clinical effectiveness and long-term benefits. The Economic Guidance Panel (EGP) was unable to explore all the uncertainties in the long-term extrapolation of overall survival (OS) given immaturity of the data. pERC agreed that until more robust evidence is available to determine the long-term impact of niraparib on OS, a price reduction is required to manage the uncertainty in the cost-effectiveness of niraparib. **Time-Limited Need for Niraparib in Patients Currently Being Monitored for Disease Progression or on Bevacizumab Treatment** At the time of implementing a reimbursement recommendation for niraparib, jurisdictions may wish to consider addressing the short-term, time-limited need to offer niraparib maintenance 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 Canada. **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

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

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

In 2020, it was estimated that 3,100 women in Canada would develop ovarian cancer, with 1,950 deaths directly attributable to the disease. High-grade serous epithelial ovarian cancer is the most encountered histology, representing 60% of all epithelial ovarian cancers. Unfortunately, because of delayed presentation and diagnosis, almost 70% of patients with ovarian cancer are diagnosed in the later stages of disease. Following a response to first-line platinum-based therapy, the standard of care for most patients with newly diagnosed advanced ovarian cancer is active surveillance where patients are monitored for clinical progression. Advanced ovarian cancer (stage III to stage IV) is associated with a high rate of recurrence and poor outcomes. The median time to recurrence is approximately 18 months, and median OS is typically less than 4 years. Five-year survival rates vary between 45% in stage IIIA disease to less than 20% in stage IV disease. Due to the high rate of recurrence, maintenance strategies have been evaluated to potentially delay or prevent recurrence. Poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors have emerged as an effective therapeutic strategy in ovarian cancer, particularly for those patients with breast cancer susceptibility gene (BRCA) mutations (BRCA-mut). The PARP inhibitor olaparib is approved and reimbursed in almost all Canadian jurisdictions as maintenance treatment after a response to first-line platinum-containing chemotherapy for patients who have a confirmed BRCA-mut. However, since most patients do not have a BRCA-mut, they are ineligible for olaparib maintenance and receive active surveillance after the completion of platinum-based chemotherapy. According to the Clinical Guidance Panel (CGP) and registered clinicians, maintenance treatment with bevacizumab is infrequently used in Canada due to variable access across jurisdictions. Therefore, there remains a significant unmet need for effective treatments that may extend remission in the majority of patients with newly diagnosed advanced ovarian cancer.

pERC deliberated on the results of one double-blind, placebo-controlled, phase III trial (PRIMA), which evaluated the efficacy and safety of niraparib maintenance treatment in adult patients with predominantly high-grade serous advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (henceforth, referred to as ovarian cancer) who were in a complete response or partial response (CR or PR) to first-line platinum-based chemotherapy after completing between 6 and 9 treatment cycles. pERC noted that the eligible patient population in the PRIMA trial included patients who were classified as stage III or IV according to FIGO criteria, which included patients who had either inoperable stage III or IV disease, stage III and IV disease with visible residual disease measuring less than or equal to 2 cm after primary debulking surgery and chemotherapy, or stage III or IV disease treated with neoadjuvant chemotherapy. There were no requirements related to residual disease for patients treated with neoadjuvant chemotherapy after interval debulking surgery. The trial enrolled patients regardless of their BRCA status; therefore, pERC considered placebo an appropriate comparator for the majority of trial patients who were BRCA wild-type (BRCA-wt), but not for patients who were BRCA-mut, for whom the appropriate comparator would be olaparib. pERC noted there was no indirect treatment comparison (ITC) to olaparib submitted by the sponsor. pERC also discussed two notable amendments to the PRIMA trial protocol, the first of which was the removal of the requirement that all enrolled patients be homologous recombination deficient (HRD); and the second, which was the implementation of an individualized dosing scheme based on a patient's weight and/or platelet count. pERC noted that the majority of patients were randomized the before dosing scheme amendment and therefore received the fixed starting dose (i.e., 300 mg); whereas a smaller proportion of trial patients received the individualized starting dose (i.e., 300 mg or 200 mg) based on baseline body weight and platelet count. The trial protocol prespecified that the assessment of efficacy was tested hierarchically in two efficacy populations, first in the HRD-positive patient population and then in the overall patient population.

At the primary efficacy analysis, which was performed after a median follow-up of 13.8 months, the PRIMA trial reported a statistically significant prolongation in PFS (the primary end point of the trial) in favour of niraparib compared with placebo. pERC discussed that a PFS benefit was observed in both primary efficacy populations, with a larger magnitude of benefit observed in the HRD-positive population. pERC also noted the consistency of the PFS benefit in terms of exploratory subgroup analyses performed

in the overall population, which included analyses by best response to chemotherapy (i.e., partial or complete), receipt of neoadjuvant chemotherapy (i.e., yes or no), BRCA status (i.e., mutated or wild type), starting dosing scheme (i.e., fixed or individualized), and homologous recombination status (i.e., HRD-positive and HRD-negative). pERC discussed that at present, HRD testing is not a clinically validated or standardized test and therefore is not routinely performed in Canadian clinical practice. Therefore, the results based on HRD status need to be interpreted with caution; and pERC agreed with the CGP that treatment decisions should not be guided based on the results of HRD testing alone. pERC commented that the median duration follow-up in the trial was short and therefore, although the treatment effect estimates for the secondary efficacy outcomes assessed in the trial numerically favoured niraparib, the data on OS, PFS on next line of therapy (PFS-2) and time-to-first subsequent therapy were immature. pERC discussed that even with additional follow-up, the OS data will be confounded by the use of post-trial treatments given after disease progression and included the use of PARP inhibitors in both treatment groups. In the absence of mature OS data, pERC agreed with the CGP and patients that PFS is a clinically meaningful end point in ovarian cancer given that the goals of maintenance treatment are to delay disease recurrence and the need for further chemotherapy. The committee therefore concluded that the PFS benefit observed in the PRIMA trial represents a clinically meaningful improvement in the setting of newly diagnosed advanced ovarian cancer. The CGP, registered clinicians, and the patient advocacy group providing input for this submission all indicated that reimbursement of niraparib would fulfil an unmet need for a maintenance treatment option in patients who are BRCA-wt.

