Poly ADP-Ribose Polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness & Value

Response to Public Comment on Draft Report

August 30, 2017

Prepared for

##	Commenter	Comments on Ovarian Cancer Draft	ICER Response
1	Tesaro	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-gBRCAmut 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%). **We believe that this constitutes a substantial benefit for this population with high unmet need and poor prognosis. ICER should amend its assessment to recognize the substantial benefit that ZEJULA offers patients without germline BRCA mutation.**	Thank you for the comment. While we agree that the results described are important, and that the incremental gain in median progression free survival in this cohort (5.4 months) approaches what the FDA advisory committee considered clinically significant (6 months), we note that this benefit was observed to varying degrees based on type of mutation (i.e., somatic vs. wild-type) and HRD status. We have amended the report to describe "small to substantial benefits" to account for this variability.
2	Tesaro	**We request clarification in the report regarding whether the cost of ZEJULA was calculated based on its average dose intensity.**	Dose intensity was based on a weighted average calculation using dose adjustment guidance from product labels or FDA clinical reviews as well as rates of discontinuation from Study 19 of olaparib, the only study in our set that reported detailed information on discontinuation rates over the duration of the trial. For niraparib, we used the FDA clinical review data, which reported the percent of patients reducing from 300mg dose to 200mg dose as well as to 100mg dose over the course of the trial; these increments of dose reduction are also reflected in the product label. The model begins by starting all patients on the 300mg dose, and over time patients who are on treatment and do not discontinue receive a decreasing dose until median discontinuation of 11 months (i.e., discontinuation observed in Study 19). Once patients reach the 11-month point, all patients who are still on treatment and did not discontinue are assumed to receive a weighted average of 220mg of niraparib. Those that discontinued and stayed in the progression-free state did not incur treatment costs from that point forward. We have clarified this information in the revised report. See Table E6 in the Appendix for a full description.

3	Tesaro	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.	We already acknowledge the high level of uncertainty in reference to overall survival within section 6.4 (limitations) and will acknowledge this in our presentation as well. As with many new cancer agents, mature and comparative data on overall survival will aid in reducing this uncertainty.
4	Tesaro	Based on the information provided in the report, we could not replicate the PFS, OS, or QALY gain estimates. The ICER lung cancer assessment 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.**	Our revised report includes an updated Table E5, as well as a new Table E6 in the Appendix that incorporates the shape and scale parameters, and lowest AIC values for the curves used in the final model. The shape and scale parameters can be used to calculate the time-dependent transition probabilities over the time horizon of the model.
5	Tesaro	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). We request that the report **describe how the assessment team has addressed the limitations of the modeling approach outlined in the NICE DSU report.**	Given the lack of survival evidence, but with the goal of generating long-run cost-effectiveness, we must make assumptions. We've addressed concerns about these assumptions in two ways. First, our analysis separately considers PFS during periods "on" and "off" treatment using a discontinuation curve from Study 19. All patients that discontinue but do not progress are not allocated any additional cost of treatment. Second, we've calibrated the model to reflect the proportional gain in OS from gains in PFS as compared to placebo using the most current and best available evidence. For example, from Study 19 (Ledermann 2016, Lancet Oncology), in the BRCA mutated sub-group, the gain in time to first subsequent treatment was 9.4 months vs. placebo, which translated into a gain in OS of 4.7 months vs. placebo. Therefore, for every 1-month gain in progression-free survival, a 0.5-month gain in OS was observed within this subgroup. For all maintenance population comparisons, the model was also calibrated to reflect this proportional gain in OS achieved from gains in progression-free states such as time to first subsequent treatment.
6	Tesaro	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 gBRCAmut patients in the NOVA trial. This was **done without any adjustment for the difference in PFS**	Please see our response above. For niraparib, within the maintenance germline BRCA-mutated sub-group, our proportional assumption increased overall survival for niraparib by approximately 2 months for a gain in overall survival vs. placebo of 8 months. For the non-germline BRCA-mutated cohort, the proportional assumption would

