CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Registered Clinician Feedback on a pCODR Expert Review Committee Initial Recommendation

Olaparib (Lynparza) for Ovarian Cancer

September 29, 2016

1 Feedback on pERC Initial Recommendation: GOC Clinician Feedback

Name of the drug indication(s):	Olaparib as monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy
Name of registered clinician(s):	Dr.'s Walter Gotlieb, Alon Altman, Michael Fung Kee Fung, Katia Tonkin, James Bentley, Susia Lau, and Shaundra Popowich

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the registered clinician(s) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part __**X**__ disagree

Please explain why the registered clinician(s) agrees, agrees in part or disagrees with the initial recommendation.

GOC was very surprised and respectfully but strongly disagrees with pERC's initial negative recommendation for the first Parp-inhibitor, Olaparib. It appears that pERC was not confident that there is a net clinical benefit of olaparib maintenance treatment compared with placebo. Following a detailed analysis at a National Communities of Practice Meeting, GOC published a position statement on February 9 2015, that reached consensus amongst our membership, strongly endorsing the net clinical benefit of olaparib in the women following relapsed ovarian cancer. Olaparib achieves primary goals of maintenance therapy (PFS and OS), maintains QoL compared to placebo, and addresses the critical unmet need and gap in treatment that is present in women suffering from ovarian cancer.

GOC would like to emphasize the complexity of relapsed ovarian cancer and challenges faced by women with this devastating disease and their caregivers. Most patients will present with advanced disease and unfortunately have a poor prognosis, despite good response rates to initial therapy. Recurrence is unfortunately likely in around 80% of women, and no cures are expected following recurrence. Timely access to emerging cancer therapies profoundly affects the lives of women with ovarian cancer. There has been a lack of significant progress in treatment options for ovarian cancer for two decades, heightening the urgent unmet need that must be addressed for patients with this disease.

To date, olaparib has been evaluated by a number of other countries worldwide with the same Study 19 trial results as presented to pERC and is accessible to patients. This

negative recommendation by pERC places Canadian women with BRCA-mutated ovarian cancer at a significant disadvantage compared to other women around the world. GOC genuinely hopes that the members of pERC will reconsider their recommendation by reassessing the clinical data in the context of the significant unmet need in the interest of women with incurable ovarian cancer resulting from BRCA mutations, as the caregivers who treat ovarian cancer have all witnessed the benefits of this oral medication with excellent tolerance.

b) Notwithstanding the feedback provided in part a) above, please indicate if the registered clinician(s) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.	_**X**___ Do not support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.	Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
8	Overall Clinical Benefit	4	When reviewing the recommendation, GOC identified a misunderstanding of the clinician feedback we initially submitted. The pERC recommendation, by mistake, stated that GOC recommended use of olaparib following first-line chemotherapy. GOC would like to clarify that we are aligned to the indication that was approved by Health Canada, i.e. that olaparib is to be used as maintenance treatment for patients after relapse (at least 2 prior lines of chemotherapy) who have responded to their last round of chemotherapy and remain sensitive to platinum-based chemotherapy.
7	Key Efficacy Results	4	*RE: SOLO 2 data results basis of resubmission.*
8	Registered Clinician Input	4	*RE: Study 19 pERC greatly limited in drawing conclusions on the magnitude of PFS and OS benefit given the considerable limitations of the trial design.* Given the significant unmet need in this space for new treatment options and the devastating symptoms that

