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 monotherapy for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Submitted By: GlaxoSmithKline Inc.	**Manufactured By:** GlaxoSmithKline Inc.
NOC Date: June 27, 2019	**Submission Date:** February 7, 2020
Initial Recommendation: July 3, 2020	**Final Recommendation:** September 3, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	Niraparib costs $131.79 per 100 mg capsule. At the recommended dose of 300 mg (three 100 mg capsules) taken orally once daily, niraparib costs $395.36 per day and $11, 070.00 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 monotherapy for the maintenance treatment of adult patients with recurrent 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 platinum-sensitive disease, which is defined as disease progression occurring at least six months after completion of platinum-based chemotherapy. Patients must have completed at least two prior lines of platinum-based chemotherapy and be in response (complete or partial) to their most recent platinum-based chemotherapy regimen. Patients must have received at least four cycles of their most recent platinum-based chemotherapy before starting treatment with niraparib. Maintenance therapy with niraparib should start within eight weeks of the last dose of platinum-based chemotherapy and continue until unacceptable toxicity or disease progression. Patients should have good performance status (PS) and no active or uncontrolled metastases in the central nervous system.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of niraparib maintenance treatment compared with placebo (i.e., best supportive care with 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 agreed that niraparib aligns with patient values because it delays disease recurrence while maintaining QoL and fulfills a need for new treatments, especially in patients with BRCA wild type who have limited treatment options. pERC concluded that, based on the sponsor's submitted price, niraparib cannot be considered cost-effective compared to active surveillance in the patient population requested for reimbursement. pERC also concluded that niraparib cannot be considered cost-effective when compared to olaparib in patients with germline BRCA mutations. pERC noted the cost-effectiveness results are highly uncertain given that the overall survival (OS) associated with niraparib is currently unknown. There is substantial uncertainty related to the assumptions and methods used in the economic analysis to estimate the long-term OS of niraparib. Additionally, there is a lack of direct evidence and a lack of robust indirect evidence to estimate the comparative cost-effectiveness of niraparib to olaparib.
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 that would improve the cost-effectiveness of niraparib to an acceptable level. pERC noted that a reduction in the price of niraparib would be required in order to improve the cost-effectiveness to an acceptable level. **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**

Epithelial ovarian cancer comprises a heterogeneous group of epithelial malignancies arising from the ovaries, fallopian tubes, or peritoneum. Ovarian cancer is the eighth leading cause of all deaths in Canadian women and the fifth leading cause of cancer-related death. The Canadian Cancer Society estimated that, in 2020, 3,100 women in Canada will have developed ovarian cancer, with 1,950 deaths due to the disease. High-grade serous is the most common histology, representing 60% of all epithelial ovarian cancers. Due to delayed presentation and diagnosis, almost 70% of women with ovarian cancer are diagnosed at an advanced stage of disease (III or IV), which is associated with a high rate of recurrence and is considered incurable. The median time to recurrence is approximately 18 months, and median OS is typically less than four years. Standard of care treatment for recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer — hereinafter referred to collectively as ovarian cancer — involves platinum-based systemic therapy that is most often carboplatin based. Platinum-sensitive disease is commonly defined as disease that has recurred six or more months from the completion of platinum-based therapy. Following a response to platinum-based therapy, the standard of care for most patients is active surveillance (i.e., watch and wait) where patients are monitored for clinical progression, at which point they will be offered another platinum-based chemotherapy or single agent chemotherapy with or without bevacizumab. According to the Clinical Guidance Panel (CGP), bevacizumab is used infrequently in Canada due to variable access across jurisdictions. All patients eventually develop platinum resistance, with increased resistance to chemotherapy with repeated exposure. Maintenance strategies have been investigated to potentially delay or prevent recurrences. In patients with a BRCA mutation, either germline (inherited) or somatic (limited to tumour), the poly adenosine diphosphate–ribose polymerase (PARP) inhibitor olaparib is approved and reimbursed in almost all Canadian jurisdictions as maintenance treatment after a response to platinum-containing chemotherapy. Approximately 15% to 20% of ovarian cancer patients have a BRCA mutation and are eligible to receive olaparib maintenance. However, most patients do not have BRCA mutations, and 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 platinum-sensitive, recurrent ovarian cancer.

pERC deliberated the results of one double-blind, placebo-controlled, phase III trial (NOVA), which evaluated the efficacy and safety of niraparib as maintenance treatment in patients with predominantly high-grade serous, platinum-sensitive, recurrent ovarian cancer. pERC noted that the NOVA trial enrolled patients regardless of BRCA mutation status; therefore, they considered placebo an appropriate comparator for trial patients without BRCA mutations, but not for patients with known germline or somatic BRCA mutations, where the appropriate comparator is olaparib. The trial randomized two independent cohorts of patients based on germline BRCA status (germline BRCA mutation and non-germline BRCA mutation). Patients in the non-germline BRCA mutation cohort were also grouped based on the homologous recombination deficiency (HRD) status (positive or negative) of their tumour and the presence of a somatic BRCA mutation. Accordingly, the trial pre-specified three primary efficacy populations that included the germline BRCA mutation cohort, patients who had HRD-positive tumours in the non-germline BRCA mutation cohort, and the overall non-germline BRCA mutation cohort.

The NOVA trial reported a statistically significant prolongation in PFS (the primary outcome of the trial) in favour of niraparib compared with placebo. pERC discussed that a PFS benefit was observed in all three primary efficacy populations, with the largest treatment effect observed in the germline BRCA mutation cohort, followed by the HRD-positive non-germline BRCA mutation cohort, and then the overall non-germline BRCA mutation cohort. pERC also noted the consistency of the PFS benefit in terms of all exploratory subgroup analyses, which included analyses by demographic and clinical characteristics, and subgroups of the non-germline BRCA mutation cohort (HRD positive and somatic BRCA mutation, HRD positive and BRCA wild type, and HRD negative). pERC discussed that HRD testing is not a validated clinical test and is not routinely performed in Canadian clinical practice. Therefore, the subgroup analysis

results based on HRD status need to be interpreted with caution. pERC agreed with the CGP that treatment decisions should not be guided based on the results of HRD testing alone. pERC noted that the treatment benefit of niraparib was observed across all secondary efficacy outcomes, which included time-to-first subsequent therapy (TFST), time-to-second subsequent therapy (TSST), chemotherapy-free interval (CFI), progression-free survival on next line of therapy (PFS-2), except for OS. The OS data from the NOVA trial were immature at the time of the primary efficacy analysis and pERC noted that even with additional follow-up, the OS data will be confounded by the post-trial treatments given after disease progression which includes a different PARP inhibitor. In the absence of mature OS data, pERC agreed with the CGP and patients that PFS is a clinically meaningful end point in relapsed ovarian cancer given that the goals of maintenance treatment are to delay disease recurrence and chemotherapy. The Committee therefore concluded that the PFS benefit observed in the NOVA trial, which was observed irrespective of BRCA mutation status, represents a clinically meaningful improvement in PFS in the setting of recurrent ovarian cancer. The CGP, as well as the registered clinicians and the patient advocacy group providing input for this submission, all highlighted that reimbursement of niraparib would fulfil an unmet need for a maintenance treatment option in patients without BRCA mutations (BRCA wild type).