		observed in the two trials, even though the difference in median PFS in the ZEJULA NOVA trial was 15.5 months, while the difference in median PFS in BRCA mutated patients Study 19 was 6.9 months. Further, in the non-gBRCAmut population, **no difference in OS between ZEJULA and placebo treated patients is assumed without a clear rationale provided for this assumption.**	actually *decrease* survival for niraparib vs. placebo. For example, in Study 19, in the non-germline BRCA-mutated sub-group, median overall survival for olaparib was 24.5 vs. 26.6 for placebo. Because this difference was not statistically significant, however, we assumed that overall survival did not differ from placebo in this subset, given that no other overall survival data were available.
7	Tesaro	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. 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.	Please see our responses to the above two comments. In addition, as we note in the report, there have been many instances, across many cancers, in which progression-free survival gains do not translate into an overall survival benefit when mature data become available. Furthermore, the only available evidence with comparative estimates of both progression-free survival and overall survival, suggested an approximate benefit in overall survival of 0.5 months for every gain in progression-free survival of 1 month. Therefore, the model uses the best available evidence on the relationship between progression-free survival and overall survival that is relevant to the treatment settings of interest for this review.
8	Tesaro	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. 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**.	We've added a footnote to Table E5 to indicate that the cohort of interest from Hanker et al. is comprised of both BRCA-mutated and non-mutated patients, and have also added language to the report to note the uncertainty this brings to the relevant analyses.

9	Tesaro	Multiple studies have shown that BRCA mutated patients have a better prognosis in terms of survival compared to patients without a BRCA mutation. 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.**	Thank you for suggesting additional evidence; however, the citations you list did not separate survival by line of therapy, which is also a significant predictor as well as a necessary factor in approximating the FDA-indicated uses of olaparib and rucaparib. To address your comment, we've added additional text acknowledging the limitations of the available evidence for estimating gains in overall survival within the recurrent, BRCA-mutated population. Specifically, given that the evidence is from single-arm trials only, we cannot apply the same proportional PFS to OS gain as we did in the maintenance population.
10	Tesaro	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. 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. 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**	At the time of our draft report, the SOLO2 trial had not yet been published. As such, we had no information related to issues with the blinded independent central review (BICR) secondary endpoint (i.e., informative censoring). With the full published trial, we have revised our report to articulate all three evaluations of progression-free survival from SOLO2 (i.e., investigator assessed, BICR and BICR sensitivity analysis for informative censoring). We have also updated the cost-effectiveness model to focus on inputs from the study's primary endpoint, investigator-assessed PFS, as these results were comparable to those seen in the exploratory analysis focused on informative censoring. The base-case model estimate now uses the investigator-assessed curve, with the BICR curve included as a sensitivity analysis.

		that the model use the primary endpoint from SOLO-2 rather than one of the many sensitivity analyses.	
11	Tesaro	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.	All adverse-event costs were varied by lower and upper values that represent a wide range of costs (that may or may not be associated with a hospitalization). For example, the base-case cost of managing anemia is approximately $7,533 but the lower cost estimate is $5. As noted in the report, even wide variations in adverse-event costs such as these did not change the conclusions of the base-case analyses.
12	AstraZeneca	ICER should provide **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	Overall survival data were only available in Study 19, necessitating its widespread use in the model as well as in informing proportionality assumptions. We have clearly articulated why formal indirect comparisons across PARP inhibitors were infeasible in the clinical effectiveness section of the report.
13	AstraZeneca	ICER should **list 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**	See comment 2 above. For olaparib, we used evidence from the recently updated FDA label as well as rates of discontinuation from Study 19 of olaparib, the only study in our set that reported detailed discontinuation rates over the duration of the trial. Based on recent pricing and dosing changes for olaparib, dose reductions were not associated with reductions in price. Therefore, the same discounted price was applied to the on treatment and progression-free state. Cost of treatment was not applied to those that discontinued and remained in the progression-free state. See Table E6 in the Appendix for a full description.
14	AstraZeneca	ICER should **explain whether the impact of dose reductions on efficacy were considered, and how efficacy adjustments were incorporated into the model**	See comment above. Dose reductions affect cost only, as efficacy was based on intent-to-treat findings from the trial reports.
15	AstraZeneca	ICER should **provide details for the distribution of subsequent treatments and best supportive care (BSC), and provide a reference supporting why this distribution was chosen**	For each cycle of the model, there is a proportion of patients that pass into states of progressive disease. We apply 6 cycles of chemotherapy to all incident patients passing into the progression states. Best supportive care costs included office visits and CT scans, and are applied to all surviving patients in each cycle of the model for both treatment and placebo arms. Blood test costs for treatment were applied to only those on PARP treatment who have not progressed.