pERC deliberated on the safety profile of niraparib and noted that the incidence of all categories of adverse events (AEs) was higher in the niraparib group compared to the placebo group. The most common AEs of any grade in patients treated with niraparib were primarily comprised of hematologic toxicity, as well as constipation and fatigue. The most frequent grade 3 or higher AEs included anemia, thrombocytopenia, decrease in platelet count, and neutropenia. pERC discussed that most patients in the niraparib group required a dose interruption or dose reduction to manage these toxicities but AEs leading to treatment discontinuation were relatively low. pERC noted that the incidence of hypertension was higher in the niraparib group compared to placebo but this did not lead to treatment discontinuation. No treatment-related deaths occurred in the trial, and pERC noted that the only case of MDS occurred in a patient treated with the fixed starting dose of niraparib. pERC discussed that the analysis of safety data by dosing scheme demonstrated that the incidence of all AEs was lower among patients who received the individualized starting dose of niraparib except for neutropenic sepsis, which occurred in one patient who received niraparib based on individualized dosing. pERC concluded that the toxicity profile of niraparib is not insignificant but can be managed in patients through appropriate initial dosing and dose adjustment during maintenance treatment.

pERC deliberated on the patient-reported outcome (PRO) data from the PRIMA trial that was collected using multiple instruments that included the Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI), the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Cancer 30 (QLQ-C30) and Ovarian Cancer Module (OV28), and the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) utility index and visual analogue scale (VAS). pERC discussed that the data from each instrument did not suggest any between-group differences in ovarian cancer symptoms or QoL based on changes in score from baseline except for some worse gastrointestinal symptoms (i.e., constipation, nausea and vomiting, and appetite loss) in the niraparib group at specific timepoints. However, pERC considered that missing data were a concern in the analysis of PROs at later time points where the number of patients completing assessments was notably reduced. pERC agreed with the CADTH Methods Team that this raises uncertainty about how representative patients completing assessments at later timepoints may be compared to all patients randomized to each treatment group. Nevertheless, pERC noted that the time-to-event analyses of PRO data, which incorporated data from all timepoints, showed no differences between the treatment groups in the time to worsening of gastrointestinal symptoms based on the prespecified minimal clinically important difference (MCID). pERC therefore concluded that the results from these analyses suggest patient QoL was maintained during niraparib maintenance treatment.

pERC deliberated the input received from one patient advocacy group, Ovarian Cancer Canada (OCC), and noted that patients value new treatments that lengthen the time to recurrence, prolong survival, improve QoL, delay the time to chemotherapy, and can be administered at home. pERC noted that fatigue, hair loss, neuropathy, bowel problems, and aching joints were the treatment-related side effects which patients reported having the most significant impact on their QoL. Patients had different opinions about the effectiveness of current treatments (excluding niraparib) and were concerned about having limited treatment options, particularly for BRCA-wt disease. pERC considered that patients indicated that they were willing to tolerate side effects from a new treatment for improved prognosis, however, they were

not willing to tolerate bone marrow problems or blood cancer as potential side effects of niraparib. Based on the evidence from the PRIMA trial, pERC agreed that niraparib aligns with patient values because it delays disease recurrence and future chemotherapy, offers the convenience of oral administration, and fulfills an unmet need for a treatment option in patients who are BRCA-wt. pERC acknowledged that patients also value improvement in QoL. While the PRIMA trial did not demonstrate an improvement in QoL with niraparib maintenance, pERC considered that QoL was maintained in patients treated with niraparib.

Considering the evidence from the PRIMA trial, pERC concluded that there is a net overall clinical benefit of niraparib as maintenance treatment when compared to placebo (i.e., active surveillance) based on a clinically meaningful improvement in PFS that was observed regardless of BRCA-mutation status, no apparent detriment in QoL, and a manageable but not insignificant toxicity profile.

pERC deliberated on the cost-effectiveness of niraparib compared to active surveillance, for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy. A key limitation discussed by the Committee was the sponsor's approach to address the immature OS data for niraparib. The sponsor's use of indirect methods to derive the niraparib OS was considered inappropriate by pERC. Expected gains in OS were calculated as the gains in PFS between niraparib and active surveillance (derived from the PRIMA trial) multiplied by the ratio of OS benefit to PFS benefit (assumed to be 2:1). The magnitude of the life-years and quality-adjusted life-years (QALY) benefits associated with niraparib was considered highly uncertain. It is unknown if there is an OS benefit associated with niraparib based on the available trial data. CADTH conducted scenario analyses exploring alternative approaches to estimating mean OS with niraparib and pERC noted that the approach to estimating OS with niraparib was a key driver of the cost-effectiveness results. pERC further commented that the extrapolation methods based on direct trial data would have been the preferred approach to inform OS beyond the trial data. The lack of direct evidence and lack of robust indirect evidence to estimate the comparative cost-effectiveness of niraparib versus olaparib was also a concern. pERC was unable to determine cost-effectiveness between niraparib and olaparib in the BRCA-mut population and additional data on clinical comparisons between these treatments are needed. pERC concluded that niraparib was not cost-effective at the submitted price compared with active surveillance in the ITT population studied in the PRIMA trial and that a reduction in drug price is required to improve cost-effectiveness to an acceptable level. As the cost-effectiveness of niraparib in the BRCA-wt population remains unknown and given the differential efficacy between BRCA-mut and BRCA-wt patients, the cost-effectiveness of niraparib in the ITT population remains highly uncertain given that inappropriate methods were used to derive the incremental cost-effectiveness ratio estimates for this population.

pERC noted that the budget impact was sensitive to the assumptions surrounding the market share of niraparib and the proportion of patients achieving a response rate to platinum-based chemotherapy.

pERC also deliberated on the input from the Provincial Advisory Group (PAG) regarding factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

Upon reconsideration of the Initial Recommendation, pERC reviewed the feedback received from all stakeholder groups and focused its deliberation on the feedback received from the registered clinician group (Ontario Health — Cancer Care Ontario Gynecologic Cancers Drug Advisory Council [Ontario Health — CCO GC DAC]), which was the only stakeholder group that did not support early conversion of the Initial Recommendation to a Final Recommendation. The Ontario Health — CCO GC DAC raised concerns about offering niraparib maintenance to patients who are homologous recombination proficient (HRP)/BRCA-wt; they questioned whether the absolute median PFS benefit of 2.7 months based on subgroup analysis from the PRIMA trial was clinically meaningful considering the significant toxicities associated with niraparib and the surveillance required to monitor for toxicity given that they believe this patient group will comprise a large proportion of the patients who will be eligible for niraparib. The Ontario Health - CCO GC DAC also disagreed with pERC's position that HRD testing should not be required to receive niraparib because it is not clinically validated. The Ontario Health — CCO GC DAC believes that HRD testing is essential for identifying the patients who will derive the most clinical benefit from niraparib maintenance; and the clinician group considered its use in the PRIMA trial as the highest level of validation of a predictive biomarker, given the trial was powered to assess a difference in outcome based on HRD status. pERC discussed that the PRIMA trial met its primary end point in both pre-specified efficacy populations (HRD-positive patients and the overall trial population) demonstrating a statistically