pERC deliberated the toxicity profile of niraparib and noted that the incidence of grade 3 or higher adverse events (AEs) was much higher in the niraparib group compared to placebo (74.1% versus 22.9%). The most common grade 3 or higher AEs were primarily hematologic toxicities and included thrombocytopenia, anemia, neutropenia, fatigue, and hypertension. pERC discussed that most patients in the niraparib group required a dose interruption (66.5%) or reduction (68.9%) to manage toxicities. Dose adjustments occurred early in treatment with most patients reaching their individual adjusted dose level by month four of maintenance treatment. Following a reduction in the dose of niraparib to 200 mg, which was the dose received by the majority of patients in the NOVA trial, the incidence of most grade ≥ 3 AEs decreased, except for anemia and hypertension, which decreased at a dose of 100 mg. pERC discussed that patients still derived clinical benefit despite receiving a reduced dose of niraparib. Based on these data, as well as the findings of additional exploratory analyses of the trial data related to dose and safety outcomes, pERC agreed with the CGP that a starting dose of 200 mg should be considered for patients who are at risk for AEs, including patients with body weight less than 77 kg and low platelet count (< 150,000/µL). pERC noted that the incidence of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) was low in the trial, with a similar incidence in the niraparib and placebo groups (1.4% versus 1.1%, respectively). There were no on-treatment deaths in either treatment group; however, one patient in the niraparib group and two patients in the placebo group died from AML and MDS during trial follow-up, with one death in each treatment group assessed as treatment-related by the investigator. pERC concluded that the toxicity profile of niraparib is not insignificant but can be managed through initial dosing choices and dose adjustments during the early phase of maintenance treatment.

pERC discussed the patient-reported outcome data from the NOVA trial, which was measured using the Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI), the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) health utility index (HUI) and Visual Analogue Scale (VAS), and the Chemotherapy Induced Peripheral Neuropathy (CIPN) questionnaire. The most common symptoms reported by patients were lack of energy, pain, and nausea. pERC noted that in the niraparib group, all symptoms except for nausea either remained stable or improved over treatment; however, for all of the assessed symptoms (pain, fatigue, nausea, vomiting, bloating, cramping, worry, and QoL), there were no differences between the treatment groups at any time point that met the defined minimal important difference (MID). Similarly, the results for the EQ-5D-5L and the CIPN also showed no differences that met the MID between treatment groups in either patient cohort. For both the FOSI and EQ-5D-5L, analyses demonstrated that hematological toxicity associated with niraparib had no negative effect on these measures in either patient cohort. pERC therefore concluded that patient QoL is maintained during niraparib maintenance treatment despite the higher incidence of hematologic toxicity associated with this drug.

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, and improve QoL. Many patients surveyed believe their disease was not well-managed by currently available treatments or approaches; specifically, patient respondents cited key concerns as having limited treatment options, particularly for BRCA wild-type disease, and the high risk of disease recurrence. Patients indicated that they were willing to tolerate many side effects from a new treatment if overall daily functioning and prognosis were improved. Based on the evidence from the NOVA trial, pERC agreed that niraparib aligns with patient values because it delays disease recurrence and fulfills a need for a new treatment option, particularly for patients with BRCA wild type who do not currently have a funded maintenance treatment option. pERC acknowledged that patients also value improvement in QoL. While

the NOVA trial did not demonstrate an improvement in QoL with niraparib maintenance, pERC considered that QoL was maintained in patients treated with niraparib.

In addition to the NOVA trial, pERC also deliberated the results of three indirect treatment comparisons (ITC) that compared niraparib to olaparib. Two ITCs were included as part of the submission to CADTH to inform the pharmacoeconomic (PE) model supporting the reimbursement request, and the third ITC/network meta-analysis (NMA) was identified by CADTH and requested for review. The CADTH Methods Team noted that the two ITCs included in the submission were only available in conference form and lacked important information needed to perform a thorough critical appraisal. Based on the reported results, both ITCs showed no differences in treatment effect between olaparib and niraparib for PFS. For the analyses of safety outcomes, both ITCs showed olaparib was favoured over niraparib, demonstrating lower odds of grade 3 or 4 AEs and AEs leading to dose interruption. Neither treatment was favoured over the other for the odds of AEs leading to treatment discontinuation or dose reduction. pERC discussed that based on these results, the sponsor assumed equivalent efficacy of olaparib and niraparib in terms of PFS and time on maintenance treatment. The third ITC/NMA, conducted by the sponsor of niraparib for its submission to the National Institute for Health and Care Excellence (NICE), was provided to CADTH as an unpublished report. The NICE ITC/NMA showed similar results to the ITCs provided for the PE model. pERC discussed the limitations of the NICE ITC/NMA identified by the CADTH Methods Team and agreed these limitations have the potential to bias estimates of relative treatment effect. pERC considered that these limitations apply to all three ITCs given that they considered the same trial evidence. pERC therefore concluded there is uncertainty with respect to the assumption of equivalent PFS efficacy of olaparib and niraparib based on the indirect evidence reviewed for this submission.

pERC deliberated the cost-effectiveness of niraparib compared with active surveillance in the non-germline BRCA patient population and compared with active surveillance and olaparib in the germline BRCA population per the CADTH reanalysis, which stratified results according to germline BRCA mutation status. A key limitation discussed by the Committee was the sponsor's approach to estimating OS with niraparib. Given that the OS data from the NOVA trial were immature and not utilized in the sponsor's PE analysis, the magnitude of the life-year and quality-adjusted life-year (QALY) benefit 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. The lack of direct evidence and lack of robust indirect evidence to estimate the comparative cost-effectiveness of niraparib compared with olaparib was also a concern, particularly with regards to OS. pERC therefore concluded that niraparib, at the submitted price, cannot be considered cost-effective compared with active surveillance in the non-germline BRCA population or with active surveillance or olaparib in the germline BRCA population. pERC discussed that the sponsor's base-case incremental cost-effectiveness ratio (ICER) was lower than CADTH's reanalyzed ICER estimate in the non-germline BRCA population. In both the sponsor's analysis and CADTH's reanalysis of the germline BRCA population, niraparib was dominated by olaparib (i.e., niraparib was associated with the same number of QALYs but was more expensive); therefore, results should be interpreted with caution given the uncertainty associated with the mean OS estimated for niraparib.

