CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Olaparib (Lynparza) for Ovarian Cancer - Resubmission

September 20, 2017

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to **pCODR by Astra Zeneca** compared olaparib monotherapy as maintenance treatment of adult women with platinum sensitive relapsed (PSR) *BRCA1/2*-mutated (germline or somatic) high-grade serous ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response following platinum-based chemotherapy. The population in this analysis is consistent with the patient population in SOLO-2 as well as the pre-planned subgroup of patients in Study 19 with confirmed *BRCA* mutation status.

Table [1]. Submitted Economic Model

Funding Request/Patient Population Modelled	Aligns with funding request
Type of Analysis	*Cost-utility analysis and cost-effectiveness analysis*
Type of Model	*Partitioned-survival model*
Comparator	*Watch and wait (observation)*
Year of costs	*2016*
Time Horizon	*15 years*
Perspective	*Government*
Cost of olaparib	• $16.74 per 50 mg capsule • $267.84 per day • $7,500.00 per month
Cost of watch and wait	• No active treatment ($0)
Model Structure	*A mathematical model with three health states including progression-free survival (PFS) or pre-progression state, progressed disease (PD) and death.*
Key Data Sources	*SOLO-2 (September 19, 2016 data cut-off)* *Study 19 (September 30, 2015 data cut-off)*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the use of watch and wait as a comparison is appropriate because there are currently no approved medications or comparable monotherapy with evidence for maintenance therapy of ovarian cancer after induction of remission with chemotherapy.

The CGP concluded that there is a net clinical benefit to olaparib as maintenance treatment for adult patients with platinum sensitive relapsed BRCA-mutated (*BRCA1 or BRCA2* germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy. The conclusion is based on the results of the Phase II Study 19 trial and the results of the confirmatory SOLO-2 phase III randomized controlled trial that demonstrated a clinically and statistically significant benefit in progression-free survival for olaparib compared with placebo.

The economic model incorporated both effectiveness and safety profiles of olaparib. The Submitter addressed the question about immature OS data obtained from SOLO-2 by using OS data from a subgroup of Study 19.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered olaparib as an oral drug with improved toxicity that will significantly extend patients remission and potentially delay the time to next chemotherapy. The effects of olaparib on progression free survival, its adverse events and the costs of subsequent therapies were considered in the economic analysis.

Summary of patient input relevant to the economic analysis
Patients considered olaparib as a treatment that can prolong survival, improve quality of life, reduce the health services use, and extend the time of recurrence. All factors were taken into accounted in the economic evaluation.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for olaparib which are relevant to the economic analysis:

- Costs associated with the BRCA testing as the BRCA mutation is not routinely tested at this time. The PAG also noted that olaparib would add substantial pressure to genetic testing resources given that there will be a large number of patients requiring BRCA testing to identify patients who are eligible for olaparib. The Submitter included the costs of BRCA mutation test and the number of patients requiring the test in the sensitivity analyses.
- The PAG is concerned about the high rate of grade 3 and 4 anemia and may reduce quality of life and increase the demand for health system resources. The Submitter addressed this concern by including the costs of grade 3 or higher adverse events occurred in ≥ 2% in the model. This includes anemia which occurred in 19.5% of treatment group. Disutilities associated with these events were also taken into accounted.
- The PAG considered that the oral formulation may cause financial burden on patients and their families because pharmacare programs in some provinces require co-payments and deductibles. This concern was not incorporated in the economic analysis because the base case analysis was based on the perspective of Canada's health care system. The adopted perspective is appropriate and consistent with the current health economic guideline.

