AstraZeneca Response to ICER's Draft Report on Ovarian Cancer and PARP inhibitors

AstraZeneca would like to thank ICER and Midwest CEPAC for the opportunity to submit comments on Midwest CEPAC's draft report *Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value*.

In 2014, Lynparza® (olaparib) was the first PARP inhibitor approved for the treatment of ovarian cancer. Olaparib was approved in the late line, where there was a high unmet medical need. It is currently undergoing review by the FDA based, in part, on the Phase III SOLO2 trial and Phase II Study 19 trial, for maintenance treatment after a response to platinum-based therapy. In SOLO2, olaparib demonstrated a significant improvement in progression-free survival (PFS, 19.1 months (olaparib) vs 5.5 months (placebo)). Results from this study further demonstrated a significant improvement in time without symptoms of disease or toxicity versus placebo and quality-adjusted PFS. Using the validated FACT-O assessment tool, no deterioration in health-related QOL was observed. The Study 19 trial, with longer follow-up, has shown long term benefit for patients, including a longer median overall survival (OS, 29.8 months (olaparib) vs 27.8 months (placebo)). Patients can benefit from prolonging duration of remission while maintaining QOL.

While AstraZeneca welcomes the opportunity to share data and insights to support the value of Lynparza we do continue to have concerns around certain aspects of ICER's methodology and the limited level of transparency around the models used by ICER. At this time, we cannot endorse ICER's methods or the conclusions outlined in ICER's draft report. However, AstraZeneca would like to continue to engage with ICER fairly, and as appropriate further the discussion around appropriate mechanisms to effectively evaluate emerging therapies.

AstraZeneca has identified five key areas of concern with the report: 1) transparency of methods and results 2) lack of justification for key aspects of report, 3) presentation of information, 4) measurement of value, and 5) budget impact framework. We are providing recommendations to ensure the full value of innovation is incorporated to produce a report that provides an assessment that is meaningful to a broad range of stakeholders, including patients and their families, clinicians, manufacturers, and payers.

1. Transparency of Methods and Results

Lack of details surrounding ICER's assumptions, methodology, and data in the report makes interpretation of the results challenging and limits the ability of researchers to engage in meaningful discourse in response to the report. Consequently, individuals who read ICER's report are more likely to be burdened in understanding the approach and results based on a subset of relevant information rather than focusing on the benefits of PARP inhibitors to patients with ovarian cancer.

Recommendation: ICER should present detailed information around all assumptions, methods, and results. More specifically, we request that ICER provide the following additional information and justification for any decisions made with respect to their methodology:

- Justification for using olaparib OS data as model inputs for niraparib and rucaparib in absence of conducting an indirect treatment comparison, along with published examples of this approach being taken in other studies

- Specific details for what dose reductions were incorporated in the model; how reductions were incorporated, and the impact on costs, Adverse Events (AE), and utility
- Whether the impact of dose reductions on efficacy were considered, and how efficacy adjustments were incorporated into the model
- Details for the distribution of subsequent treatments and best supportive care (BSC), and provide a reference supporting why this distribution was chosen
- Present the set of functional forms considered for survival in the analysis, and justification for the final chosen form
- Justification for why the 4L population size for olaparib in the budget impact analysis is the same size as the 3L population for rucaparib (4L population should be smaller)

Additionally, we request that at a minimum, ICER present additional relevant results in their report, including:

- Present plots of estimated OS/PFS against actual data used in the model
- One-way sensitivity results for OS, PFS, dose reductions, discontinuations
- Model fit statistics and plots of estimated OS/PFS against actual data for *all* considered functional forms
- Sensitivity analyses for all considered parametric functional forms for survival

2. Lack of justification for inconsistent decisions in key aspects of the report.

ICER's cost-effectiveness (CE) thresholds are arbitrary and too low for the oncology setting.

A wide range of value thresholds have been proposed in oncology, with thresholds closer to $300,000 among patients with metastatic cancer.[1] Olaparib would be cost-effective in both the 4L and maintenance setting under this threshold. ICER's chosen thresholds of $50-150K result in olaparib being deemed not cost-effective in the maintenance setting, which could potentially limit access to effective treatment for ovarian cancer patients.

Recommendation: ICER should either select higher CE thresholds that are better aligned with patient preferences in oncology (e.g., 300K) or remove CE thresholds from their report entirely.

ICER's utility weights in their CE model are counterintuitive given the relative toxicities associated with olaparib and PLD+C.

In their CE model, the utility weight for olaparib (on treatment) is 0.77 and PLD+C is 0.79. However, in their comparative clinical effectiveness assessment, ICER points out that they believe olaparib has a better safety profile than chemotherapy. Additionally, PLD+C is administered intravenously, which places additional burden on patients (one study found that 30-minute and 2-hour infusions have disutilities of -0.02 and -0.04, respectively).[2] Given these points, the rank order of the utility weights for olaparib and PLD+C is counterintuitive.

Recommendation: ICER should adjust the relative size of the utility weights for olaparib and PLD+C to reflect the better tolerability of olaparib and decreased burden associated with tablets compared to IV administration.

In the maintenance setting, ICER does not justify incorporating PFS and OS data from different trials or the application of olaparib OS data to niraparib.

ICER's model incorporates PFS from SOLO2 and OS from Study 19, and additionally applies OS data from Study 19 to niraparib. We recognize that OS data for SOLO2 and niraparib is not yet mature. However, absence of data is not sufficient justification to mix data across trials and therapies from a methodological perspective, particularly in light of ICER's determination that an indirect treatment comparison was not feasible.

Recommendation: ICER should provide additional justification for mixing OS and PFS data from different trials in their model and discuss the implications of applying olaparib OS to niraparib for the results. Finally, ICER should discuss whether they considered alternative approaches to incorporating OS and PFS data from different trials and why they ultimately chose not to implement those alternatives.

ICER's decision to exclude bevacizumab from the final set of comparators in the maintenance setting but include in the budget impact analysis requires additional justification.

