pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Olaparib (Lynparza) Ovarian Cancer

September 29, 2016

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Lynparza (olaparib) for PSR BRCAm Ovarian Cancer
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	AstraZeneca Canada Inc.

**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 Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part __X__ Disagree

AstraZeneca Canada (AZ) respectfully disagrees with pERC's initial recommendation on olaparib. In alignment with pCODR's deliberative framework, AZ strongly believes that olaparib, the first PARP inhibitor approved in Canada, provides a net clinical benefit when the following factors are considered: **effectiveness** (clinically meaningful benefit in PFS and OS, maintenance of QoL vs. placebo), **safety** (well tolerated with manageable AEs), **burden of illness** (high rate of recurrence and significant disease symptom burden) and **unmet need** (currently no strategies to delay subsequent chemotherapy and onset of debilitating symptoms of ovarian recurrence – ascites, bowel obstruction). The clinical benefits of olaparib in BRCA-mutated ovarian cancer patients and pERC's concerns with uncertainty in the data are addressed below:

Study 19 statistical analysis provides a robust PFS result in both ITT and BRCAm populations
Study 19 was a large (n=265) phase II, randomized, placebo-controlled, multinational trial conducted in 16 countries including Canada. While patients with BRCA mutation represent a small minority of all ovarian cancer patients, Study 19 was enriched for BRCAm patients: >50% of all trial patients (136/265). Clinicians have estimated the number of BRCAm patients in Canada to be 1,000 over the next 5 years (CGR, p. 20). Thus, a sample size of 136 in the BRCAm subgroup represents more than half the number of patients in a given year or over 10% of patients in the next 5 years in Canada. Study 19 was designed to assess whether there was sufficient promise to warrant a phase III study with a hypothesized HR=0.75 (3 month improvement in PFS), in the overall population allowing for a type 1 error rate of 20% (1-sided) with 80% power. Therefore, 137 PFS events would be needed for an analysis to show promising results in favour of olaparib in the overall population. However, statistical significance was defined in the protocol as a p-value of <0.025 (2.5%), 1-sided for PFS in the overall population (Study 19 CSR, p. 51, 58-59). The observed PFS treatment effect in the overall population was HR=0.35, which met the criteria for statistical significance (p<0.025) with a statistically significant p-value <0.00001 based on 154 events in 265 patients. In the pre-defined BRCAm subgroup and consistent with olaparib's mechanism of action and biologic rationale, the treatment effect for PFS had an even more impressive HR=0.18 and a statistically significant p-value <0.00001, based on 72 events in 136 patients. Furthermore, during Health Canada regulatory review, a biostatistics consult conducted by the Office of Science at Health Canada concluded that for the BRCAm subgroup: "A positive result [PFS] suggests that the test is powered and sample size is sufficient" (Clinical PSEAR Efficacy Data & Overall Risk-Harm, p. 88). Although a larger sample size would provide greater statistical precision, a standard sample size calculation with HR=0.2 and 95% power indicates only 28 events would be necessary to demonstrate statistical significance at a 1% 2-sided level. Study 19 sample size exceeds such requirements (i.e. 28 events) with 154

events and 72 events in the overall population and BRCAm subgroup, respectively. Given the observed treatment effect in the overall population, there is <0.001% chance that there is no difference between olaparib and placebo.

The correct timing for SOLO2 results and implications for Canadian patients

While AZ agrees that the results of SOLO2 will potentially provide additional evidence on olaparib in the maintenance setting of relapsed ovarian cancer, deferring a decision until these results are available will substantially delay Canadian patient access to olaparib. Database lock for SOLO2 is currently scheduled for Q4 2016 with data availability in the first half of 2017 (not September). It should also be noted that the SOLO2 database lock in 2016 is for the primary analysis of PFS. OS is a secondary endpoint and to achieve an OS result with similar maturity to that of Study 19 (i.e. 70% maturity in BRCAm with a median follow-up of 5.9 yrs) would not be anticipated until 2019-2020 (and is dependent on number of events). As well, patients whose disease progresses may go on to receive other treatments outside of the trial (e.g. placebo patients receiving PARP inhibitors), which will confound the OS results, resulting in uncertainty of the true OS benefit of olaparib. SGO has noted the challenges in the feasibility of using OS as an endpoint in relapsed ovarian cancer trials due to "prolonged time-line for final analysis in some populations and the potential for unintended loss of treatment effect from active post progression therapies" (Herzog, 2014). Most importantly, because SOLO2 uses a different non-bioequivalent formulation (tablet), this will require a complete regulatory review by Health Canada. Assuming a typical 12 month review timeframe, regulatory approval is not expected until mid to late 2018. If AZ waited to resubmit with SOLO2 data, Canadian patients would wait an additional 2+ years for access to olaparib – this means that an estimated 188 patients at minimum would not have access to olaparib. This places Canadian patients at a distinct disadvantage compared to other jurisdictions, as olaparib is currently marketed in over 45 countries worldwide and broadly reimbursed in a number of HTA markets (e.g. UK, France, Germany, Sweden, Norway, Denmark, and the Netherlands) as a maintenance therapy based on the results of Study 19 (using the earlier Nov 2012 data cut-off with 52% maturity in OS in the BRCAm subgroup).