			This is now clarified in the report and Appendix.
16	AstraZeneca	ICER should **present the set of functional forms considered for survival in the analysis, and justification for the final chosen form**	See comment 4 above.
17	AstraZeneca	Icer should justify **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)**	In the absence of robust data on the percentage of patients receiving fourth-line treatment, we have now assumed that 65% of patients receiving third-line treatment would go on to fourth-line treatment. (Note that our budget impact threshold was not exceeded, even with the larger estimated third-line population.)
18	AstraZeneca	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**	See comment 4 above. Additionally, we discuss the limitations of our model structure and ability to assess uncertainty around transition probabilities for PFS and OS. This was in part addressed through the partitioned survival structural sensitivity analysis and our one-way and probabilistic sensitivity analyses using variation around the input parameters.
19	AstraZeneca	**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.	ICER believes that the thresholds of $50,000-150,000 per QALY is an appropriate range for cancer treatments. Commentary from Neumann and colleagues, while acknowledging the variety of thresholds that have been proposed, argues that, for comparisons of interventions across all disease categories, a single threshold of $100,000 or $150,000 per QALY is reasonable. This also dovetails with World Health Organization guidance that, based on patient preferences and risk attitudes, relevant cost-effectiveness boundaries for any given country/region fall generally in the range of 1-3 times per capita annual income. In the US, this equates to approximately $50,000 - $150,000.
20	AstraZeneca	**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.**	Please see above.

21	AstraZeneca	ICER's **utility weights in their CE model are counterintuitive given the relative toxicities** associated with olaparib and PLD+C.	Mean utility weights were derived from the best available evidence, including AstraZeneca's own submission to the National Institute for Health and Care Excellence (NICE). Additional disutilities were incorporated for each treatment based on adverse events (the rates of which were generally higher for PLD+C vs. the PARP inhibitors) as well as time spent in progressed vs. progression-free health states. Please see Table E7 for disutilities and Table 11in Section 6 for adverse event percentages. To address any residual concern on mean starting utility weights, we've set "on-treatment" utility for PLD+C, which was originally slightly higher than that for the PARP inhibitors, to be equivalent.
22	AstraZeneca	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.	We are not aware of any consensus on the level of disutility for oral vs. IV administration, and also point out that disutility may vary by duration of treatment. Furthermore, any significant grade 3/4 adverse events are accounted for using disutility estimates from the best available evidence.
23	AstraZeneca	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.** Although OS data for SOLO2 and niraparib is not mature, that 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.	We acknowledge the high level of uncertainty in reference to overall survival within section 6.4 under limitations. Additionally, we applied survival data to similarly indicated populations to produce quality-adjusted life-year (QALY) and life-years gained estimates. Please also see our previous response (comments 5-7) on the proportional link between PFS and OS that has been recently updated in the model.
24	AstraZeneca	**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. 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.**	Please see previous comment.

25	AstraZeneca	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. 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. **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.**	We did not include bevacizumab as a comparator in the maintenance population for the cost-effectiveness analysis due to lack of available data in the specific population of interest (i.e., recurrent disease, at least two prior platinum-based regimens, in response to the most recent regimen). However, we received guidance from several clinical experts that bevacizumab remains a key treatment alternative for patients on maintenance therapy. We therefore included it in the budget impact analysis, as use of PARP inhibitors could potentially displace bevacizumab as well as observation only. As noted in our report, due to a lack of comparable data, we assumed the non-intervention costs for bevacizumab to be the same as those for the PARP inhibitors, hence cost differences seen in the budget impact model are driven by differences in drug costs.
26	AstraZeneca	**ICER should conduct a sensitivity analysis around any assumed parameter values.**	Please see our one-way and probabilistic sensitivity analysis results, described in both the full report and Appendix E.
27	AstraZeneca	Presentation of NCCN guidelines for olaparib in the maintenance therapy is incomplete and may cause readers to draw inappropriate conclusions. **ICER should update their content in the NCCN section for olaparib to include the full NCCN statement for the maintenance population.**	Thank you for this comment, we have updated the report to reflect the updated NCCN guidelines.
28	AstraZeneca	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 should apply the higher CE thresholds to the baseline analysis.**	Please see comment 19 above.
29	AstraZeneca	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.	As stated in multiple sections of the report, we did not attempt to conduct any explicit or implied comparisons across PARP inhibitors. The decision to use overall survival data from olaparib studies to support modeling was based on a dearth of mature evidence for the other PARP inhibitors.
30	AstraZeneca	ICER **should conduct an appropriate analysis (i.e., indirect treatment comparison) so that comparisons can be**	Due to key differences in study eligibility criteria, baseline characteristics of study populations, and outcome measurements, we

