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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Olaparib (Lynparza) for Ovarian Cancer

September 29, 2016

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TABLE OF CONTENTS

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 patients with platinum-sensitive recurrent (PSR) BRCA-mutated epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy to "watch and wait".

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*Aligns with funding request*
Type of Analysis	*CUA*
Type of Model	*Partitioned survival model*
Comparator	*Placebo*
Year of costs	*2015*
Time Horizon	*15 years*
Perspective	*Government*
Cost of Olaparib	Olaparib costs $16.7411 per capsule At the recommended dose of 400mg twice daily, olaparib costs • $267.8576 per day • $7500.0128 per 28 day course
Cost of placebo	• Not applicable
Model Structure	*A three health-state partition survival model: pre-progression, post-progression, and death. Time spent in each of these states was determined by two end-points of Study 19: PFS (primary outcome), OS (Study 19 not powered for OS). All patients assumed to start in the pre-progression state.*
Key Data Sources	*Study 19[1] (September 2015 data cut-off)—BRCAm sub-group population used*
CUA: cost-utility analysis; PFS: progression-free survival; OS: overall survival; BRCAm: BRCA mutation	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

- Relevant issues identified by the CGP included:
  - *Given the small patient numbers, the statistical design of the study combined with the multiple time point analyses in Study 19, there was concern that results demonstrated in the BRCA-m population may be due to type I error (accepting a false hypothesis as correct). The CGP concluded that there may be a net clinical benefit to olaparib in the treatment of patients with recurrent, platinum-sensitive ovarian cancer and that confirmatory data is required to validate these results.*
  - *The demonstrated magnitude of benefit on the PFS from olaparib in the BRCA mutated subgroup is considered clinically meaningful.*
  - *The data provided by the three instruments used to measure patient reported outcomes in the trial suggest no change in the physical and functional well-being of patients on the olaparib maintenance arm as compared to those on the placebo arm, irrespective of BRCA status.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered that olaparib is an oral drug with fewer adverse events (toxicities) than other chemotherapies and provides a maintenance treatment option for BRCAm positive, platinum-sensitive ovarian cancer after first-line platinum-based chemotherapy. Adverse events, and the cost associated with maintenance therapy were considered in the economic analysis. Clinician input also noted that after platinum based chemotherapy, there currently is no maintenance therapy given. Trials have previously shown benefits of continuing the initial chemotherapy, in terms of progression free survival, but not for quality of life or overall survival and cumulative toxicities usually limit the utility of those approaches. A delay of symptomatic relapse is clinically meaningful in this setting since patients suffer tremendously with the symptoms of this disease.

Summary of patient input relevant to the economic analysis
Patients considered prolonged survival, adverse events and accessing therapies as important. Prolonged survival and adverse events were incorporated into the model; olaparib is administered orally and thus reduces the burden of drug administration.

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:

<u>Enablers</u>
- new treatment option that is an oral drug; and
- capsule strength allows for easy dose adjustment.

<u>Barriers</u>
- resources required for BRCA testing;
- maintenance therapy, that does not replace intravenous chemotherapy, where appropriate;
- lack of phase III overall survival data; and
- large pill burden for patients.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (LY)	1.09	0.76	Unknown
Progression-free	1.30	1.21	-
Post-progression	-0.21	-0.45	-
ΔE (QALY)	0.83	0.58	Unknown
Progression-free	0.97	0.90	-
Post-progression	-0.14	-0.32*	-
ΔC ($)	$164,492	$154,775	Unknown
ICER estimate ($/QALY)	$197,368	$266,709	Unknown

* The increase in magnitude of the negative QALY is due to treatments in the post-progression period. Specifically, in the EGP reanalysis, the subsequent treatments increased in the placebo arm and decreased in the olaparib arm. Therefore the difference in the negative QALY is greater in the EGP's estimate.

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

- *Population used to inform this analysis is a sub-group of the randomized controlled trial population. Therefore, imbalances between groups may be present. Known confounders can be adjusted for in the analysis, but it is always preferable to use randomization to balance groups for unknown confounders.*
- *Progression-free survival data was not collected after June 2010. Despite this being the primary end-point, the economic model relied on time to discontinuation of therapy as a proxy for progression-free survival.*
- *Given that the fit of parametric curves for overall survival were not good, the EGP used the Kaplan-Meir (KM) curve from the trial for the duration of the trial (76 months for the olaparib arm) with extrapolation using parametric curves on the remainder of the time horizon to estimate OS. Further, given that the BRCAm population was not powered for overall survival differences and was not statistically significant corrected for multiple time point analyses, the uncertainty in the overall survival data is high.*

1.4 Detailed Highlights of the EGP Reanalysis

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

<u>Lower bound changes:</u>

- Time horizon: 10 years instead of 15 years. The CGP identified that in clinical practice, 99% of patients will have died by 7 years.
- Extrapolation of OS: Given that the fit of parametric curves for overall survival were not good, the EGP used the Kaplan-Meir (KM) curve for the trial period (76 months maximum follow-up in olaparib group) with parametric extrapolation on the remainder of the time horizon to estimate OS.
- Proportion receiving subsequent treatment. As outlined previously, other inputs in the model utilized only BRCAm population; given that differences in BRCAm patients and non-BRCAm patients may exist for subsequent treatments, the proportion receiving subsequent treatment was based on data for BRCAm patients.