pERC also discussed the budget impact analysis (BIA) and noted that the factors most influencing the estimated budget impact was the eligible population size and the timing of when patients start treatment. pERC noted that the EGP considered the eligible population size calculated by the sponsor to be underestimated as they restricted the eligible population to patients with high-grade serous histology. They also noted that having patients start maintenance treatment every three months did not adhere to guidelines issued by the Patented Medicine Prices Review Board. The use of updated estimates by the EGP yielded a higher overall budget impact when compared to the sponsor's estimate. pERC also deliberated 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 (Cancer Care Ontario Gynecologic Cancers Drug Advisory Council [DAC]), which was the only stakeholder group that did not support early conversion of the Initial Recommendation to a Final Recommendation. The registered clinician group raised concerns about offering niraparib maintenance to patients who are BRCA negative and HRD negative. They argued that while this subgroup of patients was included in the non-germline BRCA mutation cohort of the NOVA trial, they expressed concerns about

whether the absolute median PFS benefit of 3.1 months (hazard ratio [HR] = 0.58; 95% confidence interval [CI], 0.36 to 0.92) was meaningful compared to the significant toxicities of the drug and the potentially huge expense, given they believe this patient group will comprise a large proportion of the patients who will be eligible for the drug. The registered clinician group also disagreed with pERC's statement that HRD testing should not be required as it is not clinically validated, and believe the contrary — that the test is essential for identifying the patients who will derive the most clinical benefit from niraparib maintenance. pERC discussed that the efficacy of niraparib in the non-germline BRCA mutation HRD-negative patient subgroup was evaluated as an exploratory analysis of the NOVA trial that was not powered to detect a difference in PFS between the treatment groups. Based on the results of the primary efficacy analysis of the trial, which demonstrated that the primary end point was met in all three pre-specified efficacy populations (germline BRCA mutation, HRD-positive non-germline BRCA mutation, and the overall non-germline BRCA mutation cohort) with a statistically significant and clinically meaningful improvement in PFS, pERC agreed with the CGP that there is no statistical justification for excluding patients who are BRCA negative and HRD negative from receiving niraparib given that they comprised part of the overall non-germline BRCA mutation cohort. As noted by the CGP, there are no data from the NOVA trial on the efficacy of niraparib in patients who are exclusively HRD negative with no BRCA mutations given that the subgroup of patients who were non-germline BRCA mutated and HRD negative included patients with somatic BRCA mutations. pERC concluded that the Initial Recommendation was based on the available evidence from the NOVA trial and clinicians can use their discretion and clinical experience when discussing 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 that the test has yet to be clinically validated in terms of predicting a response to PARP inhibitors based on specific genomic changes in HRD, the lack of standardization of available tests in Canadian centres, and its limited access and use in Canadian practice.

Additionally, following a request for clarification from PAG, CADTH conducted scenario analyses on the cost-effectiveness and budget impact to explore the impact of initiating niraparib at a 200 mg dose rather than a 300 mg dose given that a starting dose of 200 mg may be considered in patients with a body weight of less than 77 kg or a platelet count of less than 150,000/μL to reduce the risk of AEs among these patients. It is important to note that these scenario analyses only accounted for the reduction in cost associated with a reduced starting dose and did not factor in any potential changes to the efficacy or safety associated with niraparib. Initiating niraparib at 200 mg led to a lower ICER in the non-germline BRCA population. In the germline BRCA population, the scenario analysis showed that olaparib was dominated by niraparib. Initiating niraparib at a 200 mg dose reduced the budget impact of niraparib in both the germline BRCA and non-germline BRCA populations.

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 clinical and economic review panels
- input from one patient advocacy group, OCC
- input from one registered clinician group, Cancer Care Ontario Gynecologic Cancers DAC
- input from pCODR's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- one patient advocacy group, OCC
- one clinician group, Cancer Care Ontario Gynecologic Cancers DAC
- PAG
- the sponsor, GlaxoSmithKline Inc.

The pERC Initial Recommendation was to recommend the reimbursement of niraparib as monotherapy for the maintenance treatment of adult patients with recurrent 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 (Cancer Care Ontario Gynecologic Cancers 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 efficacy and safety of niraparib as monotherapy compared to standard of care (i.e., best supportive care and active surveillance, and olaparib for patients with germline BRCA mutations) for the maintenance treatment of female adult patients with recurrent epithelial ovarian cancer who are in a complete or partial response to platinum-based chemotherapy.

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

NOVA is an international, double-blind, placebo-controlled, phase III randomized trial that evaluated niraparib compared to placebo as maintenance treatment in female adult patients with platinum-sensitive, recurrent ovarian cancer. The trial was conducted in 107 sites in 15 countries, including nine sites in Canada.

Eligible patients had relapsed, predominantly high-grade serous ovarian cancer, an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1 and demonstrated sensitivity to platinum-based treatment. Patients were required to have received at least two prior platinum-based therapies. For their penultimate (i.e., second-last) platinum-containing therapy before trial enrolment, patients must have demonstrated platinum-sensitive disease following this treatment, which was defined as having a complete or partial response and disease progression more than six months after completion of the last round of platinum therapy. For their last platinum-containing therapy received before trial randomization, patients were required to have received a minimum of four cycles of treatment and, following treatment, have a complete or partial response to their last platinum regimen with observable residual disease of less than 2 cm and CA-125 values either within the normal range or a CA-125 decrease of more than 90% that was stable for at least seven days. Patients were randomized no later than eight weeks after completing their last dose of platinum-based-therapy. Patients were excluded from the trial if they had symptomatic uncontrolled brain metastases or prior treatment with a PARP inhibitor. Biomarker testing was performed for all patients to determine both their BRCA status and the status of their individual tumours for HRD.

A total of 553 eligible patients were randomized in a 2:1 ratio to receive either niraparib or placebo. Randomization occurred separately in two cohorts of patients based on the germline BRCA mutation status of the patient: 203 patients comprised the germline BRCA mutation cohort and 350 patients comprised the non-germline BRCA mutation cohort. Patients in the non-germline BRCA mutation cohort were also grouped based on HRD status and the presence of a somatic BRCA mutation; this cohort comprised patients who had HRD positive tumours and a somatic BRCA mutation (n = 47), HRD positive tumours and BRCA wild type (n = 115), and HRD negative tumours irrespective of somatic BRCA mutation status (n = 134). Randomization was stratified by the following factors: time-to-progression after the penultimate platinum therapy received before trial enrolment (six to < 12 months and ≥ 12 months), use of bevacizumab in the penultimate or last platinum regimen received, and best response during last platinum treatment (complete or partial).

Patients randomized to niraparib received a 300 mg once daily oral dose in 28-day cycles until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Patients randomized to placebo received a dose and schedule equivalent to niraparib. At the time of database lock (DBL), the median duration of study drug exposure was longer in the niraparib group compared to the placebo group at approximately nine cycles versus six cycles, respectively. Although the starting dose of niraparib was 300 mg once daily, the most commonly used dose of niraparib was 200 mg.