significant improvement in PFS over placebo. pERC agreed with the CGP that the magnitude of clinical benefit is greater for patients who are HRD or BRCA-mut when compared to patients who are HRP or BRCA-wt; however, they also agreed that there is no statistical justification for excluding patients who are HRP or BRCA-wt from receiving niraparib given that they comprised part of the overall trial population. Further, pERC also agreed with the CGP that with clinician experience and proper dose adjustment, toxicity and quality of life would be acceptable with niraparib. pERC concluded that the Initial Recommendation was based on the available evidence from the PRIMA trial and clinicians can use their discretion and clinical experience when discussing the risks and benefits of niraparib maintenance with individual patients. pERC also discussed the registered clinician group's comments on HRD testing, but maintained its original position that treatment decisions in ovarian cancer should not currently be guided by HRD status. This position takes into consideration the proprietary nature of the Myriad myChoice HRD test that makes it unclear which specific genes other than BRCA play a role in predicting a response to niraparib. As such, it will be difficult to validate the otherwise arbitrary HRD score outside of the commercial Myriad myChoice test, which is principally used for treatment with niraparib in ovarian cancer and has not been approved for use with other PARP inhibitors or in other tumour types. As a result, there is a lack of standardization of available tests in Canadian centres and limited access and use in Canadian practice.

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 sponsor's economic model and budget impact analysis (BIA)
- guidance from the pCODR CGP and EGP
- input from 1 patient advocacy group (OCC)
- input from 5 registered clinicians/groups that included:
    - 3 individual inputs (one each from Ontario, British Columbia, and Saskatchewan)
    - 2 group inputs (2 clinicians from the Ontario Health —CCO GC DAC; and 5 clinicians from the National BRCA Collaborative through the Society of Gynecologic Oncology of Canada).
- input from CADTH's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group, OCC
- one clinician group, Ontario Health — CCO GC DAC
- The PAG
- The sponsor, GlaxoSmithKline Inc.

The pERC Initial Recommendation was to recommend the reimbursement of niraparib as maintenance treatment of adult patients with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy conditional on cost-effectiveness being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the patient advocacy group (OCC), PAG, and the sponsor all agreed with the Initial Recommendation and supported early conversion to a Final Recommendation, while the registered clinician group (Ontario Health - CCO GC DAC) agreed in part with the Initial Recommendation and did not support early conversion. The registered clinician group cited concerns related to the eligible patient population and disagreed with statements related to HRD testing not being required because it has not been clinically validated.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of niraparib as maintenance treatment of adult patients with advanced epithelial ovarian cancer who are in a CR or PR to first-line platinum-based chemotherapy.

Studies included: One double-blind, placebo-controlled, randomized phase III trial

The pCODR systematic review included one ongoing international, double-blind, placebo-controlled, phase III randomized trial, PRIMA, that compared niraparib to placebo as maintenance treatment in adult patients with newly diagnosed ovarian cancer. Patients were randomized 2:1 to receive niraparib or placebo once daily in 28-day cycles for 36 months or until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Patient enrolment occurred between July 2016 and June 2018. Prior to Protocol Amendment 2 on November 16, 2017, patients received a fixed dose of 300 mg daily of study medication; however, following the amendment, an individualized dose option based on a patient's weight and/or platelet count was implemented. Patients with a baseline body weight of less than 77 kg and/or a baseline platelet count of less than 150 000 µL were administered a 200 mg dose once daily.

Eligible patients had newly diagnosed, histologically confirmed advanced ovarian cancer with high-grade serous or endometrioid features that were classified as stage III or IV according to FIGO criteria. The following stage III and/or IV patients were eligible for inclusion:

- stage III with visible residual disease after primary debulking surgery (patients with complete cytoreduction with NVRD after primary debulking surgery were excluded)

- inoperable stage III disease
- any stage IV disease
- stage III or IV patients treated with neoadjuvant chemotherapy (patients with NVRD after interval debulking surgery were included).

Enrolled patients had to have received 6 to 9 cycles of first-line platinum-based chemotherapy that resulted in an investigator-assessed CR or PR after 3 or more cycles. Any residual disease following chemotherapy must have been less than or equal to 2 cm, and cancer antigen 125 (CA-125) values had to be either within the normal range or show a decrease of more than 90%. Patients were randomized within 12 weeks after completing the last dose of platinum-based chemotherapy. Patients who received intraperitoneal chemotherapy were eligible. At least 2 post-operative cycles of platinum-based therapy were required for patients who had received interval debulking surgery.

Tumour samples underwent central testing for a BRCA-mut and homologous recombination status using the myChoice HRD test by Myriad Genetics. Any tumour that had a score greater or equal to 42 or had a deleterious or suspected deleterious BRCA 1/2 mutation (germline or somatic) was considered HRD-positive. Before the Protocol Amendment 1, trial enrolment was restricted to HRD-positive patients. Following this amendment, the eligibility criterion requiring HRD positivity was removed. Patients with an undetermined HRD status were eligible. Randomization was stratified according to clinical response after first-line platinum-based chemotherapy (CR or PR), receipt of neoadjuvant chemotherapy (yes or no), and tumour homologous recombination status (HRD versus HRP or not determined).

Patient populations: Majority of patients ECOG PS of 0, BRCA-wt, HRD-positive, FIGO stage III, and had received neoadjuvant chemotherapy

A total of 733 patients were enrolled in the PRIMA trial, with 487 patients randomized to niraparib and 246 patients randomized to placebo. In the niraparib group, 247 (50.7%) patients had HRD-positive tumours of whom 152 (31.2%) had a BRCA-mut and 95 (19.5%) were BRCA-wt, 169 (34.7%) patients had HRP tumours (i.e., HRD-negative), and the HRD status was undetermined for 71 (14.6%) patients. In the placebo group, 126 (51.2%) patients had HRD-positive tumours of whom 71 (28.9%) had a BRCA-mut and 55 (22.3%) were BRCA-wt, 80 (32.5%) patients were HRD-negative, and the HRD status was undetermined for 40 (16.3%) patients.