			patients experience at recurrence of symptomatic disease, GOC strongly disagrees that pERC should wait until results from SOLO2 are available. In event driven trials, there is no certainty as to when data will read out, and women with recurrent ovarian cancer cannot afford the luxury of waiting what could be two years. In addition, presently available data already provides sufficient evidence on the overall net benefit of olaparib. Olaparib achieves the primary treatment goal of significantly extending the progression-free interval in the maintenance setting after treatment of recurrent disease, maintains QoL, has a manageable safety profile and provides a clinically meaningful survival benefit of 4.7 months in the BRCA-mutated subgroup. In addition Study 19, that is a randomized phase II trial, already provided clear survival benefit at 70% maturity for patients with the BRCA mutation.
8	Registered Clinician Input	4	*RE: Disease Burden* There is currently no standard maintenance therapy given to patients and the standard practice after response is observed in patients it to keep patients in "watch and wait" until further disease progression occurs. With each subsequent recurrence of disease, the response rate to chemotherapy declines and the progression free interval shortens. Delaying symptomatic relapse is clinically meaningful since patients suffer tremendously with the symptoms of the recurrent disease, which include bowel obstructions, abdominal pain, nausea and vomiting, and distension by ascites requiring repeated paracentesis. GOC would like to emphasize that since recurrent disease is not curable, the goal of therapy focuses on the treatment of a chronic finite disease. As such, treatment goals in recurrent ovarian cancer are to: ▪ Improve QoL by extending the symptom-free interval ▪ Increase progression-free interval ▪ Reduce symptom intensity ▪ If possible, prolong life *RE: Clinicians also indicated that Olaparib has improved toxicity compared with chemotherapy; however, the Committee was unable to comment on this comparison as the evidence in Study 19 is in a setting where the clinical alternative is watch and wait.*

			In addition, the current chemotherapeutic regimens for recurrent ovarian cancer are associated with significant toxicities. For patients who have relapsed, treatment with an oral agent provides a manageable, tolerable alternative to continued chemotherapy. Extending response and delaying the burden of further chemotherapy is an important benefit for women with recurrent ovarian cancer. GOC would like to note that maintenance therapy is not a new concept in ovarian cancer but until now, no other treatments (i.e. chemotherapy) were suitable as a maintenance therapy.
7	Key Efficacy Results: PFS and OS in Recurrent Ovarian Cancer	4	*RE: Study 19 and pERC greatly limited in drawing conclusions on the magnitude of PFS and OS benefit given the considerable limitations of the trial design.* Not only is progression-free survival a primary goal of treatment in ovarian cancer, but GOC in agreement with the consensus reached in Tokyo in November 2015 by the GCIG (Gynecologic Cancer Intergroup), would like to highlight PFS as an appropriate primary endpoint in ovarian cancer clinical trials. PFS of sufficient duration and acceptable safety fulfills an unmet need. Olaparib achieves the primary goal of maintenance treatment which is to delay progression, ultimately extending the time period over which patients feel better. Olaparib treatment led to a clinically significant benefit in PFS in patients with BRCA-mutated disease, with a median PFS for olaparib-treated patients that was approximately 7 months longer than for placebo ('watch and wait') patients. Olaparib is an extremely valuable treatment with long-term data to demonstrate the benefit. In particular, many GOC members are continuing to treat patients ("long-term responders") that have demonstrated years of progression free survival on olaparib maintenance therapy, something we had not seen before with conventional chemotherapy. It is difficult to demonstrate overall survival in clinical trials of ovarian cancer, where multiple recurrences, crossover and post-progression therapies can confound this endpoint. Despite the difficulty in assessing overall survival, olaparib demonstrated a clinically meaningful survival benefit of almost 5 months. Due to crossover, the survival benefit is likely greater than that observed in Study 19. pERC indicated there is uncertainty in overall

			survival. It is important to underline that survival became statistically significant at the third analysis time-point, when 70% maturity was reached, and that the BRCA status analysis was pre-planned and performed post hoc. This seems to have caused problems in the review process with regards to statistical interpretation and the number of events that are needed. Indeed, in ovarian cancer, patients with platinum sensitive disease represent a group of patients with better prognosis. As a result, the number of overall survival events would be small and delayed. Therefore, the ability to reach statistical significance at an early stage would be minimal. Only with sufficient follow-up would enough events have occurred. It's not that there was an anomaly at the third look as the hazard ratio on the three analysis didn't change but the number of events did so that statistical significance was finally reached in the BRCA-mutated population and significant follow-up for approximately 6 years which clearly demonstrates the continued survival benefit of olaparib.
8	Overall Clinical Benefit: Safety	1	*RE: pERC agreed this increased incidence of grade 3 or higher AE's with Olaparib is meaningful.* GOC not only believes that olaparib is clinically effective, it also has an acceptable safety profile. Olaparib is well tolerated with manageable adverse events. The long-term responders from Study 19 who are still receiving oral treatment with olaparib and who we follow in clinic illustrate the safety profile of olaparib. The side-effects are easily managed with dose interruptions alone, but if they are not, then dose reduction usually resolves the problem. There is also remarkable compliance of nearly 100% for olaparib in Study 19. The only additional monitoring that would be required for olaparib is a CBC, to monitor for MDS or AML, that have also been associated with the chemotherapies that these patients received.