Patient populations: Median age ranged from 57 to 63 years; most patients had stage IIIC, serous histology, ECOG PS of 1, and two or more prior platinum therapies

In the germline BRCA mutation cohort, 138 patients were randomized to receive niraparib and 65 patients were randomized to receive placebo. The mean age of patients was 57.0 years and 58.0 years, respectively. In the non-germline BRCA mutation cohort, 234 patients were randomized to receive niraparib and 116 patients were randomized to receive placebo, and the median age of patients was 63.0

years and 60.5 years, respectively. Overall, the baseline demographic and clinical characteristics of trial patients were generally balanced between the treatment groups and by cohort. In both cohorts (range across treatment groups), the majority of patients were white (84.6% to 89.1%), had an ECOG PS of 0 (65.9% to 73.8%), stage IIIC cancer (55.4% to 63.7%), ovary as their primary tumour site (81.5% to 88.4%), and less than three metastatic sites (61.5% to 68.1%). The mean weight of patients ranged from 66.7 kg to 69.6 kg. Almost all trial patients had more than three previous lines of chemotherapy and two or more prior platinum therapies; and a small proportion of patients had prior treatment with bevacizumab (23.9% to 26.2%). The majority of patients had more than 12 months elapsed between completion of their penultimate platinum therapy and disease progression (60% to 62.1%). A similar proportion of patients in each treatment group had a complete (50% to 51.7%) or partial (48.3% to 50%) response as the best response to their most recent platinum therapy.

Key efficacy results: Statistically significant and clinically meaningful prolongation in PFS regardless of mutation status; OS data immature

The key efficacy outcome deliberated by pERC was PFS by independent central radiological and clinical review (which was the primary end point of the trial). The secondary outcomes assessed included OS, TFST, TSST, CFI, PFS-2, and patient-reported outcomes, which included the FOSI, EQ-5D-5L, and CIPN questionnaires.

Three primary efficacy populations were analyzed: the germline BRCA mutation cohort, patients who had HRD positive tumours in the non-germline BRCA mutation cohort, and the overall non-germline BRCA mutation cohort. Additional exploratory analyses were also pre-specified and performed in three subgroups of the non-germline BRCA mutation cohort: patients who had HRD positive tumours and a somatic BRCA mutation, HRD positive tumours and were BRCA wild type, and those who had HRD negative tumours.

As of the June 20, 2016, DBL, the median duration of follow-up was 16.4 months in the germline BRCA mutation cohort, 17.4 months in the non-germline BRCA mutation cohort, and 16.9 months in the full trial population. At that time, the NOVA trial met its primary end point by demonstrating a statistically significant longer duration of PFS in the niraparib group compared to the placebo group in all three primary efficacy populations. In the germline BRCA mutation cohort, median PFS was 21.0 months in the niraparib group and 5.5 months in the placebo group, corresponding to an absolute PFS benefit of 15.5 months (HR = 0.27; CI, 0.17 to 0.41; P < 0.0001). In the HRD positive non-germline BRCA mutation cohort, median PFS was 12.9 months in the niraparib group and 3.8 months in the placebo group, corresponding to an absolute PFS benefit of 9.1 months (HR = 0.38; 95% CI, 0.24 to 0.59; P < 0.0001). In the overall non-germline BRCA mutation cohort, median PFS was 9.3 months in the niraparib group and 3.9 months in the placebo group, corresponding to an absolute PFS benefit of 5.4 months (HR = 0.45; 95% CI, 0.34 to 0.61; P < 0.0001). For all three efficacy populations, the estimated proportion of patients who were progression-free at six, 12, 18, and 24 months was greater in the niraparib group compared to the placebo group. The results of all pre-specified subgroup analyses for PFS were consistent with the primary efficacy analysis results.

At the time of the June 20, 2016, DBL, OS data were immature based on a total of 95 deaths (17% maturity), with data censored for over 75% of patients in both treatment groups. The median OS was not estimable for either treatment group in the full trial population (HR = 0.74; 95% CI, 0.45 to 1.20) nor in either treatment group of any of the three primary efficacy populations. In the germline BRCA cohort, a total of 24 patients had died; this included 16 (12%) deaths in the niraparib group and eight (12%) deaths in the placebo group (HR = 0.91; 95% CI, 0.36 to 2.28). In the HRD positive non-germline BRCA mutation cohort, 30 patients had died; this included 23 deaths (22%) in the niraparib group and seven deaths (13%) in the placebo group (HR = 1.39; 95% CI, 0.57 to 3.42). In the overall non-germline BRCA mutation cohort, 71 patients had died; this included 44 deaths (19%) in the niraparib group and 27 deaths (23%) in the placebo group (HR = 0.74; 95% CI, 0.45 to 1.20). The results of the other secondary outcomes assessed (CFI, PFS-2, TFST, and TSST) were consistent with the primary efficacy analysis and all showed treatment effect estimates that favoured niraparib compared to placebo. The sponsor indicated that an update to the analysis of OS will be performed when a data maturity of 60% is achieved.

Patient-reported outcomes: QoL is maintained with niraparib maintenance

To assess health-related QoL, the FOSI, EQ-5D-5L, and CIPN questionnaires were administered at the screening visit, throughout treatment (every eight weeks through cycle 14, then every 12 weeks thereafter), at the time of study treatment discontinuation, and eight weeks after the last dose of

niraparib or placebo. If a patient discontinued treatment, patient-reported outcome data were collected at discontinuation and during a post-progression visit eight ± two weeks later. In both treatment groups of each cohort, completion rates were greater than 75% at all assessment time points up to Cycle 6; completion rates beyond this treatment cycle were not reported except for post-progression FOSI assessments. At baseline, mean FOSI scores were similar between niraparib and placebo treatment groups in both the germline BRCA mutation and the non-germline BRCA mutation cohorts; the most common symptoms reported by patients were lack of energy (79%, with 18% reporting severe symptoms), pain (44%), and nausea (22%). Scores for the individual FOSI subscales were similar between the treatment groups through the trial during both the maintenance (treatment) period and post-progression. In the niraparib group, all symptoms except for nausea either remained stable or improved over treatment. In the placebo group, approximately 20% of patients reported experiencing nausea. For all symptoms assessed there were no differences between the treatment groups at any time point that met the MID of two to three points.

At baseline, mean EQ-5D-5L HUI and VAS scores were similar between niraparib and placebo treatment groups in both the germline BRCA mutation and the non-germline BRCA mutation cohorts. Mean HUI and VAS scores were similar throughout the trial during the maintenance (treatment) period and post-progression in each treatment group and by cohort. After adjusting for histology, geographic region, age, prior treatment type, duration of previous treatment, and baseline EQ-5D-5L score, the adjusted mean HUI scores were also similar between the niraparib and placebo groups, and between-group differences were less than the MID of 0.08 when averaged across pre-progression time points.

An analysis performed to assess the relationship between hematologic AEs and response on FOSI and EQ-5D-5L (HUI and VAS) scores demonstrated that hematological toxicity had no significant effect on scores in any of the cohorts for both the unadjusted and adjusted FOSI models, or for disutility for the EQ-5D-5L HUI and VAS models.