Although the focus of the report is on PARP inhibitors, the current NCCN guidelines recommend bevacizumab in the maintenance setting if it was used upfront with carboplatin/paclitaxel.[3] Additionally, market research suggests that bevacizumab is used in the maintenance setting, making it a relevant part of the treatment landscape in ovarian cancer.[4] ICER's decision to not include Bevacizumab as a comparator is not reflective of real world practice. ICER excludes bevacizumab since they could not identify any comparable data. However, given ICER chose to apply OS data across trials for PARP inhibitors in this study, they should justify why a similar strategy was not implemented to include bevacizumab in the study. Finally, despite not incorporating bevacizumab in the CE analysis, ICER includes bevacizumab in the budget impact analysis. If ICER believes no comparable data exists for PARP inhibitors and bevacizumab, then bevacizumab should not be a relevant comparator in the budget impact analysis.

Recommendation: ICER should include bevacizumab in the CE analysis in the maintenance setting to capture the full set of relevant treatments given to patients with ovarian cancer. If ICER does not include bevacizumab in the CE portion of the report, then they should remove it from the budget impact analysis. Finally, ICER should conduct a sensitivity analysis around any assumed parameter values.

3. Readers may draw inappropriate conclusions based on the manner in which ICER presents information and results in their report.

Presentation of NCCN guidelines for olaparib in the maintenance therapy is incomplete.

ICER notes that that NCCN does not recommend olaparib as maintenance therapy. However, the full statement in the NCCN guidelines reads "the NCCN panel decided not to recommend

olaparib as maintenance therapy for patients with platinum-sensitive disease because panel members feel that current data are not sufficient for recommending olaparib in this setting."[3] This statement provides important context around the current non-recommendation, specifically that the available data has been deemed insufficient. ICER's failure to mention this point leaves readers to draw their own conclusions, and may cause some to think olaparib is not recommended in maintenance due to absence of positive trial findings or toxicity concerns, neither of which is the case.

Recommendation: ICER should update their content in the NCCN section for olaparib to include the full NCCN statement for the maintenance population.

Although ICER conducts a probabilistic sensitivity analysis (PSA) and includes CE thresholds up to $250K, these results are not pulled through to the body of the report.

ICER is inconsistent with their chosen CE thresholds across their PSA (in appendix) and baseline results. Importantly, in the 4L setting, olaparib was found to be cost-effective at the $200K ($250K) threshold in 98.9% (99.8%) of simulations.

Recommendation: Given that higher CE thresholds are considered in the PSA, these should be applied to the baseline analysis. Additionally, even if some results tables are presented in an appendix, discuss all results in the main body of the report.

Readers will potentially compare cost-effectiveness results across PARP inhibitors.

ICER presented CE results separately by therapy. In absence of an indirect treatment comparison, CE results for olaparib in the 4L and maintenance settings should not be compared to rucaparib or niraparib, respectively. The fact that ICER uses OS data from olaparib trials for rucaparib and niraparib may result in readers concluding that comparisons across therapies are reasonable. Such conclusions can only be made if appropriate methodology is used.

Recommendation: ICER should conduct an appropriate analysis (i.e., indirect treatment comparison) so that comparisons can be made across PARP inhibitors. In absence of such an analysis, to ensure readers and decision-makers do not make comparisons across therapies, ICER needs to emphasize this point throughout the final report.

4. Several aspects of ICER's approach result in an undervaluation of olaparib, and fail to reflect the goals of an effective health care system

ICER's CE model fails to capture important sources of value.

Although ICER includes a section with other benefits and contextual considerations in their report, non-clinical benefits are not incorporated into the CE model, which results in an underestimation of the value of olaparib. One study estimates productivity losses of $176K per death due to ovarian cancer, yet productivity is not incorporated into ICER's model.[5] Similarly caregiver burden is omitted, even though we expect to see a reduction in caregiver burden associated with olaparib given the improved safety profile and reduction in time spent in the doctor's office, as infusions are not needed.

Finally, ICER does not consider patient priorities or other sources of value important in oncology, which are not limited to but include option value and the value of hope. Patients

place high value ("value of hope") on therapies that give them the possibility of having improved survival in the tail of the survival distribution, allowing them to potentially achieve survival above and beyond improvements in median survival.[6] Patient perspectives such as anxiety of recurrence and value of therapy that may prolong the remission are not captured by framework used by ICER. Therapies may also provide option value by extending a patient's life long enough to survive to the next major breakthrough.[7]

Recommendation: ICER should incorporate estimates of indirect measures and other non-clinical sources of value into their analysis. At a minimum, ICER should conduct a sensitivity analysis that incorporates additional sources of value in the model. If ICER does not incorporate these measures, they should stress that their estimated CE ratios represent an upper bound since their model does not incorporate all sources of value.

ICER's recommendations for price reductions for olaparib are inappropriate.

Based on their baseline CE results, ICER determined olaparib's WAC price should be reduced by +9 (increase)-54% in 4L and 49-82% in maintenance to meet ICER's selected thresholds. These price reductions are inappropriate for several reasons, the first of which being the premature nature of the study, particularly in the maintenance population. Abstracting from any other methodological issues with the report, the fact that ICER's analysis cannot incorporate OS from SOLO2 or NOVA implies that their estimated incremental CE ratios are preliminary, and consequently the recommended price reductions should be viewed as preliminary. Second, we have already noted that ICER's estimated CE ratios do not capture the full value of olaparib, which implies recommended price reductions are overstated.

Recommendation: Remove drug price reduction recommendations as they are based on a premature analysis, arbitrary thresholds, and an underestimation of the true value of therapy. If ICER includes drug price reduction recommendations, they should stress these should be interpreted with caution.

5. Budget impact framework is not a measure of value and should be removed from the report

ICER's budget impact analysis is not a measure of value or affordability, and would be rejected by standard economic analysis.[8] Despite updating their value framework generally, ICER's budget cap is still based on the same arbitrary criteria (e.g., GDP growth, number of drug approvals, etc.). Additionally, the budget cap still penalizes therapies aimed at a cancer with high prevalence – a cure for said cancer that applies to a large population will likely exceed the budget cap despite having high value to society. Finally, inclusion of a budget impact analysis as part of the value framework increases the risk of reduced patient access to novel therapies. Moreover, it creates disincentives for manufacturers as it relates to future innovation, which may lead to fewer treatment options in society downstream.

Recommendation: Remove the budget impact section of the report since it is not an appropriate measure of value.