In the overall population, the median age was 62 years in both treatment groups. Most patients were White (niraparib group: 89.5%; placebo group: 89.0%) and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (niraparib group: 69.2%; placebo group: 70.7%). The median weight of patients in the niraparib and placebo groups was 66.00 kg and 65.55 kg, respectively. The primary tumour sites (niraparib group versus the placebo group) were ovarian (79.7% versus 81.7%), fallopian tube (13.3% versus 13.0%) and peritoneum (7.0% versus 5.3%), and histological subtypes were serous (95.5% versus 93.5%), endometrioid (2.3% versus 3.7%), and other (2.3% versus 2.4%). Most patients in each treatment group had FIGO stage III cancer (65.3% versus 64.2%), received neoadjuvant chemotherapy (66.1% versus 67.9%), and achieved a CR after their platinum-based chemotherapy (69.2% versus 70.0%). Among patients who received neoadjuvant chemotherapy, 26% had NVRD after interval debulking surgery. Most patients were BRCA-wt (63.7% versus 66.3%) and the median time from diagnosis to first dose of study treatment was 7.68 months in the niraparib group and 7.74 months in the placebo group. The distribution of baseline characteristics was similar in the HRD-positive patient population.

Before the dosing scheme amendment, a total of 473 patients in the overall population, including 315 in the niraparib treatment group, had received the fixed starting dose of 300 mg. After implementation of the revised dosing scheme, a total of 238 patients (156 in the niraparib group and 82 in the placebo group) received either 200 mg or 300 mg in accordance with body weight and platelet count; of these patients, 122 patients in the niraparib group and 61 patients in the placebo group received 200 mg as their individualized dose.

Key efficacy results: Statistically significant and clinically meaningful PFS benefit regardless of BRCA status; immature OS data

The key efficacy outcome deliberated on by pERC included PFS assessed by blinded-independent central review, which was evaluated hierarchically in HRD-positive patients and then in the overall patient population. As of the May 17, 2019 data cut-off date for the primary efficacy analysis, the median duration of follow-up was 13.8 months (range, < 1.0 to 28.0).

The PRIMA trial met its primary end point at the data cut-off date by demonstrating a statistically significant longer duration of PFS in the niraparib group compared to the placebo group in both efficacy populations. In the HRD-positive population, the median PFS was 21.9 months in the niraparib group and 10.4 months in the placebo group corresponding to an absolute median PFS benefit of 11.5 months in the niraparib group (hazards ratio [HR] = 0.43; 95% confidence interval [CI], 0.31 to 0.59; P < 0.001). In the overall population, the median PFS was 13.8 months in the niraparib group and 8.2 months in the placebo group, corresponding to an absolute median PFS benefit of 5.6 months (HR = 0.62; 95% CI, 0.50 to 0.76; P < 0.001). In both efficacy populations the estimates of PFS at 6, 12, 18, and 24 months were all higher in the niraparib group versus the placebo group at each time point. The results of prespecified subgroup analyses of PFS in the overall population were consistent with the primary efficacy analysis results, demonstrating a longer duration of PFS in the niraparib group compared to the placebo group except for the following subgroups of patients: ECOG PS of 1, stage IV disease at initial diagnosis, primary peritoneal or fallopian tube as primary tumour site, baseline CA-125 level greater than the upper limit of normal, and HRD status undetermined. In these subgroups, all the treatment effect estimates favoured treatment with niraparib, but the 95% CI included the null value of 1, suggesting no difference in PFS between the treatment groups.

At the time of the primary efficacy analysis, the interim analysis of OS indicated that the data were immature based on a total of 79 deaths (10.8% maturity) with data censored for over 87% of patients in both treatment groups. The interim OS results showed treatment effect estimates that favoured niraparib compared to placebo but the difference in deaths between the treatment groups was not statistically significant. In the HRD-positive population, 26 patients had died that included 16 deaths (6.5%) in the niraparib group and 10 deaths (7.9%) in the placebo group (HR = 0.61; 95% CI, 0.27 to 1.39). In the overall population, 79 patients had died that included 48 (9.9%) in the niraparib group and 31 (12.6%) in the placebo group (HR = 0.70; 95% CI, 0.44 to 1.11). Median OS estimates were not reported due to the low event rate and insufficient follow-up time.

At the time of the data cut-off date, the data for secondary efficacy outcomes that included PFS-2 and time-to-first subsequent therapy were considered immature at 20% and 47% maturity, respectively. Overall, the results for these outcomes were consistent with the primary outcome results and showed treatment effect estimates that favoured treatment with niraparib compared to placebo.

Patient-reported outcomes: Available data suggest QoL is maintained with niraparib maintenance

PROs were assessed using the FOSI, the EORTC-QLQ-C30 and EORTC-QLQ-OV28 questionnaires, and the EQ-5D-5L. In the overall population, patient completion rates for questionnaires were greater than 80% at all assessment timepoints. However, for all instruments, the increase in patients completing the end of treatment (EOT) assessment indicated that a sizable proportion of patients did not complete PRO assessments at earlier timepoints particularly after cycle 13.

Mean FOSI scores were similar at baseline between the niraparib and placebo treatment groups and throughout the trial with no observed differences in changes from baseline between the treatment groups during the treatment period, except for cycle 3 where placebo had a higher value indicative of less symptoms and improved QoL. The Kaplan-Meier (KM) analysis of time-to-symptom worsening, which takes all assessment timepoints into account, showed no difference between niraparib and placebo (HR = 1.10; 95% CI, 0.915 to 1.330) in the time to worsening of ovarian cancer symptoms based on the MCID of 2 points.

Mean scores for the global health status/QoL score of the EORTC-QLQ-C30 were similar at baseline between the niraparib and placebo treatment groups and throughout the trial. There were no differences in changes from baseline between treatment groups during treatment, except for gastrointestinal-related assessments. Constipation was worse in niraparib treated patients through cycle 15 and again at cycle 21 with similar trends in nausea/vomiting (through cycle 9), appetite loss (cycles 3, 5, and EOT), and dyspnea (cycles 3 and 5). Conversely, diarrhea was reported as worse in placebo treated patients at cycles 3, 5, 11, 15, and 24. The EORTC-QLQ-OV28 did not demonstrate any consistent differences in QoL scores between the niraparib and placebo groups. The KM analysis for time-to-abdominal/gastrointestinal score worsening showed no difference between niraparib and placebo (HR = 1.11; 95% CI, 0.890 to 1.372), suggesting similar time to worsening of abdominal and gastrointestinal-related symptoms in the two treatment groups based on the MCID of 10 points.

Mean EQ-5D-5L index and VAS scores were similar between the niraparib and placebo treatment groups at baseline and throughout the study, with no observed differences in changes from baseline during the treatment period, except for cycle 5 where niraparib had a higher utility index value, indicative of better QoL at this time point.