Neuropathy, measured by the degree of tingling or numbness in the feet and hands, was similar between treatment groups at baseline in both the germline BRCA mutation cohort (feet: 59% in the niraparib group versus 60% in the placebo group; hands: 80% versus 79%, respectively) and the non-germline BRCA mutation cohort (feet: 56% in the niraparib group versus 58% in the placebo group; hands: 76% versus 74%, respectively). In the germline BRCA mutation cohort, the degree of neuropathy did not meaningfully change throughout the trial, with no differences between the treatment groups that met the MID (two to three points) during the treatment (maintenance) period and post-progression for each outcome (i.e., hands and feet). In the non-germline BRCA mutation cohort, similar results were observed; however, at post-progression, a higher proportion of patients treated with niraparib had limited to no neuropathy in the feet compared to those treated with placebo (feet: 53% in the niraparib group versus 41% in the placebo group; hands: 62% versus 62%, respectively). It is unclear whether this difference met the MID threshold for the CIPN.

Limitations: Lack of robust indirect comparison to olaparib

Two ITCs were included as part of the submission to CADTH that informed the sponsor's submitted PE model. The two ITCs compared olaparib to niraparib using data from the NOVA trial; one performed the ITC in patients with germline BRCA mutations (using olaparib data from the SOLO2 trial) and the other was performed in patients with non-germline BRCA mutations (using olaparib data from Study 19). Both ITCs, which were performed by the sponsor of olaparib, were available as conference proceedings and their results remain unpublished in full in the peer-reviewed literature. These conference sources lacked important information on patient populations and methodology that is needed to perform a thorough critical appraisal. As such, the available information from these reports was summarized along with any potential limitations that could be identified. Overall, both ITCs demonstrated that for all efficacy outcomes analyzed (investigator-assessed PFS, independent central radiological and clinical review–assessed PFS, and TFST), no differences in treatment effect were shown between olaparib and niraparib. In both ITCs, for the analyses of safety outcomes, olaparib was favoured over niraparib, demonstrating lower odds of grade 3 or 4 AEs and AEs leading to dose interruption. Neither treatment was favoured over the other for the odds of AEs leading to treatment discontinuation or dose reduction.

CADTH identified a third ITC/NMA conducted by the sponsor of niraparib for its submission to NICE, which CADTH requested to review for this submission. The ITC/NMA was provided to CADTH as an unpublished report and compared olaparib to niraparib in patients with platinum-sensitive, recurrent ovarian cancer with a germline BRCA mutation. A systematic literature search identified three trials that met the eligibility criteria and were included in the ITC/NMA; the trials evaluated the following treatments, all

compared to placebo: niraparib 300 mg daily, olaparib 300 mg twice daily, and olaparib 400 mg twice daily. Results of the ITC/NMA suggested that all active treatments were favoured over placebo for the efficacy outcome of PFS; however, none of the active treatments were favoured over each other. Results of the analyses for AEs showed similar results to the ITC provided for the PE model. The key limitations of the ITC/NMA include the small size and structure of the evidence network, which had no closed loop (therefore it was not possible to check for consistency of results between direct and indirect comparisons), and potential sources of heterogeneity across the trials related to differences in patient and study characteristics. The results of the ITC/NMA should be interpreted with caution in consideration of these limitations.

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

Overall, the incidence of all categories of treatment-emergent AEs (TEAEs) was higher in the niraparib group compared to the placebo group. No on-treatment deaths occurred in either treatment group; however, one patient in the niraparib group and two patients in the placebo group died from MDS or AML during follow-up (one death in each group was assessed as treatment-related by the investigator).

At least one TEAE occurred in all patients (100%) who received niraparib and in 95.5% of patients who received placebo; and treatment-related TEAEs occurred in 97.5% and 70.9% of patients, respectively. The most common TEAEs of any grade that occurred in the niraparib group (versus the placebo group) were nausea (73.6% versus 35.2%), thrombocytopenia (61.3% versus 5.6%), fatigue (59.4% versus 41.3%), anemia (50.1% versus 6.7%), constipation (39.8% versus 20.1%), vomiting (34.3% versus 16.2%), and neutropenia (30.2% versus 6.1%). The incidence of grade 3 or higher TEAEs was 74.1% in the niraparib group compared to 22.9% in the placebo group, of which most were hematological laboratory abnormalities, and included (niraparib versus placebo) thrombocytopenia (33.8% versus 0.6%), anemia (25.3% versus 0%), neutropenia (19.6% versus 1.7%), fatigue (8.2% versus 0.6%), and hypertension (8.2% versus 2.2%).

At least one dose interruption due to TEAEs occurred in 66.5% of patients in the niraparib group and 14.5% of patients in the placebo group; and at least one dose reduction due to TEAEs occurred in 68.9% and 5.0% of patients, respectively. The majority of dose interruptions and dose reductions in the niraparib group were attributable to thrombocytopenia (30.8% and 30.5%, respectively) and anemia (19.6% and 17.7%, respectively). The incidence of grade 3 or higher TEAEs decreased following a reduction in the dose of niraparib to 200 mg, except for anemia and hypertension, which decreased at a dose of 100 mg. Most of the hematologic laboratory abnormalities occurred within the first three treatment cycles, after which the incidence of grade 3 or 4 thrombocytopenia, neutropenia, and fatigue was infrequent beyond the cycle following dose adjustments. Treatment discontinuations attributable to TEAEs were also higher in the niraparib group at 14.7% compared to 2.2% in the placebo group. Fatigue accounted for the majority of non-hematologic TEAEs leading to treatment discontinuation in the niraparib group at 2.7% followed by nausea at 1.6%; and thrombocytopenia accounted for the majority of hematologic TEAEs leading to treatment discontinuation at 3.3%. Exploratory analyses from the NOVA trial based on baseline body weight and platelet count showed that the incidence of all categories of TEAEs (i.e., grade ≥ 3 AEs, serious TEAEs, AEs leading to dose interruption, dose reduction and treatment discontinuation) during the first 30 days of the first dose of niraparib were higher in patients with a body weight less than 77 kg or a platelet count less than 150, 000/μL, when compared to patients with a higher weight (≥ 77 kg) and platelet count (≥150, 000/μL) at baseline.

The incidence of MDS and AML was similar in the niraparib group versus the placebo group (1.4% versus 1.1%). Most patients who developed MDS and AML had a prior history of myelosuppression (eight out of nine) and had received other DNA damaging drugs and radiotherapy.

Need and burden of illness: Need for additional treatment options

Advanced ovarian cancer (stage III or IV) is associated with a high rate of recurrence and poor outcomes. Given the high rate of recurrence, maintenance strategies have been investigated in order to potentially delay or prevent recurrences and give the longest absolute increase in PFS, which is an outcome highly valued by patients. Prolonged use of cytotoxic drugs (i.e., alkylators, platinum drugs, and taxanes) has demonstrated improvements in PFS but not OS. Consequently, most patients with recurrent ovarian cancer go on active surveillance after the completion of chemotherapy. There is a significant burden of disease morbidity and mortality due to progression of cancer upon recurrence; therefore, there is a significant unmet need for additional treatment options for patients with recurrent ovarian cancer.