References

1. Seabury, S.A., et al., *Patients value metastatic cancer therapy more highly than is typically shown through traditional estimates.* Health Aff (Millwood), 2012. **31**(4): p. 691-9.
2. Matza, L.S., et al., *Utilities associated with subcutaneous injections and intravenous infusions for treatment of patients with bone metastases.* Patient preference and adherence, 2013. **7**: p. 855-865.
3. National Comprehensive Cancer Network. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (Version 2.2017) July 30, 2017]; https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.
4. Kantar Health, *Treatment Architecture: United States Ovarian Cancer*, in *CancerMPact*. July 2017.
5. Bradley, C.J., et al., *Productivity Costs of Cancer Mortality in the United States: 2000–2020.* JNCI Journal of the National Cancer Institute, 2008. **100**(24): p. 1763-1770.
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8. National Pharmaceutical Council. *Comments on Proposed Updates to ICER's Value Assessment Framework*. 2017; http://www.npcnow.org/newsroom/commentary/npc-comments-proposed-updates-icers-value-assessment-framework#_edn2.

Genentech
A Member of the Roche Group

August 9, 2017

Institute for Clinical and Economic Review (ICER)
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Dear ICER Review Panel:

Thank you for the opportunity to provide comments on the ICER draft evidence report titled "Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness & Value". This letter is in response to your request for comments relevant to Avastin® (bevacizumab). To enhance the robustness of the final report, Genentech recommends ICER address the following:

- **In Section 6.1 Long-Term Cost Effectiveness (page 46), we support the decision to exclude Avastin in the cost-effectiveness modeling.** Avastin is not an appropriate comparator in Population 1 due to the lack of data in BRCA-mutated patients in the recurrent setting, or in Population 2 for the reasons described in Appendix A. We therefore recommend the removal of the following references to Avastin from Section 6.1 Long-Term Cost Effectiveness for clarity:
    - Figure 3, page 44: Avastin is currently listed as a comparator.

- **In Section 6.3 Potential Budget Impact, there are some methodological details omitted or that require clarification, without which the interpretability of the findings is limited.** Specifically:
    - On pages 60-61 and in Tables 21 and 23, it remains unclear what the current market share distributions for observation and Avastin are assumed to be, and whether the PARP inhibitors are assumed to completely replace observation and Avastin, or whether some use of observation/Avastin is assumed to continue in the future. Please clarify in the final version.
    - Due to differences in trial design and population, comparable clinical data is not available for Avastin in the populations of interest, and the assumptions and limitations of extrapolating the olaparib data to Avastin should be explicitly discussed within the report. It is our understanding that the treatment duration of Avastin in the platinum-sensitive maintenance setting is assumed to be the same as olaparib for both gBRCA and non-gBRCA patients. The Avastin clinical trials conducted in platinum-sensitive ovarian cancer (OCEANS[1] and GOG-0213[2]) support its use per the FDA-approved indication[3]; however, the designs of the Avastin trials differ considerably from the PARP inhibitor trials[4,5] (see Appendix A).

- The net price assumption for Avastin for the budget impact analysis is inaccurate and overestimates the net price compared to our internal analyses.

- **Use the latest version of the NCCN Ovarian Cancer Guidelines v2.2017[6] and remove the statement "in patients who have received prior bevacizumab" (Section 3.2 Clinical Guidelines, Page 12).**
  - For Avastin-containing regimens in platinum-sensitive and resistant ovarian cancer, the following footnotes were revised/added in the latest version:
    - "In patients who have not previously received bevacizumab" was removed and replaced with "There are limited data on the efficacy of bevacizumab in the recurrence therapy setting for patients previously treated with bevacizumab".

Please refer to the full prescribing information for complete product indication and safety information, available at:

https://www.gene.com/download/pdf/avastin_prescribing.pdf

We welcome the opportunity to provide clarification should ICER have questions on any of these points. Please contact me directly at (650) 243-7134 or hansen.jan@gene.com.

Respectfully Submitted,

Jan Hansen, Ph.D.
Vice President, Evidence for Access
U.S. Medical Affairs, Genentech

References:

1. Aghajanian C, Goff B, Nycum LR, et al. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. Oct 2015;139(1):10-16 [63]; Aghajanian C, Blank SV, Goff BA, et al. OCEANS: A randomized, double-blind, placebo controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30:2039-2045.
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5. Mirza MR, Herrstedt, Oza AM, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med 2016;375:2154-64.
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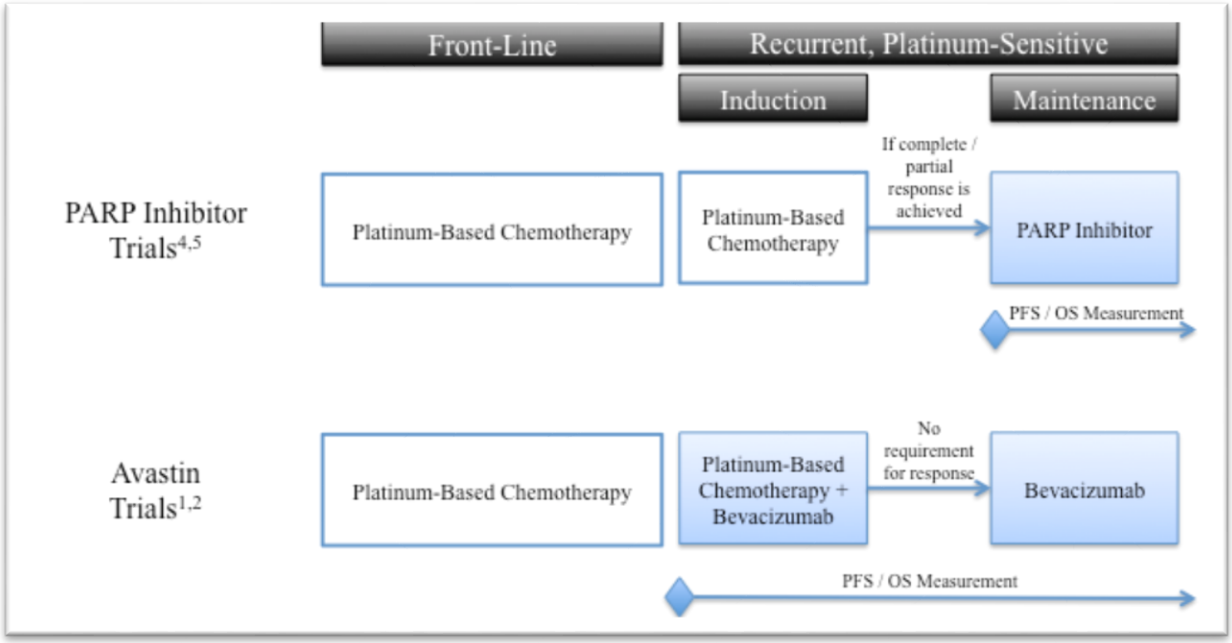
Appendix A: Differences Between PARP Inhibitor and Avastin Trials in Recurrent, Platinum-Sensitive Ovarian Cancer



