pan-Canadian Oncology Drug Review

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

Olaparib (Lynparza) for Ovarian Cancer - Resubmission

September 20, 2017

3 Feedback on pERC Initial Recommendation

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

**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:

__x__ agrees ____ agrees in part ____ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.*

AstraZeneca Canada supports pERC's initial recommendation for reimbursement of olaparib monotherapy maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated ovarian cancer and supports early conversion to a positive final recommendation.

As noted by pERC, CGP and clinician input, women with advanced and/or recurrent ovarian cancer have incurable disease and limited treatment options. Relapsed ovarian cancer has a terrible prognosis characterized by repeated recurrences with progressively shorter progression-free intervals. Delaying symptomatic progression is crucial for patients to maintain quality of life, defer onset of debilitating symptoms and delay time to next cytotoxic chemotherapy.

There is a recognized gap in treatment for patients with relapsed ovarian cancer, thus, a need for effective therapies that may extend remission. As noted by CGP and recognized by pERC in this clinical setting, the goal of maintenance therapy is to delay progression and time to the next chemotherapy.

AstraZeneca is pleased to receive a positive clinical recommendation from pERC on the basis of the net clinical benefit observed with olaparib maintenance treatment.

Olaparib, the first and only poly (ADP-ribose) polymerase (PARP) inhibitor available in Canada, is a targeted therapy which addresses a significant unmet need and gap in therapy. Data from two randomized control trials (Study 19 and SOLO-2) has confirmed that maintenance therapy with olaparib substantially prolongs the progression-free interval and delays the need for further chemotherapy without interfering with the benefit from subsequent treatments. SOLO-2 demonstrated a statistically significant and clinically meaningful improvement in the median progression-free survival (PFS) for olaparib over placebo of 13.6 months.[1] Importantly, olaparib has been shown to increase

survival, is generally well tolerated and has not demonstrated a detrimental impact on quality of life (QoL).[1-3]

As per clinician input and pERC's recommendation, AstraZeneca agrees that reflex BRCA testing should occur at diagnosis. AstraZeneca also agrees with the CGP and pERC assessment on the similar clinical effectiveness of the capsule and tablet formulations and the recommendation that olaparib capsules be reimbursed until the olaparib tablets are approved and available in Canada.[4] AstraZeneca will work with the provincial jurisdictions on the implementation of tablets when available in Canada.

As highlighted by pERC and the CGP, the goal of maintenance therapy is to delay progression and time to the next chemotherapy. Within economic models, it can be difficult to appropriately represent the clinical pathway of a maintenance therapy and accurately capture the expected benefits of olaparib in delaying progression and postponing subsequent chemotherapy.[5] As a result of this, AstraZeneca believes the lower bound estimate provided by the EGP's reanalysis is most appropriate.

CADTH guidelines state that time horizon should be long enough to capture the benefits of treatment. Data from Study 19, where the duration of follow up is now >6 years, provide robust evidence of the long-term clinical benefit of olaparib maintenance treatment. More than 20% of olaparib-treated patients from Study 19 remained on therapy for ≥3 years, 16% ≥4 years, and 15% ≥5 years. At the DCO of 09 May 2016, 14 patients were continuing on olaparib maintenance therapy. These 14 patients have been taking maintenance olaparib treatment for a minimum of 6.3 years (maximum 7.1 years).[6] This data along with long-term survival studies support the rationale that patients with BRCA mutation may survive past 10 years, therefore, the 15-year time horizon seems to be the most appropriate estimate.[6,7] In addition, assuming equal survival beyond trial end is not clinically reasonable as data from Study 19 demonstrates that there are patients who have progression delayed beyond 6-years.[6]

AstraZeneca agrees with pERC that the appropriate clinical endpoint in the maintenance setting is PFS and that even with sufficient overall survival (OS) follow-up, the OS results may be confounded by post-trial treatments. It was observed in both Study 19 and SOLO-2 that >20% of patients went on to receive subsequent PARP inhibitor therapy thus confounding the observed overall survival.[1,3] Despite crossover, based on Study 19, olaparib resulted in a clinically meaningful increase in OS of 4.7 months [(34.9 vs. 30.2 months), HR = 0.62 (95% CI 0.41, 0.94)].