Registered clinician input: Unmet need in patients with BRCA wild type; olaparib considered better tolerated by patients; clinicians would like choice between PARP inhibitors

One joint submission on behalf of six oncologists from Cancer Care Ontario's Gynecologic Cancers DAC provided input on niraparib for the maintenance treatment of female adult patients with recurrent epithelial ovarian cancer who are in a complete or partial response to platinum-based chemotherapy. The registered clinicians noted that there is a large unmet need in the population of patients who are non-BRCA mutated; and for patients with a BRCA mutation, olaparib is a treatment option. Overall, the clinicians stated that although there are no head-to-head data comparing olaparib and niraparib, treatment efficacy appears similar between the two drugs, and olaparib may be slightly more tolerable. They also felt that olaparib has a more established safety profile, and that many patients will not be able to tolerate the 300 mg dose of niraparib due to toxicity. Nevertheless, the DAC noted that they would appreciate having a choice between PARP inhibitors.

PATIENT-BASED VALUES

Experience of patients with ovarian cancer: Fear of disease recurrence and limited treatment options

OCC provided input on niraparib for the maintenance treatment of female adult patients with ovarian cancer who are in a complete or partial response to platinum-based chemotherapy. Input from patients living with ovarian cancer and their caregivers was elicited through an anonymous online survey conducted from November 26, 2019, to January 15, 2020. A total of 56 people responded to the survey, including 51 patients with ovarian cancer and five caregivers, none of whom had received or cared for a patient who had experience with niraparib. From the patient's perspective, ovarian cancer impacts many aspects of life, including sexual relationships, work life, well-being, and sleep. Caregivers reported that their work life and sleep patterns were most negatively impacted. Many patients surveyed believe their disease was not well-managed by currently available treatments or approaches, and they cited disease recurrence and limited treatment options, particularly for BRCA wild-type disease, as key concerns. Patients and caregivers felt that the side effects of current chemotherapy treatments, including fatigue, neuropathy, and hair loss, have a very or extremely negative impact on their lives.

Patient values, experience on or expectations for treatments: Prolonging OS, lengthening time to recurrence, and improvement in QoL

In terms of patients' values and expectations for new treatments, lengthening time until recurrence, prolonging survival, and improving QoL were identified as being highly or extremely important. Patients indicated they were willing to tolerate many side effects of a new treatment (i.e., tiredness, taste changes, nausea, anemia or bruising, headaches, and bowel problems) if overall daily functioning and prognosis were improved, and patients' cited that they were least willing to tolerate side effects such as bone marrow problems or blood cancer, respiratory problems, infections, and high blood pressure. Most respondents believed niraparib should be available as a treatment option in Canada for women who have ovarian cancer, and OCC highlighted the need for new treatments in this population.

ECONOMIC EVALUATION

Niraparib is available as a 100 mg capsule. The recommended starting dose of niraparib is 300 mg once daily, until progression or unacceptable toxicity. In the NOVA trial, patients initiated treatment at 300 mg once daily, but, with dose reductions, the average daily dose was reduced to approximately 200 mg at five months, after which it remained relatively constant. At the sponsor's submitted price of $131.79 per 100 mg capsule, the daily cost per 300 mg and 200 mg dose of niraparib is $395.36 and $263.57, respectively. The 28-day cycle cost for a 300 mg and 200 mg dose is $11,070 and $7,380, respectively.

The sponsor submitted a cost-utility analysis assessing niraparib in women with high-grade serous, recurrent epithelial, fallopian tube, or primary peritoneal cancer who are in complete or partial response to their most recent platinum-based chemotherapy. Niraparib was compared with olaparib and active surveillance in the germline BRCA population, and with active surveillance in the non-germline BRCA population. A decision analytic model was developed in Microsoft Excel with three health states: progression-free disease; progressed disease; and, death. The model estimated the mean number of years

of PFS, post-progression survival, OS, and time on maintenance therapy (TOMT) associated with each comparator. Mean post-progression survival was estimated as the difference between mean PFS and mean OS. The mean number of years in progression-free disease and progressed disease were then multiplied by the associated health state utility values and costs to estimate the cost-effectiveness of niraparib. Time to treatment discontinuation (TTD) was used to estimate the mean TOMT, which was used to calculate total maintenance treatment acquisition costs. Mean PFS, OS, and TOMT were estimated by fitting parametric survival distributions to individual patient data from the NOVA trial (for PFS and TTD) and reconstructed individual patient data from Study 19 (for OS). Niraparib and olaparib were assumed to be equal in terms of PFS and TTD. Given that OS data in the NOVA trial was immature, the sponsor derived mean OS for niraparib as the sum of mean OS for active surveillance (derived from Study 19) plus the expected gains in OS associated with maintenance treatment compared with active surveillance. Expected gains in OS were calculated as the gain in PFS between niraparib and active surveillance (derived from the NOVA trial) multiplied by the ratio of OS benefit to PFS benefit (derived from Study 19). The ratio of OS benefit to PFS benefit was calculated using data from Study 19, by taking the difference in mean PFS years and OS years between olaparib and active surveillance and then taking their ratio. The sponsor therefore assumed an OS benefit to PFS benefit ratio of 2:1.

CADTH identified the following key limitations in the sponsor's submitted economic analysis:

- The model structure used was inappropriate as it did not incorporate transitions between health states at different time points, as would a typical partitioned survival analysis.
- OS data from the NOVA trial were immature and not utilized in the sponsor's PE model. Consequently, the sponsor made assumptions regarding the application of olaparib OS data for niraparib.
    - Whether olaparib and niraparib are equivalent in terms of OS is unknown as there is no clinical evidence, direct or indirect, comparing OS between these treatments.
    - Study 19 (for olaparib) and the NOVA trial had differences in baseline characteristics, meaning that one may not expect to see the same results in OS had niraparib been used in Study 19 or olaparib in the NOVA trial.
    - The validity of the correlation between PFS and OS is uncertain. Aside from the previously described approach using mean PFS and OS data from Study 19, no other data were submitted to support the relationship between PFS benefit and OS benefit.
- It was assumed that niraparib and olaparib were also equal in terms of PFS and TOMT. The Clinical Guidance Report identified several limitations in the sponsor's ITC/NMA; however, the sponsor's assumption of equal efficacy for PFS between niraparib and olaparib may be reasonable according to the clinical experts consulted by CADTH. No evidence was submitted to support the assumption for TOMT.
- The sponsor's chosen parametric survival functions overestimated the percentage of patients remaining progression-free beyond the NOVA trial period for both niraparib and active surveillance, according to the clinical experts consulted by CADTH.
- CADTH had concerns regarding the selection of parametric functions of various outcomes.
    - The choice of parametric functions for TTD resulted in more patients in the non-germline BRCA population remaining on active surveillance than in the germline BRCA population in the post-trial period, which the clinical experts consulted by CADTH determined to be unlikely.
    - The choice of parametric survival functions for OS with active surveillance likely overestimated the percentage of patients remaining alive beyond the trial period (of Study 19) according to the clinical experts consulted by CADTH.
- The sponsor's time horizon was not reflective of a lifetime horizon (up to when OS ≤ 1%). At the sponsor's time horizon of seven years, 7% and 13% of patients receiving active surveillance in the non-germline BRCA and germline BRCA populations, respectively, were still alive.
- The implementation of niraparib dose reductions led to illogical average daily doses (i.e., doses that were not in increments of 100 mg, which is the smallest strength size supplied).