- Utilities from BRCA population only from Study 19. The base case analysis used utilities derived from the BRCAm population in the pre-progression period, followed by utilities from the OVA-301 trial for the post-progression period. As the remaining inputs in the model are from the BRCA population only, the EGP agreed that utilities were best used from BRCA population only for both pre- and post-progression health states.

Upper bound changes:

- Study 19 collected PFS data only up to the 2010 data cut-off. For the purpose of the economic evaluation, time to treatment discontinuation (TDT) was used as a proxy for PFS over the rest of the trial period. Use of PFS from 2010 data cut-off to model PFS instead of TDT was explored as part of the upper bound of the EGPs best case estimate.
- The base case did not include BRCA testing. The inclusion of BRCA testing was included as part of the upper bound.
- Unadjusted covariates. Although the Study 19 was randomised, the efficacy inputs used in the economic analysis were derived from within the BRCAm subgroup of patients. It is unclear how the randomization may have affected important covariates in this subgroup population. To account for potential imbalances in baseline factors, the submitter adjusted for a number of baseline covariates that are considered to be important prognostic factors (ethnic descent (Jewish *vs* non-Jewish), time to progression on penultimate platinum therapy (6–12 months *vs* >12 months), and response to platinum therapy before randomisation (complete response *vs* partial response)). It is notable that visual inspection of the distribution of patients between arms for the covariates of interest did not demonstrate a large variance. Additionally, Chi-square tests did not find any differences in these baseline covariates The EGP therefore explored the use of results unadjusted for these covariates.
- Equal benefit at trial end date. At 78 months, when trial follow-up ended, the HR between the two treatment groups was set to 1, and therefore assumed that those in the olaparib group had no additional benefit to those in the placebo group.
- In Study 19, results for OS were based on a relatively small patient number and no difference in overall survival was measured at any of the interim analysis. Additionally, there was no statistical plan for examining OS in the BRCA subgroup. Therefore, as the upper bound, the EGP examined equal survival benefit between treatment groups. Given the magnitude of difference in benefit seen in effectiveness (0.12 as a scenario analysis), this leads to a large ICER and as such the EGP did not place an upper bound on its base case.

Table 3. Detailed Description of EGP Reanalysis

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	$164,492	0.83	$197,368	-----
EGP's Reanalysis for the Best Case Estimate				
LOWER BOUND				
Time horizon – 10 years	$155,412	0.72	$214,778	$17,410
Use of KM data with extrapolation for remainder of time horizon	$164,550	0.71	$230,429	$33,061
Utilities – BRCA population only	$164,492	0.82	$200,843	$3,475
Proportion receiving subsequent Tx- BRCAm only	$163,741	0.83	$196,567	$901

Best case estimate of above parameters	$154,775	0.58	$266,709	$69,341
UPPER BOUND				
PFS to inform PFS curve	$153,410	0.76	$214,269	$16,901
Inclusion of BRCA testing, 20% previously tested	$168,492	0.83	$202,167	$4,799
Unadjusted covariates	$165,591	0.74	$223,794	$26,426
Equal benefit at trial end	$164,673	0.74	$221,095	$23,727
Equal overall survival	$164,844	0.12	$1,326,919	$1,129,551
Best case estimate of above parameters			Difficult to estimate	

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the number of patients eligible under the Ontario Drub Benefit plan for coverage, the inclusion of BRCA mutation testing, and cost of the drug (see Table 18 for magnitude).

Key limitations of the BIA model include the assumption that not all patients would be eligible for olaparib from a funding perspective. This parameters was able to be modified and explored by the EGP, however, the model is not designed in the most transparent fashion.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for olaparib when compared to placebo ("watch and wait") is:

- At least $266,709/QALY; the upper bound is undeterminable due to uncertainty in overall survival data
- The extra cost of olaparib at the lower bound is $154,775. *Factors that most impact costs are the time horizon, treatment duration and the cost of olaparib.*
- The extra clinical effect of olaparib at the lower bound is 0.58 (ΔE). *Factors that most impact effectiveness include the magnitude of OS benefit, use of KM data for overall survival, time horizon and the source of PFS data.*

Overall conclusions of the submitted model:

- *There is significant uncertainty in the modeled overall survival, and the fit of time to discontinuation data to progression-free survival data from a previous data cut-off.*
- *Data inputs were not consistent across the submitted model. In some instances, data from BRCAm patients were used and in others the ITT population was used.*
  If there is an overall survival benefit with olaparib, as observed in the trial, then the EGP best estimate lower bound is likely. If there is no net overall survival benefit with olaparib, the ICER is significantly higher; the EGP is unable to determine the magnitude of this increase.

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 [drug name and indication] 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 non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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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