CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Sponsor)

Olaparib (Lynparza) for Newly Diagnosed Ovarian Cancer

December 5, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Olaparib (Lynparza) for newly diagnosed ovarian cancer
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Submitter and Manufacturer AstraZeneca Canada

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

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☒ agrees in part ☐ disagree

AstraZeneca agrees with pERC's Initial Recommendation to reimburse olaparib for newly diagnosed ovarian cancer (OC) based on the statistically significant and clinical meaningful improvement in progression-free survival (PFS), no appreciable detrimental effect on quality of life (QoL), and manageable toxicity profile as demonstrated in the SOLO-1 trial. AstraZeneca also agrees with pERC's assessment that "there is an unmet need for a new, effective therapeutic option in ovarian cancer" as "more than 80% of patients with stage III or IV ovarian cancer, and almost all of those who have suboptimal bulking or no debulking, relapse with incurable cancer."

Patients with newly diagnosed advanced ovarian cancer are the only patients with ovarian cancer in whom treatment has curative potential.[1] Thus, first-line treatment for women with newly-diagnosed advanced OC is **curative in intent.** In contrast, recurrent OC is considered incurable and treatment goals focus on preserving QoL and extending time to progression and time free from chemotherapy, rather than on cure.[2,3,4,5]

The results from SOLO-1 demonstrate the clear benefit of olaparib in the front-line setting through substantial, practice-changing, efficacy gains and by providing exceptional benefit beyond the end of treatment. The magnitude of clinical benefit observed with olaparib versus current standard of care (watch and wait) is unprecedented in this disease setting, with a 70% reduction in the risk of progression or death, and a minimum estimated 3-year improvement in PFS with olaparib versus placebo.

Given the substantial benefit associated with olaparib in the front-line setting, AstraZeneca appreciates that pERC a) recommends consideration be given to providing access to olaparib for patients on non-platinum-based chemotherapy on a case-by-case basis; b) recognizes there may be a time-limited need to offer to switch patients currently being monitored or receiving maintenance bevacizumab to olaparib when reimbursement is implemented; and c) supports the need for access to reflex testing (tumour or germline) at diagnosis for BRCA-mutation status to identify patients that may benefit from olaparib treatment.

Criteria for olaparib use

To provide further clarity for clinicians and payers, and to allow identification of all eligible patients who may benefit from olaparib treatment in the front-line setting, AstraZeneca is requesting the following additions and revisions be made to the criteria for olaparib use:

1. As per the Clinical Guidance Panel (CGP) report and pERC's response to PAG questions in the Initial Recommendation which highlight that multiple factors such as chemotherapy side effects and treatment logistics can prevent some eligible patients from starting olaparib within eight weeks as mandated in SOLO-1, the statement "Maintenance therapy with olaparib should begin within eight weeks of the last dose of platinum-based chemotherapy" (page 1, paragraph 3) should be revised to within 12 weeks of the last dose of platinum-based chemotherapy. This also aligns with the olaparib Product Monograph which does not specify treatment must begin within a set period of time following completion of first-line platinum-based chemotherapy. In addition, the following statement could be added: "If more than eight weeks has elapsed, consideration should be given to exclude disease progression before starting maintenance therapy" to provide further clarity.
2. The statement regarding treatment duration "Treatment should continue until unacceptable toxicity, disease progression, or completion of two years of therapy" (page 1, paragraph 3) should have "whichever comes first" added to the end to provide greater clarity regarding when olaparib treatment should be discontinued.
3. To align with pERC's recommendation (page 11, row 1), the addition of the following statement to page 1, paragraph 3, would provide clear guidance regarding the administration of olaparib: "Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years."

Cost-effectiveness analysis

AstraZeneca believes the broad ICER range and choice of upper bound ICER cited by pERC in their Initial Recommendation does not reflect the findings of the Economic Guidance Panel (EGP), cannot be used for decision-making purposes and does not contribute positively to the process of providing access to patients. Therefore, we are requesting that pERC present the findings of the EGP as reported in the Economic Guidance Report to support informed decision-making and timely access to treatment in an area where the unmet treatment need is significant and well-recognized.