PFS is an appropriate primary endpoint in relapsed ovarian cancer (CGR, p6)

PFS was the primary endpoint in Study 19 and clinically extending the time to progression is recognized as an appropriate endpoint (Herzog, 2014) and an important goal of therapy for patients with relapsed ovarian cancer by both national (GOC, 2007) and provincial guidelines (CCO, 2011), and by CGP (CGR, p. 6). Delaying symptomatic progression is critical for patients to maintain quality of life, defer onset of debilitating symptoms and delay time to next cytotoxic chemotherapy as noted by GOC (CGR, p. 20-21). The interval following chemotherapy and prior to next recurrence ('watch and wait') has a significant psycho-social impact on patients as highlighted in OCC's input: "…fear of recurrence became paralyzing…" and "…in permanent state of anxiety" (CGR, p. 11-12). The CGP concluded that olaparib demonstrated both a statistical and clinically meaningful improvement in PFS for both the ITT and BRCAm populations in Study 19 (CGR, Section 1.2.4, p. 1-2). It should also be noted that a number of patients have had extremely long durations of PFS on olaparib maintenance therapy: more than 20% remained on therapy for ≥3 years, 16% ≥4 years, and 15% ≥5 years. This is unprecedented in the relapsed ovarian cancer setting. Lastly, the primary efficacy endpoint of PFS is further supported by the exploratory endpoints TFST (time to first subsequent therapy) and TSST (time to second subsequent therapy) which clearly demonstrate that olaparib delays time to next chemotherapy and that the PFS benefit of olaparib is maintained through subsequent lines of therapy (Ledermann, 2014, 2016).

Clarification on Study 19 "exploratory" endpoints (CGR, p 25)

All primary and secondary efficacy endpoints (PFS, OS, ORR, DoR, tumor response, QoL) were pre-specified in the statistical analysis plan for the BRCAm population (Study 19 CSR, p. 77). Consistent with the ITT population, the only "exploratory" endpoints assessed in Study 19 for BRCAm population were TFST, TSST, and TDT (time to discontinuation of treatment) as requested by European regulatory agencies and which provide additional clinical context to the PFS observations (CGR Table 4, p. 25; Study 19 CSR, p. 49,111; HC module 2.7.3, p. 28).

Olaparib provides a clinically meaningful survival benefit of 4.7 months (CGR, p4)
Study 19 was not designed to show a statistically significant difference in OS, however the evidence, consistent with the scientific hypothesis, demonstrated a 4.7 month advantage in OS (median OS 34.9 months olaparib vs. 30.2 months placebo) in the BRCAm population which was deemed clinically meaningful by CGP (CGR Conclusions, p. 5) without adjusting for confounding due to subsequent PARP therapy. This magnitude of survival benefit is unprecedented for patients with relapsed BRCAm ovarian cancer. Of note, the observed treatment effect over the totality of the trial period was greater than that indicated by the median point estimate difference. A supportive restricted means analysis indicates a 7.4 month benefit in OS in the BRCAm group (44.3 months olaparib vs. 36.9 months placebo) (Ledermann, 2016). CGP also noted that 23% of patients in the placebo arm of BRCAm patients received subsequent PARP inhibitors following progression and, therefore, the OS result is likely confounded (CGR, p. 2). Thus, the true treatment benefit of olaparib on OS is likely to be even greater. It should also be noted that the latest data cut off (Sept 2015) is based on 70% maturity in the BRCAm population representing a median follow-up 5.9 yrs. This duration of follow-up provides considerable certainty on the long-term efficacy and safety of olaparib maintenance therapy. Additional clinically meaningful survival was noted to be highly valued by both patients and their caregivers (CGR, p. 13,15-16).

Olaparib is well tolerated and maintains QoL during the progression free interval (CGR, p4)
While adverse events were more common with olaparib compared with placebo, most toxicities were mild to moderate, and manageable with simple treatment interruption and dose reductions (CGR, p. 3). This was supported by input from the GOC who noted that these AEs can be managed by non-specialists (CGR, p. 21). PROs did not suggest any deterioration in QoL with olaparib, which is important in the maintenance setting where patients would not normally receive active treatment. Patients with direct experience on olaparib commented "the symptoms from olaparib are very manageable" (CGR, p. 17) and noted improvements in their quality of life (CGR, p. 17). From Study 19, 15% of the BRCAm patients remained on treatment >5 years supporting the long term tolerability of olaparib. The only additional monitoring for olaparib-treated patients, as recommended in the product monograph and consistent with clinical practice, is monthly blood counts for the first 12 months of therapy (and periodically thereafter based on physician's discretion).