- Patient population: The PARP inhibitor trials were limited to the maintenance setting only, whereas OCEANS and GOG-0213 examined induction with Avastin and chemotherapy for 6-10 cycles followed by maintenance with Avastin monotherapy.[1,2,4,5] Additionally, the PARP inhibitor trials were conducted in patients who had shown sensitivity to prior platinum-based treatment and had received at least two such regimens (front-line and recurrent setting), whereas in the Avastin trials, patients received only one prior platinum-based treatment (front-line setting), and the second platinum-based treatment (recurrent setting) was incorporated in the trial design and thus represented in the clinical trial results.

- Response criteria for inclusion: In OCEANS and GOG-0213, patients were not required to have a response to the induction cycles in the recurrent setting in order to continue on to maintenance Avastin.[1,2] On the other hand, the trials for the PARP inhibitors required patients to have a complete or partial response to chemotherapy treatment in order to be eligible to receive PARP inhibitors in maintenance.[4,5] This is a significant difference in the patient populations that were included in the clinical trials, as patients who respond to induction chemotherapy treatment are a clinically different population (responders) compared to a mixed population of responders and non-responders to induction treatment, as was the case in the Avastin trial populations.

- Timeframe for measurement of outcomes: Progression-free survival (PFS) and overall survival (OS) were measured from the time of randomization, and therefore included

induction and maintenance treatment for the Avastin trials; however, PARP inhibitor trials' PFS and OS were limited to post-induction maintenance only.[1,2,4,5]

- Subgroup analyses: The OCEANS and GOG-0213 trials for Avastin were conducted in all-comer populations, and subgroup analyses for gBRCA and non-gBRCA patients were not conducted.[1,2] Therefore, to our knowledge there is no direct evidence to support the assumptions of Avastin's clinical effectiveness in gBRCA and non-gBRCA subgroups in recurrent, platinum-sensitive ovarian cancer.

August 8, 2017

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We at TESARO appreciate the opportunity to submit comments on ICER's Draft Evidence Report assessing the effectiveness and value of PARP inhibitors, a paradigm-shifting class of medicines for ovarian cancer — a disease with limited treatment options.

We recognize the challenge in performing such analyses given the differences in study design and varying approaches for assessing Progression Free Survival (PFS) across the different trials, including substantial differences in the frequency at which scans were conducted. Hence, we fully concur with ICER's decision to evaluate each product separately, and to avoid cross-trial comparisons that would be inappropriate given the differences in trial populations and endpoint assessment methodology. We also concur with the finding in the report that the budget impact of this class does not reach the threshold requiring active management that would restrict access to these important new therapies. Further, we appreciate the efforts that ICER has made to seek and incorporate input from stakeholders.

However, we have significant concerns about ICER's draft evidence report. The results of the analysis are driven primarily by assumptions regarding overall survival. Since these data are not yet mature for ZEJULA, ICER made assumptions regarding ZEJULA's OS benefit that are not supported by evidence. The results of the ICER model are almost entirely dependent on these assumptions which are not evidence based, leading to conclusions that we view as flawed. Given this, we believe the release of these findings is premature, and we do not consider them ready for a broad discussion. We also have significant concerns about basing any policy discussions that could restrict patient access on these results.

We believe that any discussion of the value of maintenance treatment in ovarian cancer should fully capture all patient benefits, including prolonging time without disease progression and delaying the need for additional toxic IV chemotherapy. In a study of women with ovarian cancer, participants' ratings and rankings placed the highest level of importance on PFS compared to any other attribute.[1] We do not believe that the ICER approach fully captures patient perspectives regarding benefits of prolonging PFS.

More detailed comments and recommendations regarding the content of the report are provided below.

Summary and Evidence Ratings:

1. We appreciate ICER's recognition that ZEJULA provides substantial benefits to patients with a germline BRCA mutation. However, we disagree with the characterization of the benefit of

ZEJULA in patients without a germline BRCA mutation. Patients without germline BRCA mutation have a very poor prognosis. As shown in the NOVA trial, the median progression free survival in the standard of care group was only 3.9 months. ZEJULA reduced the risk of disease progression or death by 55% in this population. In this non-g*BRCA*mut cohort, the estimated probability of progression free survival was more than double in the ZEJULA group compared to the control group both at the end of year 1 (41% vs 14%) and year 2 (27% vs 12%).[2] We believe that this constitutes a substantial benefit for this population with high unmet need and poor prognosis. We request that ICER amend its assessment to recognize the substantial benefit that ZEJULA offers patients without germline BRCA mutation.

Dosing and relationship to cost:

2. On page 55, the report states that dose intensity and dose adjustments were taken into account in calculating drug costs. However, we could not find additional details in the document as to what dose was used to calculate the cost of ZEJULA. The average dose intensity (sum of the daily doses actually consumed divided by total duration of treatment) of ZEJULA in the NOVA trial was approximately 200mg. We believe that at the cost based on this average dose ZEJULA delivers excellent value relative to other treatment options for both patients and payers. We request clarification in the report regarding whether the cost of ZEJULA was calculated based on its average dose intensity.