3.2 Comments Related to the Registered Clinician(s) Input

Please provide feedback on any issues not adequately addressed in the initial recommendation based on registered clinician(s) input provided at the outset of the review on outcomes or issues important that were identified in the submitted clinician input. Please note that new evidence will be not considered during this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR program.

Examples of issues to consider include: Are there therapy gaps? Does the drug under review have any disadvantages? Stakeholders may also consider other factors not listed here.

Page Number	Section Title	Paragraph, Line Number	Comments related to initial registered clinician input
8	Need: Active maintenance treatment to prolong PFS and time to next treatment	2	Most women with BRCA associated ovarian cancer recur, and will undergo repeated cycles of chemotherapy with decreasing response rates and shrinking progression free survivals, ultimately dying of the disease. Timely access to emerging cancer therapies are desperately required, and represent an urgent unmet need. With the results available, Canadian women with BRCA-mutated ovarian cancer should not be at a significant disadvantage compared to other women around the world. Health Canada and the EMA did not share the concerns raised, using the exact same data. Olaparib meets the unmet need in ovarian cancer and fills a current gap in treatment. Any delay in patients receiving access to olaparib while pERC waits for more data might be interpreted as neglect to the women affected by ovarian cancer.
7	Patient Reported Outcomes	5	*RE: pERC agreed that results from Study 19 suggest Olaparib showed no decrement of QoL, which pERC considered to be reasonable in the setting of maintenance treatment.* The addition of olaparib, an oral therapy that can be taken at home, in a maintenance setting in which patients are already in response to their platinum-based chemotherapy results in no detrimental impact on health-related QoL scores. Importantly, olaparib maintains QoL for patients receiving olaparib compared to placebo in patients with BRCA-mutated ovarian cancer. It is not expected that an improvement in QoL would be seen, because all patients had responded to the chemotherapy which maximized their response and reduced tumour burden, and so all patients in both arms of the trial started out with a high performance status and no symptoms due to tumor burden. Using olaparib at this stage as a maintenance therapy is intended to maintain the progression-free interval and quality of life.

3.3 Additional comments about the initial recommendation document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

About Completing This Template

- The following template form should be used by the registered clinician(s) to submit input at the beginning of a drug review. Please note that there is a separate template for providing feedback on an initial recommendation.

- The clinician(s) **must be registered with the pCODR program** to provide input. (See https://www.cadth.ca/pcodr/registration for information on eligibility and registration.)

- The registered clinician(s) must also complete the *pCODR Clinician Conflict of Interest Declarations Template* when providing input at the beginning of a drug review (see Appendix A of this document). While CADTH encourages collaboration among registered clinicians and that feedback submitted for a specific drug or indication be made jointly, each registered clinician must complete their own separate *pCODR Clinician Conflict of Interest Declarations Template*.

- Please ensure that the input is in English, and that it is succinct and clear. Please use a minimum 11-point font and do not exceed six (6) typed, 8 ½″ by 11″ pages. If a submission exceeds six pages, only the first six will be considered.

- The registered clinician(s) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the registered clinician(s) should not feel restricted by the space allotted on the form and can expand the tables in the template as required. The categories and questions outlined are only examples, to guide identification of relevant clinical factors for pERC's consideration. Please note that comments may be attributed to a specific individual clinician and that registered clinicians who submit input will be identified as a contributor to the specific input. CADTH's pCODR program maintains the discretion to remove any information that may be out of scope of the review.

- It is important to note that scientific published references are not required, as pCODR has access to current scientific literature through the manufacturer's submission, tumour groups, and a rigorous, independent literature search.

- The registered clinician(s) must be submitted by the **deadline date** for this drug, posted on the pCODR section of the CADTH website under *Find a Review* so that it can be available in time to be fully used in the pCODR review process. If more than one submission is made by the same registered clinician(s), only the first submission will be considered.

- In addition to its use in the pCODR process, the information provided in this submission may be shared with the provincial and territorial ministries of health and Provincial cancer agencies that participate in pCODR, to use in their decision-making.

Should you have any questions about completing this form, please email submissions@pcodr.ca