To account for these limitations, CADTH considered: a 1:1 ratio of OS benefit to PFS benefit when estimating mean OS for niraparib; alternative parametric distributions to extrapolate PFS, TTD, and OS beyond the provided trial data; and a lifetime horizon of 13 years. Additionally, a calculation error for the dose of niraparib used in cycle five and beyond was corrected. Some identified limitations could not be addressed, including the uncertainty regarding the assumption of equal efficacy between niraparib and olaparib and the illogical average daily doses of niraparib. In the CADTH reanalysis, the ICER of niraparib compared with active surveillance was $194,360 per QALY gained in the non-germline BRCA population. In the germline BRCA population, niraparib remained dominated by olaparib, as per the sponsor's results (i.e., niraparib was as effective as olaparib but more costly). Price reductions of 76% and 61% would be required for niraparib to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained in the non-germline BRCA and germline BRCA populations, respectively, when compared with active surveillance.

Given that the OS data in the NOVA trial were immature and not utilized in the sponsor's pharmacoeconomic model, the OS estimates used in the model for both the non-germline BRCA and germline BRCA populations are highly uncertain. It remains unknown whether there is an OS benefit associated with niraparib compared with active surveillance. There is no data to support that niraparib and olaparib will be equal in terms of OS as no direct treatment comparisons or ITCs have been conducted.

ADOPTION FEASIBILITY

Considerations for budget impact and implementation: Submitted BIA is underestimated
The sponsor provided a BIA, based on an epidemiological approach, from the perspective of national and provincial health care payers to show the three-year potential budgetary impact of the introduction of niraparib for women with high-grade serous, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. The sponsor included drug costs only and excluded all other health care system costs. The reference scenario included the following treatments: active surveillance for the full and non-germline BRCA populations and olaparib and active surveillance for the germline BRCA population. The new drug scenario included the same comparators with the addition of niraparib.

Treatment dosages for niraparib and olaparib were based on exposure data from the NOVA and SOLO-2 trial data, respectively. The sponsor assumed that patients would start treatment with a 300 mg dose of niraparib, which could then be reduced based on toxicity and/or AEs. It was assumed that every three months 25% of the annual eligible patient population would start treatment and that 100% of patients with high-grade serous ovarian cancer at stage III and IV would receive platinum-based therapy. The proportion of patients with a germline BRCA mutation in the eligible population at second-line therapy was assumed to be 37% based on the NOVA trial.

The Economic Guidance Panel identified the following key limitations with the sponsor's BIA:

- The average daily dose of niraparib remained constant after 12 months, which was not aligned with the pharmacoeconomic analysis, in which the dose of niraparib was reduced to approximately 200 mg at month five, after which it remained constant.
- According to the clinical experts consulted by CADTH, the sponsor's assumption that 100% of patients with stage III and IV ovarian cancer would receive platinum-based therapy was an overestimate. The experts indicated that 10% of patients would likely receive no form of treatment.
- The patient population in the submitted BIA was not aligned with the Health Canada indication, which did not include the stipulation that patients must have ovarian cancer with high-grade serous histology.
- The initiation of treatment for patients every three months does not adhere to the guidelines issued by the Patented Medicine Prices Review Board.
- The proportion of patients with the germline BRCA mutation at second-line therapy was assumed to be 37%, which is higher than what was reported in a Canadian cross-sectional study.
- The clinical experts consulted by CADTH noted that patients with non-germline BRCA and germline BRCA have different characteristics and that it may be beneficial to present the split population budget impacts.

CADTH reanalyses included removing the restriction for patients with high-grade serous disease only, aligning the niraparib dose from month 5 onwards with the dose applied in the pharmacoeconomic analysis, correcting the proportion of patients who receive first-line platinum-based chemotherapy, and correcting the timing of starting therapy so patients begin treatment once annually. The CADTH reanalysis suggests that the sponsor underestimated the budget impact of introducing niraparib to the market by 16.4% in the full population. Supplemental split results for the non-germline BRCA and germline BRCA populations were also presented.

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	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. Avram Denburg, Pediatric Oncologist	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.

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	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. Avram Denburg, Pediatric Oncologist	Dr. Marianne Taylor, Oncologist
Dr. Jennifer Bell, Bioethicist	Dr. W. Dominika Wranik, Health Economist

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

- Dr. Avram Denburg, who was not present for the discussion and deliberation on niraparib (Zejula) for ovarian cancer
- Dr. Maureen Trudeau, who did not vote due to her role as the pERC Chair.

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 niraparib for ovarian cancer, through their declarations, no pERC members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, therefore no member was excluded from voting. For the Final Recommendation, no members had a real, potential, or perceived conflict, and, based on application of the pCODR Conflict of Interest Guidelines, none of the members were excluded from voting.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the pCODR Disclosure of Information Guidelines.

Use of this Recommendation

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

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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	
PAG is seeking clarity on the definition of "partial response" to be used in clinical practice.	pERC agrees with the CGP that the definition of "partial response" as described by RECIST version 1.1 should be used in clinical practice.
PAG is seeking clarity on whether the following patient subgroups should be eligible for niraparib:	
• Diagnosis other than high-grade serous histology	• pERC agrees that it is reasonable to consider niraparib for any high-grade histology based on the eligibility criteria of the NOVA trial, which specified that patients have predominantly high-grade serous histology. pERC agrees with the CGP that the NOVA trial results are not be generalizable to low-grade cancer (i.e., low-grade serous cancer).
• Known to have BRCA mutation that is other than germline (germline BRCA mutation) (i.e., somatic); patients without or unknown BRCA or HRD mutation	• Based on the results of pre-specified subgroup analyses of PFS, all patients in the NOVA trial derived benefit from treatment with niraparib regardless of mutation status and therefore should be eligible for treatment with niraparib.
• Has received fewer than two previous courses of platinum-containing therapy	• pERC agreed that the number of prior lines of platinum-containing therapy should align with the NOVA trial eligibility criteria; therefore, at least two previous courses of platinum-containing therapy are required to be eligible for niraparib (i.e., first course is for first-line therapy and the second course is for recurrence).
• Has received two previous courses of platinum-containing chemotherapy and has disease that was considered platinum sensitive following the penultimate (next to last) platinum course (more than six month period between penultimate platinum regimen and progression of disease) but it has been more than eight weeks since completion of the last platinum regimen. If yes, what is the maximum time frame since last platinum treatment?	• pERC agrees with the CGP that certain circumstances (e.g., logistics and chemotherapy side effects) may prevent the initiation of niraparib within eight weeks of the last platinum-based therapy, as per the NOVA trial. Therefore, pERC agrees that it is reasonable to initiate niraparib within 12 weeks of the last chemotherapy treatment. If more than eight weeks have elapsed from the last chemotherapy treatment, consideration should be given to exclude disease progression before starting maintenance therapy, as patients who have had disease progression should not be treated with niraparib maintenance. At the time of implementing a reimbursement recommendation for niraparib, jurisdictions may consider addressing the short-term, time-limited need to offer niraparib to patients who are currently on active surveillance. Patients who have completed at least two prior lines of platinum-based chemotherapy and are in response to their most recent platinum-based chemotherapy regimen should initiate niraparib within 12 weeks of their last dose of platinum-based chemotherapy.
• ECOG > 1	• pERC agrees with the CGP that a distinction should be made among patients with an ECOG PS of greater than 1, in recognition that a patient's PS status may be due to lingering side effects from chemotherapy and/or due to non-modifiable factors (e.g., comorbidities). In clinical practice, patients with an ECOG PS of 0 to 1, as well as patients with an ECOG PS of 2, may improve in functional status in the