1.3 Submitted and EGP Reanalysis Estimates

Table [2]. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	1.068	0.531, 1.068
Progression-free	1.975	1.513, 1.975
Post-progression	-0.907	-0.982, -0.907
ΔE (QALY)	1.061	0.610, 1.287
Progression-free	1.651	1.353, 1.684
Post-progression	-0.589	-0.742, -0.395
ΔC ($)	$258,015	$251,171, $257,020
ICER estimate ($/QALY)	$243,249	$195,112, $421,637

The main assumptions and limitations with the submitted economic evaluation were:

- While Study 19 did not allow patients receiving placebo to cross over to treatment with olaparib, the EGP noted that patients receiving placebo could subsequently receive another PARP inhibitor. This might confound the observed OS from Study 19. The Submitter acknowledged this limitation and briefly described an exploratory analysis assessing the potential confounding effect of crossover. The analysis excluded crossover sites (CSE) and produced a statistically significant difference in OS between olaparib and placebo for BRCA mutation patients, with a HR of 0.49 (95% CI: 0.28 to 0.86, p-value = 0.013). The Submitter did not include the details and results of the analysis in the submitted PE report and claimed that the base case analysis was based on a conservative approach.

  The EGP disagreed with the Submitter's claim and believed that the current PE model may not provide a conservative ICER. The Submitter used a partition survival model whereby the number of patients in the PD health state were estimated by subtracting the number of patients in PFS from the number of patients who were alive (estimated from OS), i.e. nPD = nS - nPFS. If the OS observed in a placebo group was confounded by crossover to a subsequent PARP inhibitor and overestimated, the number of patients in the PD would also be overestimated.

  The EGP requested the results of additional analyses adjusted for subsequent PARP inhibitor usage. The Submitter did not provide additional results and argued that the use of CSE or other sophisticated techniques such as the inverse probability of censoring weighting (IPCW) or the rank-preserving structural failure time (RPSFT) model would not provide reliable estimates given a small sample size of BRCA mutation patients in Study 19. **Without the requested results and individual data, the effects of confounding due to subsequent PARP inhibitor usage on the ICER are unclear and have not been formally assessed by the EGP.**

- The Submitter obtained OS data derived from a BRCAm subgroup of Study 19 as opposed to that reported in SOLO-2 because OS data in SOLO-2 are immature. The submitted model used the OS data obtained from a subgroup of BRCA mutated patients. The OS data were based on a relatively small number of patients; there might be a high uncertainty around the data especially when using for prediction. Furthermore, given that the BRCAm population was not powered to detect overall survival differences and was not statistically significant and corrected for multiple time point analyses, the uncertainty in the overall survival data is high.

- The Submitter used the actual average dose from the SOLO-2 (tablet formulation), assuming 568.2 mg per day.

- The Submitter assumed that health utility values did not vary across treatment groups. The assumption was supported by the absence of meaningful difference in mean utilities measured in SOLO-2. However, the supplementary report on analysis of EQ-5D data revealed that olaparib was associated with 0.012 units increased utility values (p-value = 0.3087) compared to a placebo. Although the difference was not statistically significant, it may cause variation in the ICER and was explored in the sensitivity analysis.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- The EGP performed the reanalysis by reducing the time horizon from 15 years to 7 and 5 years to assess the impact of the time horizon on the cost-effectiveness of olaparib. Using a long time horizon can lead to erroneous predictions of long term survival based on extrapolation of trial data with limited follow-up. While the updated CADTH guideline recommends that "the time horizon of the analysis should be conceptually driven, based on the natural history of the condition or anticipated impact of the intervention (Page 31)", the guidelines also state that, in cases where that extrapolation is required to estimate long-term effect, external data sources, biology or clinical expert judgement may be used to justify the plausibility of extrapolation (Page 43).

  To support the use of a time horizon of 15 years, the Submitter cited the study by McLaughin et al (6) showing that about 25% of high-grade serous BRCA-mutated patients were alive at 12 years after diagnosis. The CGP and EGP believe that the results from this study are not entirely applicable to the target population investigated in the submitted report. The submitted model started following patients after completing their last round of chemotherapy, NOT from their diagnosis as in the McLaughlin et al study.

  Survival data from Study 19 is also based on a small subgroup of BRCAm patients with a median OS of 34.9 months. The CGP suggested using a 7 or 5 year time horizon was more clinically plausible in this patient population. This 7 or 5 year time horizon was assumed by the EGP in the reanalyses. As expected, the shorter time horizon led to a substantial increase in ICER from $243,249 (base case) to $322,069 (7 years) and $388,215 (5 years) per QALY gained, suggesting a bias in favour of olaparib with a longer time horizon.