[redacted].[2] *(A redaction was made due to a determination that the feedback was out of scope. New information was provided in the feedback that was not considered by pERC in making the initial recommendation. Of note, the reference provided by the submitter did not pertain to the new information.)* The EMA also recognizes the challenges in capturing an overall survival benefit and recommends that clinical studies should be designed to test for a difference in OS or, where this is not feasible, for a difference in PFS after next-in-line therapy (PFS2), measured by time from randomization to second disease progression or death.[5] As reported in SOLO-2 there was a statistically significant and clinically meaningful delay in time from randomization to PFS2 or death in the olaparib group compared with the placebo group.[1]

The base case economic model does not account for time to first subsequent treatment (TFST) or additional utility benefits, further supporting AstraZeneca's view of an ICER estimate closer to the EGP's lower bound estimate. In SOLO-2 there was a nominally statistically significant and clinically meaningful delay in the time to starting first subsequent therapy in the olaparib group compared with the placebo group. The median TFST in the olaparib arm (27.9 months) was substantially

longer than the median PFS (19.1 months), suggesting clinical benefit with olaparib continues beyond the strict criteria of radiological progression and delays the need to start the next round of chemotherapy, despite discontinuation of treatment at progression.[1] A scenario analysis conducted by AstraZeneca accounting for TFST resulted in an ICER lower than the submitted base case estimate, further supporting the lower bound estimate of the ICER derived from the EGP. In addition, significant 'patient-centred benefits' of olaparib compared to placebo were observed with quality-adjusted progression-free survival (QAPFS) and time without symptoms of disease or toxicity (TWiST), which weren't accounted for in the economic model. QAPFS for the olaparib arm was 6.7 months longer than in the placebo arm and patients in the olaparib arm saw a 6.3-month extension in TWiST compared with placebo.[8]

The evolution of oncology treatment and disease progression has presented unique challenges that make assessing and demonstrating value especially complex.[9] There has been a recognition that there are challenges in health economic modeling of cancer therapies.[9] Hettle et al., have reported the challenges in economic modeling of anticancer therapies, in particular for the benefit of olaparib maintenance therapy.[5] The ISPOR Task Force Report concludes that budget impact analyses are important for the economic evaluation of a new health intervention.[10] AstraZeneca believes the most appropriate way to address the value of olaparib therapy within the maintenance setting and address certainty is with the defined budget impact associated with this targeted therapy. Approximately 15-20% of women diagnosed with ovarian cancer carry a BRCA1 or BRCA2 genetic mutation, representing a small and defined subset of patients.[11] AstraZeneca will look to work with the pCPA and provincial jurisdictions to discuss the respective budget impact for the targeted patient population with platinum-sensitive relapsed BRCA-mutated ovarian cancer.

AstraZeneca strongly agrees with pERC that olaparib aligns with patient values because it is an oral treatment that delays disease progression, has no detriment to QoL and has manageable toxicities.

AstraZeneca Canada commends and supports pERC's initial recommendation for reimbursement of olaparib monotherapy maintenance treatment for patients with platinum-sensitive relapsed BRCA-mutated ovarian cancer. This is an important first step towards public reimbursement for these women who have had few treatment options in the past 20 years.

References

1) Pujade-Lauraine E. et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncology.* Sept 2017;18(9): 1274–1284.

2) Ledermann J. et al. Overall survival (OS) in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) receiving olaparib maintenance monotherapy: An interim analysis. Journal Clinical Oncology 34, 2016 (suppl; abstr 5501).

3) Ledermann J. et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncology. Jul 2014;15(8):852-861.

4) Mateo J. et al. An Adaptive Study to Determine the Optimal Dose of the Tablet Formulation of the PARP Inhibitor Olaparib. Target Oncology. 2016;11(3):401-415.

5) Hettle R. et al. Challenges in economic modeling of anticancer therapies: an example of modeling the survival benefit of olaparib maintenance therapy for patients with BRCA-mutated platinum-sensitive relapsed ovarian cancer. Journal of Medical Economics. 2015;18(7):516-24

6) McLaughlin JR, Rosen B, Moody J, et al. Long-term ovarian cancer survival associated with mutation in BRCA1 or BRCA2. Journal of the National Cancer Institute. Jan 16 2012;105(2):141-148.

7) AstraZeneca Clinical Study Report: Study D0810C00019. Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens.

8) Friedlander M. et al. Health-related quality of life (HRQOL) and patient-centered outcomes with maintenance olaparib compared with placebo following chemotherapy in patients with germline (g) BRCA-mutated (m) platinum-sensitive relapsed serous ovarian cancer (PSR SOC): SOLO2 phase III trial. Journal Clinical Oncology. 2017 35:15_suppl, 5507-5507

9) Miller JD. et al. Current challenges in health economic modeling of cancer therapies: a research inquiry. American Health Drug Benefits. 2014 May;7(3):153-62.

10) Sullican SD. et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health. 2014 Jan-Feb;17(1):5-14.

11) Hennessy BT CR, Markmann N. Ovarian cancer. Lancet. 2009; 374: 1371-82.

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 two (2) Business Days after the end of the feedback deadline date.

__x__ Support conversion to final recommendation.	____ 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

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