Modeling of PFS and OS:

3. The cost-effectiveness analysis results are driven mostly by assumptions made regarding survival gain. Robust data to estimate survival gain do not exist in the non-maintenance setting, given that none of the trials supporting the evaluation in this population had a control arm. Additionally, the survival data for ZEJULA from the NOVA trial are not yet mature. Given the lack of robust survival data, the results of ICER's analysis are highly uncertain. We recommend that ICER clearly acknowledge this high level of uncertainty in Section 6.4 when the results are presented, and request that ICER add a caveat to this section noting that the results need to be interpreted with caution due to this uncertainty.
4. Based on the information provided in the report, we could not replicate the PFS, OS, or QALY gain estimates. The ICER lung cancer assessment[3] provided detailed model fit curves for PFS and OS, which are not provided in this report. We request more detailed information regarding the parametric curves used to extrapolate PFS and OS so that we can better understand the model results.
5. The OS benefit seems to bear no relationship to the PFS benefit in the model used in the report. This disconnect creates the potentially perverse situation in which the more effective a product is in terms of PFS the higher the cost-effectiveness ratio, as the longer PFS results in higher costs, but in minimal QALY gain. A detailed critique of the approach is provided in the recently released report by the NICE Decision Support Unit (DSU).[4] We request that the report describe how the assessment team has addressed the limitations of the modeling approach outlined in the NICE DSU report

6. Specifically, we have significant concerns about the approach used to extrapolate OS from the ZEJULA NOVA trial. Data from the BRCA mutated patients in the olaparib Study 19 trial were used to estimate the OS in ZEJULA treated g*BRCA*mut patients in the NOVA trial. This was done without any adjustment for the difference in PFS observed in the two trials, even though the difference in median PFS in the ZEJULA NOVA trial was 15.5 months[5], while the difference in median PFS in BRCA mutated patients Study 19 was 6.9 months[6]. Further, in the non-g*BRCA*mut population, no difference in OS between ZEJULA and placebo treated patients is assumed without a clear rationale provided for this assumption.

   Instead of using data from Study 19 to model the survival benefit with ZEJULA, we believe that estimating OS based on the observed PFS in NOVA would be a better modeling approach. There are several reasons to expect a direct relationship between the PFS observed in NOVA and OS. First, the time between first and second progression in the NOVA trial was the same regardless of whether the patient received ZEJULA or not. This indicates that ZEJULA treatment did not have a negative impact on subsequent treatment, increasing the likelihood that longer PFS will translate to OS. In addition, more ZEJULA treated patients will be eligible for platinum therapy in the next line of treatment, as more ZEJULA treated patients will meet the eligibility criterion of a platinum free interval of more than 6 months. It is well documented that platinum eligible patients have a better prognosis than patients who are not.[7]
   We recommend that the model explicitly link PFS and OS gains so that the benefit in improving PFS is better captured in the QALY gain. For example, we suggest that the model set the mean LYG to be equal to the mean PFS gain in the basecase.
7. The olaparib and rucaparib treatment trials were single arm studies and did not have a control group. The survival data for the control group in the report were derived from the Hanker et al. study.[8] This study included patients with and without a BRCA mutation; however, in Table E5 this study is erroneously classified as being in the BRCA-mutated population. Multiple studies have shown that BRCA mutated patients have a better prognosis in terms of survival compared to patients without a BRCA mutation.[9,10] Hence, it is highly likely that the OS for the control group derived from Hanker et al. substantially underestimates what the survival would be in a control group of BRCA mutated patients. As a result, the analysis potentially substantially overstates the survival gain seen with olaparib and rucaparib in this setting. We request that the analysis of the non-maintenance population use OS from a comparable BRCA mutated population rather than data from an all-comers population.
8. For maintenance treatment with olaparib, the PFS used in the model was not derived from the primary endpoint, but from the Blinded Independent Central Review (BICR), which was a sensitivity analysis of PFS. We have concerns about this beyond the bias that could be introduced by choosing one of the sensitivity analyses rather than the primary endpoint. In the NOVA trial, the primary endpoint included a central review of both imaging and clinical symptoms. This is important in ovarian cancer, since progression is assessed in clinical practice based on both symptoms and imaging. Based on the recent publication of the SOLO-2 trial, the BICR sensitivity analysis did not include an assessment of clinical symptoms.[11,12] In addition, the appendix to the publication notes that the discrepancy in the point estimates between the

primary endpoint and BICR sensitivity analysis may have been driven by informative censoring, whereby approximately 25% of patients who had progressed according to investigator assessment had not yet been shown to progress by BICR.[12] When the patients classified as having been informatively censored were assumed to have an event at the next scan (+12 weeks) the median PFS in the olaparib group was 19.6 months (Supplementary Results section of the appendix). As is evident, the median PFS estimate for the BICR sensitivity analysis is extremely sensitive to adjustment for informative censoring of patients included in the primary endpoint but not the BICR. Hence, we recommend that the model use the primary endpoint from SOLO-2 rather than one of the many sensitivity analyses.

Adverse events and associated costs

9. In the model, cost related to hospitalization was used to estimate the cost of managing grade 3/4 AEs. However, most grade 3/4 AEs do not result in hospitalization, and hence this approach vastly overestimates the cost of AE management. This is particularly true for hematologic adverse events. We recommend that the model use a more accurate estimate of grade 3/4 AE costs and not use the cost of hospitalization to estimate these costs.

We thank you again for the opportunity to review and comment on the Draft Evidence Report. We hope that you find our comments to be helpful, and that you will take them into consideration in producing the next iteration of the report.

TESARO is a biopharmaceutical company devoted to providing transformative therapies to people bravely facing cancer. We are fully committed to ensuring access to our products for appropriate patients. For example, we offer the Together with TESARO (TwT) program to provide access and affordability solutions for patients who have no insurance or have difficulty affording their copays. While we welcome a balanced discussion of the value of treatments for patients facing ovarian cancer, we do not believe that this report should be the basis for limiting access to this important class of medications.

Sincerely,

Martin Huber, M.D.
Senior Vice President, Chief Medical Officer
TESARO, Inc.

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FORCE Response to Institute for Clinical and Economic Review (ICER) draft report, "Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value

August 9, 2017

Facing Our Risk of Cancer Empowered (FORCE) is the only national nonprofit organization serving all individuals affected by hereditary breast, ovarian, and related cancers (HBOC), and families with a BRCA or other inherited mutation that increases risk for these cancers. The following is FORCE's response to the Institute for Clinical and Economic Review (ICER) draft report, "Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value."

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, nonprofit foundations, health plans, provider groups, and health industry manufacturers.

ICER states that their review focuses on clinical outcomes, patient experience, costs, and cost-effectiveness. FORCE has concerns regarding the conclusions drawn by this report as there are significant differences in the patient populations used for comparative data and significant gaps in the costs used for value analysis. Additionally, the design of the analysis does not adequately represent the interests of patients, clinicians, and the hereditary cancer community.