- The PAG has concern regarding additional BRCA mutation tests required to support treatment decision. The EGP considers that the cost of mutation test should be incorporated in the base case analysis. In the reanalysis, the EGP included the costs of BRCA mutation test and varied the test costs by 25%. The variation caused slight changes in estimated ICERs from $243,249 (base case as shown in the PE report) to $246,070 (-25%) and $247,951 (+25%) per QALY gained. Changing the costs of downstream health services utilization including subsequent therapies, adverse events and end of life care had minimal impact on the ICER. The EGP also assessed the effect of unit cost of olaparib on the ICER; the results show that ICER estimates were highly sensitive to unit cost per milligram of olaparib.
- The submitted model used the OS data obtained from a subgroup of BRCAm patients in Study 19. The OS data were based on a relatively small number of patients; there might be a high degree of uncertainty around the data especially when used for prediction. The EGP assumed equal survival benefit between treatment groups at the end of the trial (i.e. at 78 months). This change caused a substantial increase in ICER from $243,249 (base case as shown in the PE report) to $361,365 per QALY gained.

- The EGP used the generalized gamma model to extrapolate PFS data for the watch and wait group as it has a better fit to the PFS data. This new prediction model increased the ICER from $243,249 (base case as shown in the PE report) to $258,461 per QALY gained.

- The EGP replaced the actual mean dosage of olaparib to a planned dose of 600 mg per day. This change is important because provincial insurance plans would be interested in covering for the recommended dose rather than the actual dose. The use of recommended dose is also a way of addressing wastage issue of medication nonadherence. The change increased the ICER by $13,640 from the baseline.

- The EGP used PFS from SOLO-2 to represent the duration that patients receive olaparib as the CGP believes that there would be few patients who still receive olaparib after progression in actual practice. This change reduced ICER from $243,249 to $237,816 per QALY gained.

- The Submitter assumed that health utility values did not vary across treatment groups. The assumption was supported by the absence of meaningful difference in mean utilities measured in SOLO-2. However, the supplementary report on analysis of EQ-5D data revealed that olaparib was associated with 0.012 units increased utility values (p-value = 0.3087) compared to a placebo. Although the difference was not statistically significant, it may cause variation in the ICER and therefore was explored in the sensitivity analysis. The EGP applied the unit difference obtained from the regression to utility values for PFS and PD in the base case. The variation in utilities by treatment groups improved the ICER by $11,055 from the base case. The EGP believed that the use of utility values obtained from OVA-301 was inappropriate and underestimated because they were obtained from patients who received trabectedin as an intravenous infusion. The EGP used utility values obtained from SOLO-2 (0.836 for olaparib and 0.768 for watch and wait) and applied a unit increase of 0.012 associated with olaparib to PFS and PD health states. The changes increased ICER to $257,181 per QALY gained. Increased ICER was due to the use of higher value of health utility values associated with the PD health state in the watch and wait group (0.768 vs 0.649).

Table [3]: Detailed Description of EGP Reanalysis

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
1) Reduce time horizon to 5 years	$192,362	0.496	0.377	$388,215	$144,966
2) Reduce time horizon to 7 years	$216,518	0.672	0.672	$322,069	$78,820
3) Reducing BRCA mutation test costs by 25%	$261,007	1.061	1.068	$246,070	$2,821
4) Increasing BRCA mutation test costs by 25%	$263,002	1.061	1.068	$247,951	$4,702
5) Decreasing the costs of adverse events by 25%	$257,718	1.061	1.068	$242,969	-$280
6) Increasing the costs of adverse events by 25%	$258,311	1.061	1.068	$243,528	$279
7) Decreasing the costs of subsequent therapies by 25%	$258,457	1.061	1.068	$243,666	$417
8) Increasing the costs of subsequent therapies by 25%	$257,572	1.061	1.068	$242,831	-$418
9) Decreasing the costs of end of life care by 25%	$258,358	1.061	1.068	$243,572	$323
10) Increasing the costs of end of life care by 25%	$257,672	1.061	1.068	$242,925	-$324
11) Equal survival benefit after the trial end, i.e. at 78 months	$257,529	0.713	0.531	$361,365	$118,116