Long-term benefit:

pERC noted the uncertainty associated with the long-term benefit of olaparib treatment due to immature overall survival (OS) data. EGP addressed this uncertainty in 3 of their analyses (page 8, table 3):

1. Using OS data from the SOLO-1 trial regardless of KM curves crossing resulted in an ICER of $42,614/QALY (row 1)
2. Assuming the survival benefit of olaparib would be the same as placebo at 4.17 years. And while clinically implausible, this analysis resulted in an ICER of $51,829/QALY (row 2).
3. Assuming the same OS prior to KM curves crossing resulted in an ICER of $58,425/QALY (row 3).

These EGP analyses to address the uncertainty associated with survival benefit resulted in ICERs ranging from $42K/QALY to $58K/QALY. These ICERs all fall within a range considered to be cost-effective based on a threshold of $100K/QALY in Canada.[6]

Discrepancy between Initial recommendation and EGP Guidance Report:

We note a discrepancy between the pERC Initial Recommendation and the EGP Guidance Report:

1. Guidance Report: The EGP's best estimate of ΔC and ΔE for olaparib when compared to routine surveillance is: $57,784/QALY (page 10, section 1.6, first sentence).
2. Initial Recommendation: The EGP's best estimate of the ICER was between $57,784 and $648,080 per QALY (page 8, last paragraph, last sentence).

Time horizon:

As per page 4 of their Initial Recommendation, pERC agreed that "the EGP's pessimistic analysis (by reducing the time horizon to the trial period) is an unlikely scenario as the treatment effect of olaparib is unlikely to drop off at the end of the trial period." Similarly, AstraZeneca agrees with the EGP that their exploratory analysis using a time horizon of 4.17 years is both "pessimistic and unlikely" (EGP Guidance Report, page 8, table 3, row 2) for the following reasons:

1. By truncating the time horizon to 4.17 years, the proposed sensitivity analysis only captures the very early stages of the natural history of advanced ovarian cancer, and therefore ignores the longer-term costs associated with subsequent PARP use following patient progression in the comparator arm and the positive health outcomes of remaining disease- or progression-free beyond 4 years.
2. The proportion of olaparib-treated patients who remained progression-free at 4 years in SOLO-1 was 52.6% versus only 11.4% of patients in the placebo arm.[1]
3. The analysis ignores the large body of evidence which suggests patients survive longer than 4 years. Survival in patients with locally advanced or metastatic BRCAm OC in Canada at 4 years ranged from 55%-65%.[7,8,9,10]
4. Greater than 7-year data has been reported with olaparib in platinum-sensitive relapsed (PSR) patients (Study 19).[11]
5. Finally, the analysis deviates from pCODR's previous assessment of olaparib in the generally incurable later line setting of PSR OC, where EGP's best case estimates of the reanalysis scenarios used time horizons of 15 years (lower bound estimate) and 10 years (upper bound estimate).[12]

Patients with newly diagnosed advanced ovarian cancer are the only patients for whom treatment has curative potential.[1] As such, a longer time horizon should be considered appropriate in order to capture all costs and benefits associated with olaparib treatment in this setting.

Olaparib is a cost-effective use of Canadian healthcare resources. This can be explained by:

1. Shorter treatment duration in the first-line setting compared to the PSR setting where patients are treated to progression. As per protocol, most SOLO-1 patients discontinued treatment at 2 years.
2. Continued benefit in terms of PFS was noted, despite most patients discontinuing treatment at 2 years. At Years 3 and 4, respectively, 60.4% and 52.8% of patients in the olaparib arm remained progression-free indicating an apparent enduring treatment benefit.[1]
3. First-line treatment of women with newly-diagnosed advanced OC is **curative in intent**; olaparib treatment in an earlier setting provides an opportunity to increase cure rates and offset substantial costs associated with subsequent PARP use in patients with PSR OC.
4. A clear relationship between PFS and OS has been observed in previous OC trials:
   - In studies which have demonstrated an OS benefit in the first-line treatment of advanced OC, the ratio of incremental PFS:OS gain was **1:>2** (i.e., 1 month of incremental PFS translated to more than 2 months of incremental OS).
     - In GOG-172, first-line treatment with intraperitoneal platinum-based chemotherapy improved median PFS by 5.5 months compared with intravenous administration. This translated to an OS benefit of 15.9 months and the observed ratio of incremental PFS:OS gain was **1:2.**[13]
     - In JGOG-3016, first-line treatment with a dose-dense paclitaxel and carboplatin regimen improved median PFS by 10.7 months compared with conventional treatment. This translated to a 38.3 month benefit and the observed ratio of incremental PFS:OS gain was **1:3.**[14]