Limitations: Lack of validity and standardization of HRD testing, immature OS data, and missing PRO data at later assessment timepoints

The major limitations and potential sources of bias associated with the PRIMA trial, based on the CADTH Methods Team's critical appraisal of the evidence, included the following:

- Although PFS and OS were assessed in the two efficacy populations using a hierarchical-testing procedure, there were multiple secondary efficacy outcomes assessed in the trial and numerous predefined subgroup analyses performed that were not adjusted to account for multiple comparison testing to control the risk of type I error. The trial was not powered to test specific hypotheses in these outcomes and subgroups, and therefore the results of these analyses should be interpreted as exploratory in nature.
- Protocol Amendment 2 introduced a change to the dosing scheme of the trial that occurred after the enrolment of the majority of trial patients (65%) who all received a fixed starting dose of 300 mg. The patients enrolled after the amendment received an individualized starting dose (200 mg or 300 mg according to patient weight and/or platelet count) and received fewer treatment cycles and thus less treatment exposure due to a shorter follow-up period. The results of subgroup analyses performed of PFS by dosing schedule suggested that starting dose did not affect treatment efficacy in either the HRD-positive or the overall population. The study sample size was not increased to ensure adequate power to test for differences in outcome based on dosing scheme. In addition, patients were assigned to a dosing scheme based on weight and/or platelet count and not through randomization, so there is the possibility that any differences in baseline characteristics between groups could bias treatment effect estimates based on subgroup analyses. Accordingly, the results of these analyses should be interpreted with caution.
- According to the CGP, HRD testing is not routinely performed in Canadian clinical practice because the test has not been clinically validated. Therefore, there is uncertainty in the reliability and validity of the trial results based only on HRD status.
- At the time of the primary efficacy analysis, the OS data were considered immature based on the low number of events; therefore, longer-term survival data are required to assess the magnitude of an OS benefit. Patient crossover was not permitted in the trial; however, the longer-term OS data will be confounded by the use of post-trial treatments, which was high in the trial.
- For the assessment of PROs, patient compliance rates were reported to be high (> 80%) at all assessment timepoints, however, for all instruments, the increase in patients completing the EOT assessment indicated that a sizable proportion of patients did not complete PRO assessments at earlier timepoints. Thus, the number of patients included in the analyses of PROs at later assessment timepoints was reduced and the patients left in the trial who completed PRO assessments are likely not representative (i.e., have better health-related quality of life) of all patients randomized to each treatment group. In this scenario, data are not missing at random since patients who have left the trial are likely sicker (or have died), and therefore, the results at later timepoints are likely biased. Time-to-event analysis of PROs mitigates some of the bias associated with analyses based on mean changes in scores from baseline because all available data are used in the analysis. In this trial, the time to worsening of symptoms analyses based on the MCID of the FOSI and EORTC-QLQ-OV28 showed no differences between the treatment groups with respect to the time to worsening of ovarian cancer symptoms.

Safety: Greater toxicity with niraparib requiring dose reduction and dose interruption

Overall, the incidence of all categories of treatment-emergent AEs was higher in the niraparib group compared to the placebo group. There were no treatment-related deaths reported in the trial and three deaths were attributed to AEs (2 in the niraparib group and 1 in the placebo group). The two deaths in the niraparib group were related to pleural effusion and intestinal perforation. When compared to placebo, the incidence of AEs leading to treatment discontinuation (12.0% versus 2.5%), dose reduction (70.9% versus 8.2%), and treatment interruption (79.5% versus 18.0%) were all higher in the niraparib group.

The most common treatment-related AEs of any grade that occurred in the niraparib group (versus the placebo group) were anemia (60.5% versus 12.7%), nausea (50.6% versus 20.1%), thrombocytopenia (45.2% versus 3.3%), fatigue (29.8% versus 23.0%), decrease in platelet count (26.9% versus 1.2%), neutropenia (26.0% versus 5.7%), and constipation (25.8% versus 5.7%). The most common grade 3 or higher treatment-

related AEs in the niraparib group (versus the placebo group) were anemia (30.2% versus 0.4%), thrombocytopenia (28.7% versus 0%), decrease in platelet count (13.0% versus 0%), neutropenia (12.4% versus 0.8%), and decrease in neutrophil count (7.6% versus 0%).

The incidence of any grade and grade 3 or higher AEs was lower in patients who received an individualized starting dose of niraparib compared to a fixed starting dose, except for neutropenic sepsis, which occurred in one patient treated with an individualized starting dose of niraparib. One (0.3%) patient who had received a fixed starting dose of niraparib experienced MDS (grade 3 or higher), and no patients in either the individualized starting dose of niraparib or in the placebo group experienced MDS.

Comparator information: No comparative evidence to olaparib

In the absence of direct evidence, the sponsor submitted to CADTH a feasibility assessment for conducting an ITC between niraparib and other maintenance therapies (i.e., olaparib, bevacizumab) for newly diagnosed advanced ovarian cancer. Based on the results of the feasibility assessment, the authors concluded that an ITC could not be performed as the available evidence identified by a systematic literature search did not meet current guidelines for performing objective comparative analyses of clinical effectiveness. It was noted that the inclusion criteria of the PRIMA trial led to the enrolment of patients with a high risk of disease recurrence, which differed from the study populations of comparator trials, among other sources of heterogeneity. Due to the identified heterogeneity between the trials available for the indirect comparisons, comparative analyses were considered inappropriate for use in clinical decision-making or reimbursement decisions.

The CADTH Methods Team, in consultation with the CGP, reviewed the 12 eligible randomized controlled trials considered in the feasibility assessment and agreed with the conclusion that the trials were not sufficiently comparable for the purpose of conducting an ITC (i.e., network meta-analysis or population adjusted ITC). The clinical heterogeneity observed across the trials, particularly related to the type of maintenance therapy (i.e., initiated alongside initial chemotherapy versus after chemotherapy), patient populations (e.g., risk of recurrence, imbalances in known treatment effect modifiers) and outcome assessment (e.g., method of assessment, availability of data limiting the analysis to select outcomes) was considered by the CADTH Methods Team and CGP to be a valid concern that would preclude a meaningful analysis and unbiased estimates of relative treatment effect.

Need and burden of illness: Need for additional treatment options in patients with BRCA-wt

Standard treatment for stage III and IV ovarian cancer involves cytoreductive surgery and platinum-based chemotherapy. The volume of residual disease remaining after cytoreductive surgery correlates inversely with survival; thus, the higher the volume of residual disease after surgery, the worse the prognosis and the chance of survival. Even in patients with optimal debulking, defined as less than 1cm in residual disease size, any remaining visible disease correlates with worsening survival. The goal of surgery is to remove all macroscopic disease (i.e., complete cytoreduction). This may be possible to achieve upfront, or if it is predicted that the complete cytoreduction is not possible at diagnosis, patients are usually referred for upfront preoperative (neoadjuvant) chemotherapy prior to being considered for interval cytoreduction.