We respectfully submit that this analysis of Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness & Value is premature and could be potentially harmful to patients since it may be used to drive practice as well as coverage decisions.

Concerns with the Comparators used for Effectiveness Analysis:

The first population of focus in the report is stated as "Adult women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer of high-grade serous or mixed serous/endometrioid histology who have a deleterious BRCA mutation and who have relapsed after initial cytoreductive surgery and multiple subsequent lines of chemotherapy.

However, the studies chosen as comparators for this population include women receiving only a 2nd line

of treatment and are not stratified for BRCA mutation status.

The second population of focus in the report is stated as "Adult women with platinum-sensitive, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer of high-grade serous or mixed serous/endometrioid histology who have received at least two prior platinum-based chemotherapy regimens, had a complete or partial response to the most recent regimen, and are candidates for maintenance therapy."

Again the populations included in the comparator studies are not equivalent to the PARP patient populations in terms of number of prior treatments, platinum sensitivity or BRCA mutation status.

Concerns Regarding the Economic Analysis:

We question some of the underlying assumptions used in the development of the cost models and therefore question the veracity of the resulting value conclusions.

1. A significant percentage of patients will have a platinum reaction which can result in additional costs in order to continue treatment (e.g. desensitization protocols) or result in the need to use another agent altogether in the 2+ line of treatment. There is no accounting for these additional costs in the Pegylated liposomal doxorubicin in combination with carboplatin (PLD + C) cost inputs.
2. The cost inputs also do not appear to include the cost of managing any side effects outside of grade 3 or 4 Adverse Events (AE's). The costs of managing side effects can include additional office visits, medications, additional blood tests, imaging and other functional tests, physical therapy, the use of compression garments, and so on.
3. The assumptions regarding costs associated with grade 3 or 4 AE's are not complex enough to accurately compare costs between the groups. The report uses estimated costs that are "an aggregate of emergency department and hospital costs associated with each adverse event". But this assumes that all grade 3 or 4 AE's require equal intervention and does not have a mechanism for calculating the cost of multiple episodes of an AE over the course of a treatment regimen vs. a single episode of an AE.
4. For bevacizumab adverse events, there is a 3-5% risk of bowel perforation and arterial thrombotic events (such as myocardial infarction or stroke) that needs to be included in order to accurately reflect the cost of that treatment. These events can be fatal and the costs associated with these AE's are extremely high.
5. The costs attributed to (PLD + C) and Bevacizumab treatments do not appear to fully include the cost of the infusion administration in addition to the drug cost even though the report acknowledges that the infusions require physician administration, travel, time away from work, etc., and attempts to account for it by using 120% of drug cost. We question if that accurately captures the costs associated with infusion administration – particularly for hospital based infusions.

PARP Inhibitors and the Hereditary Cancer Community

FORCE was introduced to early PARP inhibitor research in 2005, when phase 1 studies were conducted for people with solid tumors. We recognized the importance of these agents as the first targeted therapies to be developed to exploit the weaknesses in cancers caused by BRCA mutations; we then began educating the HBOC community about this early research and opportunities to participate in clinical trials. At the time, options were limited for people with advanced cancers due to a BRCA mutation. Our community was key to participation in, and completion of these clinical trials to open the possibility of new treatments for hereditary cancer.

Since that time, we have followed the research, educated our community about these agents, generated excitement about the research focus on HBOC, and facilitated clinical trial enrollment. For the HBOC community and the more than 1 million people in the U.S. that FORCE represents, a drug targeted against BRCA-associated cancers meant HOPE.

It took almost a decade of research before the first PARP inhibitor was approved. The approval of Lynparza marked the first new treatment for ovarian cancer in six years. The investment made in this personalized approach to cancer was extraordinary: a decade of research, and the participation of thousands of cancer patients enrolling in PARP inhibitor clinical trials to advance science for themselves, but also for their families. During this period of research, people who didn't qualify or who couldn't participate in a clinical trial regularly contacted FORCE, begging us to help them get access to PARP inhibitors. Many women who could not access PARP inhibitors died of ovarian cancer while waiting for these studies to be completed. For these women, the research wasn't quick enough. Many more will die if these agents are restricted. In the interim, while research has continued on these promising agents, how many other drugs have failed clinical trials? How many people have sacrificed health and life for all the research studies to test these agents?

The last few years have seen the approval of two additional PARP inhibitors for ovarian cancer, each with different indications and profiles. Some are approved for people with BRCA mutations but others are approved for a wider patient population. Each agent is different, and important to cancer survivors. It is critical that oncologists are not limited in their ability to match the right patient to the best individualized therapy for them.

The ICER value framework misses the perspective of patients affected by ovarian cancer and importantly, the value to communities such as the HBOC community; where use and continued investment into research of these agents in additional settings have the potential to improve and save even more lives than the comparative treatments. Since approval of PARP inhibitors, we have heard from the women with ovarian cancer who are living longer without chemotherapy on these agents. It does not capture the value to families and society; especially in the hereditary ovarian cancer community, where cancer tends to strike at a younger age, at the time of diagnosis these women are more likely to be working or raising young children. The median age of patients included in the PARP studies ranged from 57-62 years old which means that more than half of the patients were younger and likely still working or caring for children under the age of 18. Anecdotal data from ovarian cancer patients strongly points to fewer interruptions of activities of daily living for PARP inhibitor treatment as compared to chemotherapy treatment and higher quality of life. ICER chose not to perform a societal analysis (page 51: *Finally, given the typically advanced age and severity of disease in ovarian cancer patients, there was limited evidence on indirect costs, employment levels, and time missed at work.*

Therefore, we did not perform a societal analysis incorporating lost productivity). These are real costs that are borne by patients and their families and should have equal consideration to the cost borne by insurers in the calculations of value and cost-effectiveness.

By it's very nature, personalized medicine means fewer people may benefit from a new agent. As a society, we must decide if we want to continue to invest in progress to assure that the right patient gets the right drug with the most benefit and the least side effects or turn back the clocks to a one-size-fits-all approach. On an individual scale, these agents appear costly, but the savings in productivity, quality-of-life, and the ability to keep patients from wasting precious time on agents that won't work for them is the large-scale societal benefit of this approach. For personalized medicine to succeed, it is critical that these agents, upon FDA-approval, are accessible to patients and incorporated into clinical practice.