	short term and therefore may benefit from maintenance therapy with niraparib.
• Received prior treatment with a known PARP inhibitor	• Based on the NOVA trial eligibility criteria, patients who have progressed on a prior PARP inhibitor, regardless of treatment line (i.e., first line or relapsed setting), are not eligible for treatment with niraparib.
• Symptomatic uncontrolled brain metastasis	• Patients with symptomatic uncontrolled brain metastases were excluded from the NOVA trial; therefore, maintenance therapy with niraparib should not be offered to these patients.
• Are allergic or unable to tolerate platinum-based chemotherapy and would therefore have received non-platinum therapy	• pERC agrees with the CGP that it is reasonable to consider niraparib in a patient who has had non-platinum therapy due to an inability to complete platinum therapy (e.g., allergy), provided that the patient has had a response and otherwise meets the criteria for maintenance with niraparib. pERC noted that jurisdictions will have to assess each individual patient on a case-by-case basis to determine if a patient can receive niraparib.
• If patients discontinue niraparib at their request without experiencing disease progression, and then experience disease progression, but are considered platinum sensitive and receive a third course of platinum chemotherapy and are in response (complete or partial)	• pERC agrees with the CGP that if patients have tried a PARP inhibitor previously but discontinued due to intolerance or other reasons without disease progression, then it would be reasonable to try a maintenance strategy after chemotherapy, provided that patients have platinum-sensitive disease and can tolerate the niraparib.
PAG is also seeking to clarify whether patients who are currently receiving olaparib with BRCA mutation (whether germline or somatic) with intolerance could be considered for a treatment switch to niraparib. PAG would like to clarify that patients who had prior treatment with a PARP inhibitor are not eligible for niraparib (unless due to switching because of intolerance).	Patients who previously discontinued a PARP inhibitor due to intolerance or patient preference (e.g., treatment break or holiday) in the absence of disease progression may consider maintenance therapy with niraparib after demonstrating a complete or partial response to platinum-based chemotherapy, provided that it is thought that the patient will tolerate niraparib. Patients who have progressed on a prior PARP inhibitor in any treatment line would not be eligible for niraparib based on the NOVA trial eligibility criteria.
Implementation factors	
The recommended dose of niraparib monotherapy is 300 mg (three 100 mg capsules) taken orally once daily. For those weighing less than 58 kg, a starting dose of 200 mg may be considered to reduce grade 3 or 4 AEs, as per the proposed product monograph. PAG is seeking guidance on the recommended starting dose for patients with low body weight (e.g., < 58kg)?	The Health Canada product monograph states that for patients who have low body weight (< 58 kg), a starting dose of 200 mg once daily can be considered. However, based on the observation that the majority of trial patients in the NOVA trial required a dose interruption and dose reduction, and additional analyses of the trial data by baseline weight (< 77 kg versus ≥ 77 kg) that showed that the starting dose of 200 mg reduced the incidence of AEs and other safety outcomes without compromising efficacy, pERC agreed with the CGP that the starting dose of 200 mg should apply to patients who weigh less than 77 kg.
PAG is seeking confirmation that niraparib treatment should be continued until disease progression or unacceptable toxicity.	Niraparib maintenance treatment should be continued until disease progression or unacceptable toxicity, as per the NOVA trial protocol and the Health Canada product monograph.
PAG is seeking to confirm that the minimum number of cycles required of second or	pERC agreed that at least four cycles of platinum-containing chemotherapy should be given prior to starting niraparib

subsequent lines of platinum-based therapy prior to starting maintenance therapy with niraparib is four, as per the NOVA trial.	maintenance therapy to be consistent with the NOVA trial eligibility criteria.
Sequencing and priority of treatment	
Olaparib recently received an initial positive recommendation for reimbursement for 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 the SOLO1 trial. PAG is seeking clarity for place in therapy for niraparib:	
• For patients who may receive olaparib after first-line platinum-based treatment, should they receive another PARP inhibitor upon progression (i.e., niraparib)? Would the use of niraparib be time sensitive (i.e., duration of use more than or less than two years)? If yes, what is the reasonable time frame from time of completion of maintenance to progression that would make patients qualify for re-treatment?	• pERC agrees with the CGP that there is currently no evidence to support re-treatment with a PARP inhibitor after disease progression on a prior PARP inhibitor.
• Would sequencing between olaparib and niraparib be permitted as maintenance progression options? If yes, which would be the preferred therapy? What patient or disease factors will lead to a preference of niraparib over olaparib?	• pERC agrees that a switch between olaparib and niraparib would likely not be considered as a maintenance progression treatment option as the two drugs have a similar mechanism of action. pERC is not aware of evidence to inform the sequencing of these drugs.
Companion diagnostic testing	
PAG is seeking guidance as to whether one or both of BRCA and/or HRD testing is/are required to identify eligible patients for niraparib. PAG is seeking guidance on whether eligibility for niraparib should be extended to all patients regardless of BRCA status (i.e., germline BRCA mutation and non-germline BRCA mutation) or to specific HRD subgroups? If BRCA testing is required, would both germline and somatic testing be recommended? Is testing for somatic BRCA testing required for those with a negative germline BRCA mutation? If BRCA status was determined earlier in the diagnosis and treatment, is BRCA (both germline and somatic) testing required to be repeated to determine eligibility for niraparib?	pERC agrees with the CGP that all patients should have at least germline BRCA testing at baseline regardless of treatment consideration, as it has important implications as a predictive marker and for identification of a hereditary cancer gene. However, a treatment benefit with niraparib was observed regardless of BRCA status; therefore, all patients should be offered niraparib maintenance therapy based on the evidence from the NOVA trial. HRD testing should not be required to receive niraparib as this test has not yet been clinically validated.

AE = adverse events; CGP = Clinical Guidance Panel; ECOG = Eastern Cooperative Oncology Group; HRD = homologous recombination deficiency; PAG = Provincial Advisory Group; PARP = poly adenosine diphosphate–ribose polymerase; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PS = performance status; RECIST = response evaluation criteria in solid tumours.