After first-line chemotherapy with or without surgery, patients are observed for recurrence through active surveillance. Unfortunately, most patients with initially advanced ovarian cancer eventually experience recurrence; the 5-year survival rates vary between 45% in stage IIIA disease to less than 20% in stage IV disease. Maintenance strategies have been evaluated to potentially delay or prevent recurrences. In patients with a BRCA-mut (approximately 15% to 20% of patients), olaparib is approved and reimbursed in almost all Canadian jurisdictions as maintenance treatment after a response to platinum-containing chemotherapy. However, as most patients do not have a BRCA-mut, they are ineligible for olaparib maintenance and receive active surveillance after the completion of platinum-based chemotherapy. Therefore, there remains a significant unmet need for effective treatments that may extend remission in the majority of patients with newly diagnosed advanced ovarian cancer.

Registered clinician input: Niraparib has demonstrated efficacy and tolerable safety; unmet need for treatments in patients with BRCA-wt

A total of 5 registered clinician inputs (3 individual and 2 group) were provided for the review of niraparib as maintenance treatment of adult patients with advanced ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy. Current treatments identified by the clinicians included olaparib for first-line maintenance treatment for patients with a BRCA-mut and

bevacizumab for high-risk patients (sub-optimally debulked stage III or IV patients). It was noted that although some high-risk patients receive bevacizumab as maintenance therapy, it is not universally adopted due to toxicities, resources, and a modest clinical benefit. It was also noted that there is no available or consistent treatment for BRCA-mut-negative patients; thus, they may be on active surveillance. Most clinicians indicated there is an unmet need in this group of patients.

Overall, the clinicians considered the eligibility criteria of the PRIMA trial to be suitable for clinical practice. It was noted the criteria capture a broad range of patients except for those who are platinum-resistant, have refractory disease (and therefore unlikely to benefit), and a worse performance status (only patients with an ECOG of 0 or 1 were included). For BRCA-mutated patients, the clinicians indicated that niraparib has similar efficacy and tolerability (with the exception of thrombocytopenia and hypertension) compared to olaparib. Compared to bevacizumab, clinicians noted that niraparib has a better safety profile and requires less clinic visits due to its oral administration. Overall, the clinicians considered niraparib to be well tolerated by patients with minimal safety concerns, and it demonstrated significant efficacy among different endpoints of the pivotal trial.

All clinicians indicated they would administer niraparib in the patient population included in the pivotal trial (stage III or IV cancers in patients who have a complete or partial response to platinum-based chemotherapy). In addition, both clinician groups suggested niraparib also be used in patients with stage III disease who have undergone primary debulking and have NVRD after surgery. Clinicians stated that given there is no validated HRD test currently available in Canada, and a modest PFS benefit was demonstrated in the trial for patients without HRD (as assessed by the myChoice HRD test) or without a BRCA-mut, and therefore, consideration could be given to administering niraparib to all high-risk, high-grade serous/endometrioid ovarian cancer patients whose tumours are not platinum-resistant or refractory. The clinician groups noted that for the BRCA-mutated population, niraparib will be another treatment option (in addition to olaparib if funded). For the high-risk population (i.e., bevacizumab candidates), niraparib would be an option to replace bevacizumab, potentially allowing for bevacizumab to be reserved for patients with platinum-resistant disease.

The clinicians expressed different preferences for niraparib over olaparib in BRCA-mutated patients; however, clinicians highlighted the decision would be based on patient tolerance, availability, clinician preference, and the shorter treatment duration of olaparib. Most clinicians preferred niraparib over bevacizumab in patients with a high risk of relapse and would prefer to reserve the use of bevacizumab in the platinum-resistant setting when patients have limited treatment options.

PATIENT-BASED VALUES

Perspectives of patients with advanced ovarian cancer: significant impacts on QoL; mixed feelings on the effectiveness of current treatments

OCC provided input on niraparib as maintenance treatment of adult patients with advanced epithelial ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy. Input was gathered from patients and their caregivers through an online survey and interviews conducted between November 26, 2019 to September 21, 2020. Responses were received from a total of 61 patients with ovarian cancer from across Canada, which included 52 who completed the online survey and 9 who participated in interviews. The online survey had 5 caregiver survey respondents. Most patient respondents were diagnosed with high-grade serous, stage III or IV ovarian cancer and had experienced at least 1 recurrence and were diagnosed within the last 5 years. Among the patients in the sample, no patients who completed the online survey and 4 patients who were interviewed had direct treatment experience with niraparib.

Patients reported that ovarian cancer highly impacts one's work life, sexual relationship, sleep pattern, well-being, and physical activity. Most respondents had experience with chemotherapy and one-third had experience with a PARP inhibitor that included either olaparib and/or rucaparib. Fatigue, hair loss, neuropathy, bowel problems, and aching joints were treatment-related side effects noted to have a significant impact on one's QoL. Respondents had different opinions about the effectiveness of current treatments (excluding niraparib). From the caregiver perspective, work life and sleep patterns were most negatively impacted, and the majority spent one to three hours each day completing caregiver tasks.

Patient values on treatment: preference for treatments that delay recurrence, prolong OS, improve QoL, delay time to chemotherapy, and that can be administered at home

From the patient perspective, most patients felt that the possibility of lengthening the time to recurrence, prolonging survival, improving QoL, avoiding or delaying the time to chemotherapy, and the opportunity to receive treatment at home were the most important outcomes when considering a new treatment. More patients indicated they would require only a mild or moderate improvement in their ovarian cancer to consider treatment with niraparib. Further, OCC noted that most respondents indicated that the potential benefits of niraparib would outweigh the risks, although, no respondents were willing to tolerate bone marrow problems or blood cancer as potential side effects of niraparib. Additionally, the input highlighted that there is a particular need for new treatment options for patients who are BRCA-wt. Among the four patients with niraparib treatment experience, all had experienced at least one side effect from treatment. Fatigue, bowel problems, and high blood pressure were the symptoms experienced by most patients (each by three patients). Two patients expressed that while none of the side effects were acceptable, most were managed by using additional medications. Overall, three of the four patients indicated that niraparib had improved their QoL.