   Thus, current evidence suggests the magnitude of PFS benefit demonstrated in SOLO-1 would likely translate into a survival benefit. Importantly, olaparib significantly improved time to second progression or death (PFS2; HR 0.50, p=0.0002) and time to second subsequent therapy or death (TSST; HR 0.45, p<0.0001) compared to placebo in patients with advanced BRCAm OC.[1]

Furthermore, Study 19 evaluated olaparib in later treatment lines. Based on a median follow-up of 78 months, at the final analysis (DCO 9 May 2016), the OS hazard ratio for olaparib versus placebo in patients with PSR BRCAm OC was 0.62 (p=0.02140).[11]

If EGP's exploratory analysis using a truncated time horizon to 4.17 years is excluded, all remaining EGP analyses reported ICERs less than $100,000/QALY (range: $15,721 – $93,465/QALY). Consistent with other pCODR assessments reporting ICERs ranges less than $100K/QALY,[15,16,17] olaparib is a cost-effective treatment option in newly-diagnosed advanced BRCAm OC. The $648,080/QALY ICER is not consistent with the EGP's assessment and mispresents the value of olaparib treatment in this setting.

Given the information presented above, AstraZeneca is requesting the statement "The EGP's best estimate of the ICER was between $57,784 and $648,080 per QALY" (Initial Recommendation, page 8, last paragraph) be revised to reflect the conclusions of the EGP as stated on page 10 of the Economic Guidance Report, i.e., "The EGP's best estimate of the ICER is $57,784 per QALY."

AstraZeneca looks forward to working with pCODR, pCPA and the jurisdictions to ensure patients have access to this practice-changing treatment as soon as possible.

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☐ agrees ☐ agrees in part ☐ disagree

Not applicable to this submission.

c) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence or provisional algorithm) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
2	Potential Next Steps for Stakeholders	5	To align with the olaparib product monograph, suggest revising "as detected by approved testing" to "as detected by any validated testing method".

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would support this Initial Recommendation proceeding to Final pERC Recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

☐ Support conversion to Final Recommendation.
Recommendation does not require reconsideration by pERC.

☒ Do not support conversion to Final Recommendation.
Recommendation should be reconsidered by pERC.

If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation

based on any information provided by the Stakeholder in the submission or as additional information during the review.

Please note that new evidence will be not considered at 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.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, including the provisional algorithm, the criteria for early conversion will be deemed to have not been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

1 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC), including the provisional algorithm. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, pERC makes an Initial Recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation. It should be noted that the Initial Recommendation, including the provisional algorithm may or may not change following a review of the feedback from stakeholders.

pERC welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The Stakeholder Feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the Initial Recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part or disagrees with the Initial Recommendation, and to provide a rational for their response.

   Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder can still support the recommendation proceeding to a Final Recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a Final Recommendation ("early conversion")?**

   An efficient review process is one of pCODR's key guiding principles. If all eligible stakeholders support the Initial Recommendation proceeding to a Final Recommendation and that the criteria for early conversion as set out in the *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website two (2) Business Days after the end of the feedback deadline date. This is called an "early conversion" of an Initial Recommendation to a Final Recommendation.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), including the provisional algorithm as part of the feasibility of adoption into the health system, the criteria for early conversion will be deemed to have **not** been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. If the substantive comments relate specifically to the provisional algorithm, it will be shared with PAG for a reconsideration. Please note that if any one of the eligible stakeholders does not support the Initial Recommendation proceeding to a Final pERC Recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the Initial Recommendation. Please also note that substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the Initial Recommendation. If the feedback can be addressed editorially this will done by the CADTH staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting. Similarly if the feedback relates specifically to the provisional algorithm and can be addressed editorially, CADTH staff will consult with the PAG chair and PAG members.