		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.	did not attempt to compare the PARP inhibitors to each other through direct or indirect quantitative assessment. We feel that this point has been emphasized throughout the report, including Sections 1.1, 4.1, 4.2, 4.3, and 6.1.
31	AstraZeneca	Although ICER includes a section with other benefits and contextual considerations in their report, **non-clinical benefits are not incorporated into the CE mode**l, which results in an underestimation of the value of olaparib.	Our report and Value Assessment Framework both include the consideration of other benefits and contextual considerations. Unfortunately, data on these patient-centered outcomes are not always included in the clinical trials or other studies, making it difficult for us to incorporate them into our model. However, our updated Value Assessment Framework has expanded the impact of these other benefits and contextual considerations, incorporating them into the voting process as our voting panel considers the question of value at our public meeting. Further, we provide justification for the lack of a societal analysis in this particular report, due to lack of useable data on productivity losses in this population and the older age of many women with advanced ovarian cancer. If AstraZeneca would like to suggest specific, estimable inputs for non-clinical benefits, we would be happy to consider them.
32	AstraZeneca	**ICER doesn't represent patient perspectives/priorities in the CE model**	This is simply untrue. We spoke at length to both patient groups and individual patients to gain an understanding of what is most important to them regarding living with their disease and in considering PARP inhibitor treatment. For example, we were counseled to assume a reduced quality of life in the progression-free state, due to anxiety regarding the disease's return and toxicities experienced on maintenance therapy. These conversations are reflected in the report (see Section 2).
33	AstraZeneca	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.**	See comment 31.

34	AstraZeneca	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.**	Rather than consider our value-based price benchmarks "preliminary", they should be viewed as based on the best available evidence to date, as decision-makers must assess how best to use PARP inhibitors now. We will consider updates to our analyses and these benchmarks as new evidence comes to light.
35	AstraZeneca	ICER should **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.	See comment above.
36	AstraZeneca	ICER's budget impact analysis is not a measure of value or affordability. 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.**	As we have described many times and in many different venues, ICER's budget impact analyses serve only to generate an "access and affordability alert" if high-value interventions exceed the threshold that is tied to US economic growth, indicating that steps should be taken to improve affordability (e.g., prioritization of treatment, outcomes-based agreements, etc.). We are also unsure of the criticism in this case, since none of the agents under review exceeded the threshold for their intended uses.
37	AstraZeneca	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. **ICER should remove the budget impact section from the report.**	We will not do so, for the reasons described in the comment above.
38	SGO	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?	The rationale for each rating is discussed in detail in the full report. A C+ rating is possible in any situation in which our certainty in the evidence is moderate, which would reflect a circumstance in which much of the long-term data are not yet available.
39	SGO	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.	Toxicities are incorporated into the model based on disutilities that decrease utility estimates for a period of 3 months. Specifically, grade 3/4 adverse events are associated with significant disutilities, that are listed in Table 11 in Section 6. Additionally, grade 3/4 adverse events are