Recurrent ovarian cancer remains a significant disease burden and treatment challenge (CGR, p1)
All stakeholders acknowledged an unmet clinical need in patients with relapsed ovarian cancer, which olaparib addresses. Relapsed ovarian cancer has a terrible prognosis characterized by repeated recurrences with progressively shorter progression-free intervals (CGR Section 1.2.4, p. 1). At each recurrence, patients may be subjected to the toxicities of further chemotherapy, while experiencing the impact of worsening disease symptoms - abdominal pain and distension, nausea and vomiting and bowel obstruction, which in turn often necessitate ER visits and hospital admissions (CGR, p. 20). Olaparib is an oral therapy that is well tolerated with proven anti-tumor activity, provides significantly improved progression free survival and clinically meaningful increase in overall survival in an identifiable population (i.e. BRCA mutated) that is most likely to benefit (Ledermann 2012, 2014, 2016). Although pERC indicated there is uncertainty as to the precise magnitude of the clinical benefit, Study 19 demonstrates that the magnitude of the benefit of olaparib is clinically meaningful to patients, caregivers and the oncologists who treat this disease and that quality of life is maintained. These benefits of olaparib are well aligned with patient values and address a current unmet gap in treatment.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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.

Recommendation does not require reconsideration by pERC.

__X__ Do not support conversion to final recommendation.

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
1	pERC recommendation	1st paragraph line 9	pERC notes Study 19 is not a "non-comparative" trial; Study 19 should be referred to as a randomized, double blind, placebo-controlled trial similar to p3 paragraph 2 line 1
7	Key Efficacy results	1st paragraph lines 8-9	The one-sided alpha level of 0.2 in the ITT analysis was used to determine sample size and identify a promising difference in favour of olaparib. As noted above in comments in section 3.1(a), statistical significance was only declared for PFS if p<0.025 (1-sided). The reference to "…a 20% risk for concluding statistical difference in PFS in favour of olaparib when there is no difference" is incorrect. This statement should be revised and reference the criteria for statistical significance - 2.5% (p<0.025). E.g. The sample size calculation, conducted in the overall population for PFS, allowed a type 1 error rate of 20% and approximately 80% power to demonstrate a **promising difference** in favour of olaparib (i.e. p<0.2, 1-sided). However, **statistical significance** in favour of olaparib was only declared in the overall population for PFS if the observed p-value was <0.025 (1-sided).
2,4,7	Potential Next Steps; Summary; Key Efficacy Results	1st paragraph line 1; 1st paragraph line 4; 3rd paragraph line 2	Database lock for SOLO2 is currently scheduled for Q4 2016 with data availability in the first half 2017. Regulatory approval by Health Canada is not anticipated until mid-2018 at earliest. See further details in section 3.1(a) above.
3,7	Summary; Key Efficacy Results	2nd paragraph line 8; 1st paragraph line 2 and 2nd paragraph line 1	As reported in the Statistical Analysis Plan (Study 19 CSR, p. 77) PFS and OS were not "exploratory" endpoints in the BRCAm subgroup; consistent with ITT population these represented primary and secondary efficacy endpoints. Only "exploratory" endpoints were TDT, TFST and TSST.
1	pERC recommendation	1st paragraph lines 10-11	Statement "…olaparib produces **some** anti-tumor activity,…" is inconsistent with the conclusion made on p.7 section Key Efficacy Results, paragraph 2 line 10 which states "…pERC agreed that olaparib demonstrates anti-tumour activity."

1	pERC recommendation	1st paragraph line 15	Statement "…uncertainty…in regard to outcomes important to decision making, such as overall survival and progression-free survival **and quality of life**" is inconsistent with the statement on p3 paragraph 2 line 21 "…respect to outcomes important to decision-making, such as OS and PFS" and contradicts the conclusion on p3 paragraph 2 line 27 "pERC agreed that olaparib maintained quality of life (QoL) in the majority of patients" and on p7 Patient Reported Outcomes paragraph 2 "pERC agreed that the results from Study 19 suggest olaparib showed no decrement in quality of life (QoL), which pERC considered to be reasonable in the setting of maintenance treatment."
10	Adoption Feasibility	3rd paragraph, lines 2-3	The non-specific BIA was not limited to patients under the Trillium program but rather reflected the total # of eligible patients under the full Ontario Drug Benefit program. The only split in eligible patients was to account for those who would be eligible for the public drug plan (e.g. >65 yrs of age). For submissions to the individual provinces, each BIA has been customized to account for each jurisdictions eligibility for patients (i.e. seniors only or universal coverage).

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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 Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

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

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

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

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) 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.

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

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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 Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) 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 forwarded to the pERC.

f) 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.

g) 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 Secretariat.

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

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.