12) Using generalized gamma model to extrapolate PFS in the watch and wait group	$258,580	1.000	1.068	$258,461	$15,212
13) Full olaparib dose (600 mg/day)	$272,483	1.061	1.068	$256,889	$13,640
14) Using PFS to reflect treatment duration instead of TDT	$252,253	1.061	1.068	$237,816	-$5,433
15) Assuming utility values vary by treatment groups (olaparib vs watch and wait) PFS (SOLO-2): 0.848 vs 0.836; PD (OVA-301: 0.780 vs. 0.649	$258,015	1.111	1.068	$232,194	-$11,055
16) Assuming utility values vary by treatment groups (olaparib vs watch and wait) PFS (SOLO-2): 0.848 vs 0.836; PD (SOLO-2: 0.780 vs. 0.768	$258,015	1.003	1.068	$257,181	$13,932
EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$258,015	1.061	1.068	$243,249	--
Best case estimates of the above 14 reanalysis scenarios					
[LOWER BOUND]					
EGP's lower bound estimate: using *the time horizon of 15 years and combining the above reanalyses 5, 8, 10, 14 and 15*	$251,171	1.287	1.068	$195,112	-$48,137
[UPPER BOUND]					
EGP's upper bound estimate: including the cost of BRCA test, using a time horizon of 10 years and combining the above reanalyses 6, 9, 11, 12, 13 and 16	$257,020	0.610	0.531	$421,637	$178,388

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include BRCA mutation test costs, olaparib dosage, and downstream costs (e.g. subsequent therapies, follow-up and adverse events), pharmacy costs and olaparib market share. Inclusion of the costs of BRCA mutation test, downstream health consequences and pharmacy as well as higher olaparib dosage led to the increased overall budget impact of olaparib.

The EGP is satisfied with study design and data analyses. Key limitations of the BIA model include:

1. The submitted BIA analysis was based on the Study 19 which used the 50mg capsule formulation and a target daily dose of 800mg per day. For SOLO 2, olaparib was reformulated into 150mg tablets with a higher bioavailability which allowed an equivalent dosing of 600mg per day (800mg capsules = 600mg tablets). While the BIA used olaparib capsule at a cost of $0.33/mg and the cost-effectiveness analysis uses olaparib tablets at a cost of $0.45/mg, the daily costs are roughly equivalent (800mg per day capsules, $267.84; 600mg per day tablets, $267.86/day). The Submitter used the mean daily dose of 687.60 mg/day in the base case analysis. This dosage was 86% of the planned dose of 800 mg in Study 19. This is higher than the 568.2 or 94.7% of the planned dose of 600 mg in SOLO-2.

2. While not relevant in all provinces, the Submitter excluded pharmacy costs covering dispensing and markup in the base case analysis. Exclusion of these costs would underestimate the overall financial impact of olaparib.

These limitations were able to be modified and explored by the EGP. The re-analysis showed that the inclusion of pharmacy and downstream costs led to a substantial increase in the 3-year budget impact.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for olaparib when compared to watch and wait is between $195,112 /QALY and $421,637 /QALY.

- The extra cost of olaparib is between $251,171 and $257,818.
- Factors that most impact costs are time horizon, treatment duration and the costs of olaparib
- The extra clinical effect of olaparib is between 0.610 and 1.287 QALYs. Factors that most impact clinical effect are the time horizon, the parametric models used to predict OS and the sources of utility data.

Overall conclusions of the submitted model:
The model structure is adequate and well-justified. Assumptions used for costs estimation are also well-described; however, there is a high degree of uncertainty around the OS data used in the base case analysis. It is unclear how switching to subsequent PARP inhibitors in a placebo group would affect the cost-effectiveness findings. **A time horizon of 15 years was too optimistic and should be shortened to 10 years. The submitted PE and BIA models are based on different dosage forms (tablets vs capsules) that use different but apparently equivalent daily dosages (600mg vs 800mg). This complicates the interpretation of the BIA report.**

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Genitourinary Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of olaparib (Lynparza) for ovarian cancer. A full assessment of the clinical evidence of olaparib (Lynparza) is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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