			associated with additional costs of treatment, which we include as a one-time, event-based cost.
40	SGO	We suggest that questions 4 & 5 (regarding niraparib) s**pecify 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.	Thank you for this comment, we have updated the referenced voting questions to specify the recurrent platinum-sensitive population.
41	SGO	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?	Please refer to our Value Assessment Framework (https://icer-review.org/wp-content/uploads/2017/06/ICER-value-assessment-framework-update-FINAL-062217.pdf) for a definition of long-term value for money.
42	SGO	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 clarification. We have removed topotecan and Doxil from the taxane parentheses. Since PLD is listed in the NCCN guidelines in conjunction with carboplatin as a recommended regimen, we will keep this regimen in the discussion but amend the sentence to ensure that it is clear that it is not a taxane.
43	OCRFA	The publication of this report assessing economic impact of the use of PARP inhibitors to treat ovarian cancer is premature.	These therapies are available and being prescribed by doctors, administered to patients, and charged for by manufacturers outside of clinical trials. Such activities would be ethically questionable if it were not possible to evaluate the comparative effectiveness of the therapies. We agree that over time more information will become available, and the uses of these drugs may expand or otherwise change. All of ICER's evaluations of therapies recognize that additional information is likely to become available in the future, but patients and doctors are being asked to make decisions based on the evidence that is available right now.
44	OCRFA	The report makes assumptions in an attempt to fill in the gap in overall survival data. These assumptions are a poor substitute for actual data. The lack of comparative trials among the three drugs make it impossible to truly compare them	We agree that the data are not sufficient to make any explicit comparisons across the PARP inhibitors, and we have refrained from doing so. We agree that trials designed based on active and direct comparisons are always preferable to the many assumptions required for indirect assessments.
45	OCRFA	**ICER should update this assessment in the future when more data is available**	ICER is developing a formal update process for all of its reviews, and will consider the appropriate timing for an update of this assessment as part of this process.

46	OCRFA	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**.	Thank you for your comment. The FDA label states that pegylated liposomal doxorubicin (PLD) is indicated in ovarian cancer that has progressed or recurred after platinum-based chemotherapy, and makes no mention of whether disease is platinum-sensitive or not. In addition, the NCCN guidelines list PLD in combination with carboplatin, recommended as both a first line therapy and after recurrence in platinum-sensitive patients. Finally, we also enlisted the input of key opinion leaders who recommended a carboplatin/PLD combination as a realistic comparator to olaparib and rucaparib in recurrent ovarian cancer.
47	OCRFA	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...Different PARP inhibitors should be compared against each other.	Thank you for your comments. We agree that the needs of women change as their disease changes. With that said, if clinical trials used for approval do not include a relevant comparator, we seek input from key opinion leaders and practicing physicians regarding current treatment paradigms. We used the published literature, NCCN guidelines and clinical expert input to determine comparators for this report. In addition, as described previously, differences in study populations, outcome measurement, and reporting precluded any formal indirect comparison of the evidence on PARP inhibitors.
48	OCRFA	This report may lead to a devaluation of PARP (development) and could have a negative impact on innovation in cancer research	ICER believes that an open and public dialogue on benefits observed, gaps in evidence, costs, and contextual factors is critical to ensuring sustainable access to these drugs by patients.
49	OCRFA	…Quote from the ODAC meeting does not accurately reflect the opinion and values of survivors and patients. Survivors and Patients look forward to seeing gains in OS from treatments. But progression free survival is very important, this is especially relevant with PARP inhibitors, which are frequently very well tolerated and offer most patients good quality of life.	We agree that PFS is an important patient-centered outcome. We have tried to balance the importance of this outcome from the patient perspective with the uncertainties raised in the biomedical literature about the potential trade-off of prioritizing PFS over OS as a clinical trial outcome, and testimony from patients that there are very real tradeoffs to consider. For example, in comparing maintenance PARP inhibitor therapy to observation alone, the tradeoff relates to improved PFS vs. some level of toxicity.
50	OCRFA	The term "salvage therapy" is offensive to patients (patient centered language)	Thank you for this comment, we have removed this term from the report entirely, with our apologies to the patient community for any offense caused.