ECONOMIC EVALUATION

Niraparib is available as a 100 mg capsule, at a submitted price of $131.79 per tablet. The recommended starting dose is 200 mg daily. For patients who weigh 77 kg or more and have baseline platelet count greater than or equal to 150,000/μL, the recommended starting dose of niraparib is 300 mg (three 100 mg capsules) daily. The 28-day cycle cost of niraparib may range from $7,380 to $11,070.
The sponsor submitted a cost-utility analysis based on a three-state partitioned survival model which considered niraparib for the maintenance treatment of patients with advanced ovarian cancer following response on frontline platinum-based chemotherapy. As part of the base-case analysis, the sponsor explored the cost-effectiveness of niraparib versus active surveillance for the full Health Canada indication which consists of the PRIMA ITT population and stage III patients with NVRD. In addition, two subgroup analyses were conducted comparing niraparib with active surveillance in the overall trial population (i.e., referred to as the PRIMA ITT population) and with active surveillance and olaparib in the BRCA-mut population. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer.

The proportion of patients who were progression free, experienced progressive disease, or were dead at any time over the 20-year model time horizon was derived from non-mutually exclusive survival curves. The clinical efficacy of niraparib was primarily informed using the PRIMA trial and the sponsor further adjusted the efficacy outcomes using data from the PAOLA-1 trial to represent the inclusion of stage III NVRD patients to align with the Health Canada indication. The sponsor used an indirect approach (assuming 2:1 mean OS to mean PFS ratio) to derive mean OS associated with niraparib. The sponsor assumed olaparib would have equivalent efficacy (i.e., PFS and OS) and time-to-treatment discontinuation as niraparib.

The following key limitations were identified:

- The PRIMA trial only enrolled a small proportion of patients with stage III NVRD ovarian cancer following neoadjuvant chemotherapy and interval debulking surgery and excluded patients with stage III disease and NVRD following primary debulking surgery. To estimate the overall population (i.e., full Health Canada indication), data from the PAOLA-1 trial were adjusted to represent the inclusion of stage III NVRD patients. The sponsor's approach is uncertain as treatment effect between trials were naively incorporated despite differences in the patient population between PRIMA and PAOLA-1.
- The sponsor did not explore cost-effectiveness of niraparib in the subgroup of patients with a wild type BRCA gene (BRCA-wt) despite an expected differential treatment efficacy exists between BRCA subgroups. Interpretation of the PRIMA ITT population is limited given the included comparators do not fully reflect current clinical Canadian practice.
- Given the immaturity of the OS data in the PRIMA trial, an indirect approach to derive mean OS associated with niraparib was used which was associated with substantial uncertainty. The approach depended on confidence in the difference in mean PFS for niraparib and active surveillance which was derived from parametric survival distributions and adds further uncertainty to the mean OS benefit estimate.
- The sponsor's chosen OS and PFS parametric survival functions were overestimated in the extrapolated period beyond the PRIMA trial data for active surveillance according to the clinical experts consulted by CADTH.

- For patients who have achieved long-term remission (i.e., progression free after 10 years), the sponsor's model assumed mortality rates based on the Canadian general population. This does not accurately reflect the expected long-term mortality risk for patients with ovarian cancer.
- The time horizon did not fully capture the lifetime of the patient which would be appropriate for interventions that have differential effects on mortality.

CADTH was unable to address the multiple methodological limitations associated with the approach to model the overall population and, as such, no reanalyses were conducted on the overall population. The CADTH base case, reflecting the PRIMA ITT population included: reducing the mean OS to mean PFS ratio for niraparib; using alternate progression-free and overall survival extrapolations for active surveillance; adjusting mortality for patients in long-term remission; and adopting a lifetime time horizon.
CADTH reanalyses indicated that niraparib compared with active surveillance was not cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained with an incremental cost-effectiveness ratio of $128,557 per QALY gained at the submitted price. A reduction of 60% in the price of niraparib would be required to be considered cost-effective at a WTP threshold of $50,000 per QALY gained; however, a higher price reduction may be required when considering the treatment mix currently used in clinical practice. Niraparib remains dominated by olaparib (i.e., niraparib was equally effective but more expensive) in the BRCA-mut subgroup in a CADTH scenario reanalysis.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact underestimated

The sponsor's assumed market share uptake of niraparib in the BRCA-wt population was highly uncertain given feedback from clinical experts consulted by CADTH that only a subset of BRCA-wt patients with an exceptional response to platinum-based chemotherapy would be given niraparib. As part of reanalyses, CADTH revised the approach and inputs used to derive the total and growth of the Canadian population at risk of ovarian cancer and increased the proportion of patients who respond to first-line platinum-based chemotherapy. CADTH reanalyses suggest that the budget impact of introducing niraparib for the full Health Canada indication was estimated to be an increase of $115,729,579 over the first three years when markups and dispensing fees are included. Parameters relating to the duration of therapy were not revised as part of the CADTH reanalyses. The median duration of therapy was assumed to be 11.14 months, based on the time-to-discontinuation reported in the PRIMA trial, and the maximum duration of therapy was constrained; such that all patients on olaparib discontinued at 2 years, while the maximum treatment duration was 3 years for niraparib.

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

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

- Dr. Maureen Trudeau who did not vote due to her role as pERC Chair

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

- Dr. Maureen Trudeau who did not vote due to her role as pERC Chair.

Avoidance of conflicts of interest

All members of the CADTH 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 CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of niraparib as maintenance treatment for advanced ovarian cancer who are in a complete or partial response to first-line platinum-based chemotherapy, through their declarations, no members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, no 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 CADTH 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*.

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

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

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

PAG implementation questions	pERC Recommendation
Eligible patient population	
In view of the characteristics of the patient population and exclusion criteria in the PRIMA trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with niraparib:	
• ECOG performance score ≥ 2.	• pERC agrees with the CGP that niraparib be considered in patients with an ECOG PS of 0 to 2 with the expectation that most patients with an ECOG PS of 2 will likely improve in functional status after first-line chemotherapy as they recover from side effects of treatment, and therefore may benefit from maintenance therapy with niraparib. pERC agreed with the CGP that patients who have an ECOG PS of 3 to 4 who do not recover their functional status within 12 weeks after chemotherapy will likely not benefit from treatment with niraparib.
• Patients who could not receive first-line platinum chemotherapy and received an alternative chemotherapy regimen instead.	• pERC noted that the CGP expects that patients receiving an alternative chemotherapy regimen instead of platinum-based chemotherapy would be a rare occurrence. pERC agreed with the CGP that if a patient in this case has benefited from surgery and chemotherapy (i.e., achieved a partial or complete response) according to the eligibility criteria of the PRIMA trial, these patients should be given the opportunity of niraparib maintenance therapy.
• Patients who have not completed at least 6 cycles of platinum-based or alternate chemotherapy.	• pERC agreed with the CGP that patients should complete at least 6 treatment cycles per the PRIMA trial protocol, if possible, to achieve the best possible outcome. For patients who can only complete less cycles for various reasons (i.e., allergy or other intolerance) but have demonstrated a response to treatment, pERC agreed it is reasonable to consider niraparib maintenance on an individualized basis.
• Patient with mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer.	• pERC noted there is no evidence to suggest that patients with histologies other than serous or endometroid will benefit from niraparib maintenance, and therefore agreed with the CGP that niraparib maintenance is not recommended as treatment in other histologies.
• Patient having undergone more than 2 debulking surgeries.	• pERC agreed with the CGP that if patients otherwise meet the eligibility criteria of the PRIMA trial, patients who have undergone more than 2 debulking surgeries in the first-line setting may benefit from niraparib, and therefore should be eligible for maintenance treatment.
• Patients with intolerance of olaparib.	• pERC agreed with the CGP that if patients otherwise meet the eligibility criteria of the PRIMA trial, patients with intolerance to olaparib (whose disease has not progressed) may benefit from niraparib, and therefore should be eligible for maintenance treatment.
• PAG seeks an estimate of the maximum time between completion of chemotherapy and commencement of niraparib.	• pERC noted that some patients may require a break from treatment in order to recover from the side effects of chemotherapy. pERC agreed that if patients can initiate maintenance treatment within 12 weeks of completing platinum-based chemotherapy (and have not progressed), as