In 1998, Herceptin was approved for metastatic Her2neu-positive, metastatic breast cancer—a small subset of women with a very aggressive type of breast cancer. It took another 8 years before Herceptin was approved in an adjuvant, maintenance setting. Her2neu-positive breast cancer is particularly aggressive and cruel, and in the past when women (and men) were diagnosed, even at an early stage, they died. And now, almost 2 decades later, many are being cured. Women with ovarian cancer deserve the chance to access new therapies and the same opportunity for better outcomes. **The hereditary cancer community deserves access to these agents in earlier settings now, given the current evidence that these drugs improve outcomes, and the potential for tremendous community benefit from additional research.**

ICER states that they received input from multiple stakeholders – including patients – in developing this report. Yet, this draft appears to mainly represent and serve the interest of the health insurance industry. The cost effectiveness threshold applied in this report, represented as cost-per-quality-of-life-years, belies the fact that these life-years belong to actual people. The head-to-head PARP inhibitor studies that ICER calls for, will, (if they happen at all) cost us many more years, lives, and dollars. The ongoing studies will take many more years for the data to mature, in part as a result of the fact that so many women are doing well on these agents. **In the meantime, restricting coverage and reimbursement for these agents for women who may benefit from them will set back progress and send a discouraging message to scientists, patients, families, biotech companies and society.**

FORCE believes that discussions about cancer treatment value frameworks must include open and continued dialog between all stakeholders, including patients. The review process and resulting frameworks must focus on improving patient outcomes by maximizing patient benefit and equitable access to the best care, minimizing patient harm, and incentivizing continued research and development of more effective, less toxic therapies.

NATIONAL OVARIAN CANCER COALITION

August 7, 2017

Re: Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness & Value
Draft Evidence Report

The National Ovarian Cancer Coalition (NOCC) is pleased to have the opportunity to provide comment on the above ICER review of treatments for ovarian cancer. For more than 25 years, the NOCC has worked to fulfill our mission to prevent and cure ovarian cancer and improve the quality of life for survivors.

We take great pride in being a strong, national voice to advocate for those impacted by the disease, and therefore we feel it is important to present some of our collective concerns regarding the draft evidence report on ovarian cancer treatment, particularly with regard to PARP inhibitors.

As an organization with local chapters throughout the country, we engage directly with ovarian cancer patients, their loved ones, and caregivers on a daily basis. In addition, among the ranks of our volunteers and supporters are countless men and women who have lost mothers, daughters, sisters, and friends to this devastating disease. They remain involved in the cause in the hopes that their work and advocacy can change the course for those to come after them.

For far too many years, in a disease where recurrence is almost inevitable, those with ovarian cancer saw limited treatment options, particularly when the cancer returned. With the advent of this new class of drugs, in a short time we have witnessed our constituents go from despair to hope that a future for them is possible.

In Arlington, VA; Anne told us that when her cancer recurred for the 3rd time, she had fully expected the end of her days to include suffering through the effects of chemotherapy until they just wouldn't work anymore. Recently she was able to return to work, a meaningful part of her identity, thanks to her PARP inhibitor treatment.

In Pittsburgh, PA; Denise, a 4-time ovarian cancer patient currently enrolled in a PARP combination trial, recently planted a garden, something she has avoided for many years, fearing that she wouldn't be around to watch it grow.

Women like Anne and Denise demand that we present the value of hope in your review. For women like them, hope manifests in the ability to return to work, to plan a wedding, or to attend a graduation.

National Ovarian Cancer Coalition
2501 Oak Lawn Avenue, Suite 435
Dallas, TX 75219
Ovarian.org

As an important stakeholder in the ovarian cancer community, we feel that a review of these treatments so early into their discovery and commercialization may impact the progress we hope to see for this class of drugs and their potential use in combination therapies.

We know that there are so many variations in types of ovarian cancer, and that more personalized treatment options will improve outcomes. We see the value of Progression Free Survival for women with ovarian cancer, and support all efforts to extend quality survivorship to provide meaningful options to those living with cancer.

We respectfully submit these comments to provide additional patient perspective on the review, and would be happy to provide additional information and input as needed.

Sincerely,

David Barley
CEO, National Ovarian Cancer Coalition

Meredith Mitstifer, PhD
NOCC Board of Directors and Ovarian Cancer Survivor

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OCRFA
Ovarian Cancer
Research Fund Alliance

August 9, 2017

Steven Pearson, MD
Institute for Clinical and Economic Review
2 Liberty Square, Ninth Floor
Boston, MA 02109

Re: "Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness & Value Draft Evidence Report"

Dear Dr. Pearson:

Ovarian Cancer Research Fund Alliance (OCRFA) is the largest global non-profit organization dedicated to fighting ovarian cancer. OCRFA advances research to prevent, treat and defeat ovarian cancer, supports women and their families before, during and beyond diagnosis, and works with all levels of government to ensure ovarian cancer is a priority. We appreciate the opportunity to submit comments on ICER's recently released "Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness & Value Draft Evidence Report."

Our primary concerns are that patients are able to access medications when they and their physicians feel they are appropriate based on clinical trial data evidence, and that innovation in ovarian cancer drug development can continue to thrive. To that end, we have some specific concerns about the conclusions of this report, and about the potentially negative impact those conclusions could have on ovarian cancer patients.

Inadequate Data

Conversations with patients and clinical experts revealed a common thread: the publication of this report assessing economic impact of the use of PARP inhibitors to treat ovarian cancer is premature. PARP inhibitors represent a brand new class of medicine for ovarian cancer patients, many of whom face multiple recurrences, have few effective therapeutic options, and will eventually die of their cancer. As they are still in their infancy with respect to clinical use (rucaparib and niraparib were approved just within the past year), trials of PARPs are ongoing and much additional research on them and their use has yet to be completed. As the draft report acknowledges in section 4.3 "Controversies and Uncertainties," no overall survival data exist, and probably won't for a few years. In spite of this, the report makes assumptions in an attempt to fill in this gap. These assumptions are a poor substitute for actual data. Furthermore, as the report also acknowledges, the lack of comparative trials among the three drugs make it impossible to truly compare them. The report struggles mightily to draw conclusions, but comparing "apples to oranges" is problematic.