51	NOCC	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.**	See comment 48.
52	Genentech	**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.	Thank you, we have removed bevacizumab from the model framework figure.
53	Genentech	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.**	The budget impact model is built such that the PARP inhibitors will entirely replace existing therapies for the eligible population, in order to ascertain what the upper bound of budget impact might be, and whether access or affordability alerts would be triggered at various levels of utilization. For the population receiving maintenance therapy for platinum-sensitive disease, olaparib and niraparib would each replace observation (75%) and Avastin (25%) for those with germline BRCA mutations, and for the non-germline BRCA patients, niraparib would replace observation and Avastin taken in the ratio 67%:33%.
54	Genentech	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 and GOG-0213) support its use per the FDA-approved indication; however, the designs of the Avastin trials differ considerably from the PARP inhibitor trials(see Appendix A).	We have generally discussed the limitations associated with extrapolating olaparib survival data to all other regimens of interest in the report. We have also added text regarding bevacizumab to the budget impact and limitations sections (Section 6.4) of the report, acknowledging the assumption of the same efficacy and discontinuation as for olaparib.
55	Genentech	The **net price assumption for Avastin for the budget impact analysis is inaccurate**	We have estimated the net price for Avastin using data from SSR Health. Details of the methodology for deriving net price can be

		and overestimates the net price compared to our internal analyses.	found in Section 6.1 of the report, under 'cost inputs'. We are happy to consider alternative estimates, but note that no estimate was provided to accompany this comment.
56	Genentech	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".**	Thank you for this comment, we have updated the report to reflect the updated NCCN guidelines.
57	FORCE	**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.	We acknowledge the limitations of the available evidence in this sub-group. Unfortunately, there is very limited evidence that stratifies patients by BRCA status and also by line of therapy, which is necessary given the indications for olaparib and rucaparib. We've added some additional text acknowledging the limitations of the available evidence for estimating gains in overall survival within the recurrent, BRCA-mutated population. Specifically, given that evidence is from single-arm trials only, we cannot apply the same proportional PFS to OS gain as we did in the maintenance population.
58	FORCE	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 i**n the Pegylated liposomal	Thank you for the comment. We did not include these events because of the focus on those graded 3 or 4. We recognize that infusion reactions are often serious, but also note that, given the relatively low rate of acute and serious reactions listed in the product label for PLD used in combination with a platinum-based agent (7-11%), this is

		doxorubicin in combination with carboplatin (PLD + C) cost inputs.	unlikely to have materially affected our findings.
59	FORCE	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.	All AE costs were varied by lower and upper values that represent a range of costs (that may or may not be associated with a hospitalization). For example, the base-case cost of anemia is approximately $7,533 but the lower cost estimate is $5. Therefore, the sensitivity analyses (including one-way and probabilistic) include these variations to represent different levels of care, such as outpatient, inpatient, etc. Furthermore, varying these inputs by wide ranges did not change the conclusions of the analysis.
60	FORCE	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.**	Please see comment above.
61	FORCE	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.	Bevacizumab was not a comparator in the cost-effectiveness analysis, so we only included treatment costs of bevacizumab for the purpose of budget impact estimation. All efficacy and safety assumptions in these analyses were based on the olaparib model and evidence. This has been explicitly acknowledged in the budget impact and limitations sections of the report.
62	FORCE	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	We have acknowledged this in the limitations section of Section 6.4.

		associated with infusion administration – particularly for hospital based infusions.	
63	FORCE	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.**	We disagree. While the lack of robust data precluded any formal consideration of lost productivity or other indirect costs in our cost-effectiveness analyses, we note the potential other benefits and contextual factors associated with PARP inhibitor use in detail in Section 5. In addition, our updated Value Assessment Framework has expanded the impact of these other benefits and contextual considerations, incorporating them into the voting process as our voting panel considers the question of value at our public meeting.

64	FORCE	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.**	We at ICER feel that we are responsible to all stakeholders. As such, we feel that all stakeholders are owed a balanced, thoughtful, and comprehensive review of the available evidence. With regard to this review, we feel that we have identified clinical benefits when they have been demonstrated, raised questions about gaps in evidence where appropriate, and tried to set the appropriate context for the potential use and application of PARP inhibitors. As noted above, these therapies are available and being prescribed by doctors, administered to patients, and charged for by manufacturers outside of clinical trials. Such activities would be ethically questionable if it were not possible to evaluate the comparative effectiveness of the therapies. We agree that over time more information will become available and the drugs may be administered in different combinations. All of ICER's evaluations of therapies recognize that additional information is likely to become available in the future, but patients and doctors are being asked to make decisions based on the evidence that is available right now.