	per the PRIMA trial criteria, these patients should be eligible for niraparib.
Implementation factors	
PAG seeks clarity on the role of CA-125 testing prior to initiation of niraparib, as patients in the trial had to have either CA-125 in the normal range or a CA-125 decrease by more than 90% during their frontline therapy that is stable for at least 7 days (i.e., no increase > 15%) before starting niraparib.	pERC noted the CGP's comments on CA-125, which indicated CA-125 is a surrogate marker for response to treatment, but its rise and fall does not necessarily correspond to the degree of radiologic response such that it can be used to rule out responsiveness of subsequent treatment. The CGP noted the CA-125 cut offs used in the PRIMA trial were arbitrary, and that in clinical practice, radiologic response is key to predicting efficacy of maintenance therapy. pERC agreed with the CGP that if patients have a radiologic response to frontline treatment and otherwise meet all other eligibility criteria of the PRIMA trial, these patients will benefit from niraparib maintenance treatment.
PAG identified additional eligibility criteria in the study, notably a partial or complete tumour response and no measurable disease of more than 2 cm at the time of study entry. PAG would like to know if all these criteria need to be met for eligibility to niraparib reimbursement.	pERC agreed with the CGP that a partial or complete tumour response to chemotherapy is important to achieve prior to niraparib maintenance treatment. However, the CGP noted that the size criterion of less than 2 cm is arbitrary, and it is often difficult to measure tumour burden based on a one-dimensional size. pERC agreed with the CGP that as long as a patient had a partial or complete tumour response to chemotherapy according to RECIST criteria and otherwise meets the other eligibility criteria of the PRIMA trial, that niraparib should be offered as maintenance therapy.
PAG seeks guidance on potentially stopping niraparib to manage toxicity and then restarting the therapy.	pERC agreed with the CGP that a temporary stop of niraparib in cases of significant toxicity followed by restarting therapy once the toxicity has resolved or becomes manageable is reasonable if there is no evidence of disease progression before restarting treatment with niraparib. pERC noted that the CGP recommends appropriate dose adjustment after reinitiating niraparib.
PAG seeks advice on the frequency and type of monitoring during maintenance therapy (e.g., CA-125 testing, CT scans).	pERC noted that the CGP recommends regular bloodwork (i.e., weekly for the first month of therapy, every 4 weeks for the next 11 months, and then periodically thereafter as per the Health Canada product monograph), testing for CA-125 every 3 to 4 months, and routine CT scan at least annually if CA-125 remains stable to verify continued response.
Sequencing and priority of treatment	
PAG is seeking to confirm the place in therapy and sequencing with niraparib including the scenarios below: • Circumstances where niraparib would be preferable to olaparib should both options be available. • Options after failure of niraparib including potential retreatment with a PARP inhibitor for maintenance in the relapsed/refractory setting. • Switching between niraparib and olaparib (if BRCA-mutated) or vice versa in cases of unacceptable toxicity.	• pERC agreed with the CGP that niraparib would be preferable in patients who are BRCA-wt and in patients who are intolerant to olaparib. • pERC agreed with the CGP that there is currently no evidence to support retreatment with a PARP inhibitor in the relapsed/refractory setting after failure of niraparib in the first-line setting. In the absence of evidence, pERC agreed with the CGP that retreatment with a PARP inhibitor in the relapsed/refractory setting cannot currently be recommended. • pERC agreed with the CGP and believe that switching between niraparib and olaparib in patients with a BRCA-mut in cases of unacceptable toxicity is acceptable practice.
• Retreatment with niraparib following platinum chemotherapy	• pERC agreed with the CGP that retreatment with niraparib in patients who discontinued maintenance treatment for

in patients who discontinued maintenance treatment for reasons other than progression.	reasons other than progression (i.e., intolerance, treatment break) is acceptable. pERC noted the CGP indicated that for patients who complete niraparib maintenance treatment (i.e., 3 years) and then experience disease progression, there currently is no evidence to inform whether retreatment with niraparib (following a response to chemotherapy) would be beneficial.
Companion diagnostic testing	
PAG did not identify a companion diagnostic test required for eligibility to niraparib. However, BRCA-mut results may help inform choice of therapy between niraparib and olaparib. PAG is seeking confirmation if BRCA and HRD testing are required.	pERC noted that BRCA testing is recommended and reimbursed in most provinces; and testing for both a germline and somatic BRCA-mut is recommended. pERC also noted that the PRIMA trial used the myChoice Myriad HRD test to determine patients' HRD status, which is a commercially available proprietary product that has demonstrated a high correlation between breast cancer samples that had a BRCA defect and HRD scores based on biomarkers that include the HRD-loss of heterozygosity score, HRD-telomeric allelic imbalance score, and HRD-large-scale state transition score. Although BRCA defect and HRD score are correlated, it is currently unclear which genomic changes in HRD are linked with response to PARP inhibitors. pERC agreed with the CGP that until further studies are performed to validate the test, HRD testing should not be required to receive niraparib.

BRCA = breast cancer susceptibility gene; BRCA-mut = BRCA mutation; BRCA-wt = BRCA wild type; CA-125 = cancer antigen 125; CGP = Clinical Guidance Panel; CR = complete response; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; FIGO = International Federation of Gynecology and Obstetrics; HRD = homologous recombination deficiency; PARP: poly(adenosine diphosphate [ADP]–ribose) polymerase; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PR = partial response.