The Final pERC Recommendation will be made available to the participating federal, provincial and territorial ministries of health and provincial cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

2 Instructions for Providing Feedback

a) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:
   - The Sponsor making the pCODR Submission, or the Manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - The Provincial Advisory Group (PAG)

b) The following stakeholders are eligible to submit Feedback on the provisional algorithm:
   - The Sponsor making the pCODR Submission, or the Manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - The Board of Directors of the Canadian Provincial Cancer Agencies

c) Feedback or comments must be based on the evidence that was considered by pERC in making the Initial Recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

d) The template for providing *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

e) At this time, the template must be completed in English. The Stakeholder 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.

f) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be provided to the pERC for their consideration.

g) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the Initial Recommendation, and should not contain any

language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.

h) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at 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 considering to provide is eligible for a Resubmission, please contact the pCODR program.

i) The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.

j) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca

Note: CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.

REFERENCES

[1] Moore, K., et al., Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. 2018. 379(26): p. 2495-2505.
[2] Fotopoulou C. Limitations to the use of carboplatin-based therapy in advanced ovarian cancer. EJC Suppl. 2014 Dec;12(2):13-6
[3] Markham, M. et al. Second-line treatment of ovarian cancer. Oncologist. 2000;5(1):26-35.
[4] Hanker, LC. et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol. 2012 Oct;23(10):2605-12.
[5] Armstrong DK. Relapsed ovarian cancer: challenges and management strategies for a chronic disease. Oncologist. 2002;7 Suppl 5:20-8.
[6] Evans, G. Should different drugs have different thresholds? A CED Perspective [slide presentation]. Presented at Evidence, Decisions, Outcomes: Optimizing the Use of Drugs and Health Technologies. CADTH Symposium 2009; Ottawa, ON; 5–7 April. 2009; Available from: https://www.cadth.ca/media/symp-2009/presentations/CS-14/Gerald%20Evans%20-%20Should%20Different%20Drugs%20Have%20Different%20Thresholds%20-%20A%20CED%20Perspective.pdf.
[7] Kotsopoulos, J., et al., Ten-year survival after epithelial ovarian cancer is not associated with BRCA mutation status. Gynecol Oncol, 2016. 140(1): p. 42-7.
[8] Le Page, C., et al., Characteristics and outcome of the COEUR Canadian validation cohort for ovarian cancer biomarkers. BMC cancer, 2018. 18(1): p. 347-347.
[9] Liu, J., et al., Clinical characteristics and outcomes of BRCA-associated ovarian cancer: genotype and survival. Cancer genetics, 2012. 205(1-2): p. 34-41.
[10] McLaughlin, J.R., et al., Long-term ovarian cancer survival associated with mutation in BRCA1 or BRCA2. J Natl Cancer Inst, 2013. 105(2): p. 141-8.
[11] Friedlander, M., et al., Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. Br J Cancer, 2018. 119(9): p. 1075-1085.
[12] pCODR. Lynparza for Ovarian Cancer (Resubmission). 2017; Available from: https://www.cadth.ca/lynparza-ovarian-cancer-resubmission-details.
[13] Armstrong, D.K., et al., Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med, 2006. 354(1): p. 34-43.
[14] Katsumata, N., et al., Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. Lancet Oncol, 2013. 14(10): p. 1020-6.
[15] pCODR. Opdivo & Yervoy in combo in metastatic melanoma. 2017 [cited 2019 October]; Available from: https://www.cadth.ca/opdivo-combo-yervoy-metastatic-melanoma-details.
[16] pCODR. Velcade for Multiple Myeloma. 2013; Available from: https://www.cadth.ca/velcade-multiple-myeloma-details.
[17] pCODR. Treanda for indolent Non-Hodgkin Lymphoma. 2012; Available from: https://www.cadth.ca/treanda-indolent-non-hodgkin-lymphoma.