Research to determine who is most likely to respond to PARPs, even among BRCA mutation carriers, has yet to be completed. Discovery and validation of additional biomarkers, including tumor HRD-

ness, to identify potential non-responders is a need; this analysis could significantly impact the risk/benefit assessment of these drugs, and increase their value.

As it is clear that the coming years will offer far more data to consider more fully the clinical and cost effectiveness of these drugs, we strongly urge ICER to consider updating this assessment in the future.

Lack of Appropriate Comparators

Looking at the financial analysis, again the lack of OS data is acknowledged in the report as a major limitation. The report emphasizes the treatment of platinum resistant and platinum sensitive recurrences, yet the FDA approvals for olaparib and rucaparib are based on BRCA mutation status and have no dependency on the platinum resistance status. Furthermore, the lack of a true comparator for the different clinical scenarios is a problem here. Carboplatin and pegylated liposomal doxorubicin is used as the comparator arm versus olaparib, but carboplatin and PLD is not FDA approved in the United States for platinum sensitive cancer; rather, carboplatin/paclitaxel or gemcitabine/bevacizumab plus bevacizumab maintenance is approved. Bevacizumab is now FDA approved for platinum sensitive cancer, yet using no therapy versus a PARP inhibitor for maintenance therapy doesn't make sense since bevacizumab is continued post-platinum treatments that also incorporate bevacizumab. When assessing value in a population where cure is unlikely and long-term therapy is often used to maintain stable disease and quality of life, these treatments should not be compared with inappropriate and incorrect comparators. Perhaps different PARP inhibitors should be compared against each other? Regardless, any real financial analysis should be based on true comparators, and right now there aren't any.

Impact on Innovation

Drug pricing is a nuanced and complex issue. Certainly the financial strain of expensive treatments can be significant. The issue of financial toxicity is a very real one for our patients, and is an issue that OCRFA is actively engaged in working on legislatively. New therapies don't do our patients any good if they can't afford them. We recognize, however, that the research and development done by the companies that developed PARP inhibitors represents a massive investment of financial resources, and new therapies are going to cost more than standard of care. PARP inhibitors hold great promise for ovarian cancer patients, and we need industry to continue to invest in their development. We are concerned this report could lead to a devaluation of this breakthrough class of drugs, and could have a chilling effect on innovation in a cancer so desperately in need of more research.

Patient Perception of Value & Impact on Access

The draft report includes a comment that appears in the Uncertainty and Controversies section, which was taken from the olaparib ODAC meeting: "if you're going to pay that penalty in terms of toxicity then you want a return on that, not just that your progression is delayed but that your overall survival was beneficial." This statement does not reflect the opinion and value calculation made by many survivors, and their physicians. Patients, clinicians and researchers alike would like to see gains in OS from new treatments, but for some dealing with chronic non-curable disease (the unfortunate circumstance of many ovarian cancer patients), progression free survival is *very* important, not just small possible gains in OS. This is especially relevant with PARP inhibitors, which are frequently very

OCRFA
Ovarian Cancer
Research Fund Alliance

well tolerated and offer most patients good quality of life. Ovarian cancer patients and their physicians think about and value treatment options in a nuanced way. Despite its intended use, we fear that the data in this report will be used by payers to deny patients access to these anti-cancer medicines, when those treatment decisions should be instead made by patients and their doctors.

Salvage Therapy
The term "salvage therapy" is used several times throughout this report. While we understand its intended use, many cancer patients find this term offensive. Ovarian cancer patients are not helpless wrecks that need to be salvaged; therefore, the use of this term in the draft report could suggest to some readers that its authors believe that they are, and that this point of view has informed the analysis.

As ICER finalizes its assessment of these new medications, and plans for the Midwest CEPAC meeting next month, we encourage the organization to consider the needs of the patients facing this terrible disease, and the challenges patients and their physicians face when considering treatment options. It is essential that patients and physicians have access to all of the PARP inhibitors reviewed in this draft report. Policies that increase access to new therapies, and encourage innovation and investment in the private sector, are essential.

On behalf of OCRFA, thank you for your consideration of these comments.

Sincerely,

Audra L. Moran

Audra L. Moran
President and CEO

Society of Gynecologic Oncology

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Institute for Clinical and Economic Review
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August 9, 2017

Dear ICER Review Committee,

The Society of Gynecologic Oncology Clinical Practice Committee would like to comment on the ICER Draft Evidence Report assessing the comparative clinical effectiveness and value of three poly ADP-ribose polymerase (PARP) inhibitors for treatment of ovarian cancer: olaparib (Lynparza™, AstraZeneca), rucaparib (Rubraca®, Clovis Oncology), and niraparib (Zejula™, Tesaro). Overall, the data are presented well, will appropriate clinical reviewers for clinical expertise.

Draft Evidence Report:
We are somewhat concerned about how a "C+" is received for comparative clinical effectiveness when much of the long-term data for these new treatments are yet to be published. Is ICER able to provide some context on how the information may be interpreted and used?

We also inquire as to how the cost of toxicities of comparative therapies may be incorporated (i.e. Carbo/Doxil versus olaparib for treatment; bevacizumab versus olaparib for maintenance) when considering value and QALY.

Draft Voting questions:
We suggest that questions 4 & 5 (regarding niraparib) specify the setting of recurrent platinum-sensitive disease to avoid confusion with maintenance after primary treatment, which is still currently studied as a clinical trial question.

In addition, questions 10-18 refer to "long-term value for money"—should this term be better defined, in either the question or the Draft Evidence document?

A minor comment: Section 2.1 refers to taxane agents for first-line therapy. Topotecan and Doxil are not taxanes and are not considered standard of care.

Thank you for the opportunity to review this important work by ICER. The SGO remains excited about this new class of drug for ovarian cancer and look forward to future understanding of the optimal utilization of these drugs either singly or in combination for the treatment of gynecologic malignancies. If you are able to answer our questions or wish to ask for further clarification, please contact SGO Director of Practice, Quality and Outcomes, Jessica Oldham at Jessica.oldham@sgo.org or call 312-676-3903.

Sincerely,

Lee-May Chen, MD
SGO Clinical Practice Committee Chair

William Burke, MD
SGO Clinical Practice Committee Vice Chair