NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer after 2 courses of platinum-based chemotherapy (managed access review of TA620) [ID3788]

Committee Papers

NICE National Institute for Health and Care Excellence

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CANCER DRUGS FUND REVIEW

Olaparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer after 2 courses of platinum-based chemotherapy (managed access review of TA620) [ID3788]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (managed access review of TA620)

04 January 2023

Dear Company,

Following the first committee meeting for the appraisal of olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (managed access review of TA620) on 13 December 2022, the committee has requested further information to aid its decision-making.

The committee reached the conclusion that estimation of overall survival based on the adjusted overall survival data in the routine surveillance arm was not appropriate for decision-making. In order to reflect the clinical pathway at the point of CDF entry, the committee believed that both the cost and the benefit of subsequent olaparib use among people in the routine surveillance arm should be included in the cost effectiveness analyses. It concluded that that the unadjusted SOLO2 data may best reflect NHS clinical practice at the point of CDF entry.

Given the above points, the committee kindly request that you provide the following:

1. Estimation of overall survival in the routine surveillance arm based on unadjusted data from SOLO2. The committee would like to see a range of OS extrapolations based on this unadjusted data in scenario analyses with clear justification for the extrapolation curve selected for

your base case (statistical goodness of fit measures, graphical representation, examination of hazard plots etc.) Further detail on the suggested methods for assessing survival models can be found in NICE DSU Technical Support Document 14.

2. Updated cost-effectiveness analysis based on the extrapolated overall survival mentioned above. The analysis should include the costs for subsequent olaparib based on the rates of subsequent PARP-inhibitor-use in SOLO2.

The committee asks that you use the following assumptions in your analyses:

- Assume that all subsequent PARP inhibitor use in SOLO2 is olaparib. This is based on the assumption that all PARP inhibitors have similar efficacy and tolerability.
- Assume that all subsequent PARP inhibitor use in SOLO2 is limited to third-line maintenance only.
- The rate of subsequent PARP inhibitor use should be estimated based on data from SOLO2.

Please let us know the earliest date by which you could supply this information. We have provisionally scheduled a second discussion of this topic for 07 March 2023. Please do not hesitate to contact me if you have any questions.

Kind regards,
Janet Robertson

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy

(Managed Access Review of TA620)

Company Response to NICE Requested Analysis

February 2023

File name	Version	Contains confidential information	Date
ID3788_Olaparib CDF exit_CompanyResponse_NICECQs_ACICredacted_v1.0	v1.0	Yes	February 06 2023

Section A: Requested analysis on overall survival data

04 January 2023

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Given the above points, the committee kindly request that you provide the following:

- Estimation of overall survival in the routine surveillance arm based on unadjusted data from SOLO2. The committee would like to see a range of OS extrapolations based on this unadjusted data in scenario analyses with clear justification for the extrapolation curve selected for your base case (statistical goodness of fit measures, graphical representation, examination of hazard plots etc.) Further detail on the suggested methods for assessing survival models can be found in NICE DSU Technical Support Document 14.

- Updated cost-effectiveness analysis based on the extrapolated overall survival mentioned above. The analysis should include the costs for subsequent olaparib based on the rates of subsequent PARP-inhibitor-use in SOLO2.

The committee asks that you use the following assumptions in your analyses:

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Please let us know the earliest date by which you could supply this information. We have provisionally scheduled a second discussion of this topic for 07 March 2023. Please do not hesitate to contact me if you have any questions.

Kind regards,
Janet Robertson

Executive Summary

AstraZeneca welcomes the opportunity to provide further information to aid the Committee's decision making. Although we maintain that the rationale for the assumptions applied in the original base case are robust, AstraZeneca acknowledge the Committee's request to consider the unadjusted dataset for decision-making. As previously outlined in the company submission (see Section **Error! Reference source not found.** of the submission dossier) and responses to technical engagement, the high rate of subsequent PARP inhibitor use in the SOLO2 placebo arm ([redacted]) relative to the olaparib arm ([redacted]) confounds the overall survival (OS) estimates and likely underestimates the true OS benefit achieved with olaparib in this setting. Since retreatment with PARP inhibitors is not permitted in UK clinical practice, only a small minority of patients would be PARP inhibitor naïve and would therefore be eligible to receive olaparib beyond the second line. The analysis including the adjusted OS estimates therefore improves the generalisability of the SOLO2 study by aligning the subsequent treatments to better reflect UK clinical practice.

With respect to the historical clinical pathway, the company recognises that the scope of the CDF exit should be consistent with the original decision problem and aligned with the Terms of Engagement to sufficiently resolve the uncertainties. However, this does not preclude the need to ensure that the outcomes are generalisable to current clinical practice. Furthermore, at the time of the publication of olaparib appraisal in November 2019, niraparib, in same positioning, TA528, was already available in the UK following a positive recommendation by NICE in May 2018, therefore receipt of PARP inhibitor maintenance in an earlier setting was a part of clinical practice.

The economic model has been updated as per the Terms of Engagement to address the uncertainties highlighted in the original appraisal and now includes the following range of analyses to aid the Committee in their decision making:

1) Adjusted OS dataset which forms part of the company base case following technical engagement; the OS for the routine surveillance arm was adjusted such that the treatment effects or benefits derived from subsequent PARP

inhibitor use are removed to ensure the OS outcome from the SOLO2 trial are aligned with clinical practice.

2) Scenario analysis based on placebo arm from Study 19; this scenario utilises the final OS estimates for olaparib derived from SOLO2 with survival estimates for the routine surveillance arm from Study 19, which also investigated olaparib in the released BRCA-mutated setting. This methodology is consistent with the recent approach adopted in the NICE appraisal of TA784 for estimating survival outcomes for routine surveillance which was accepted by the Committee for decision making. The cost-effectiveness estimates based on this analysis are presented in Table 6.

3) The requested unadjusted OS analysis based on final OS for SOLO2 where no adjustments to remove the treatment effect of switching to olaparib in the routine surveillance arm is carried out hence interpretation of the OS is limited. AstraZeneca would like to highlight that by virtue of this approach and the likely overestimation of survival in the routine surveillance arm during the observed period (see Section A.2), the cost-effectiveness estimates resulting from this analysis presented in Table 3 are conservative and likely represent the upper bounds of the cost-effectiveness estimate.

Updated cost-effectiveness analyses presented in this response (see Table 3 and Table 6) are provided using the current approved commercial arrangement for olaparib ([redacted] PAS applied to the list price).

Although the eligible population in the second-line only setting is expected to diminish over time, there remains an important small minority (up to ~15 patients per year) who may potentially benefit from maintenance olaparib in the short term. AstraZeneca remain committed to working with both NICE and NHS England to ensure access is maintained for these patients, and in our response to the Committee's request, we aim to address the Committee concerns and help inform appropriate decision making in this population.

A.1. Overall survival based on unadjusted data from SOLO2

Overall survival data from the final data cut-off (DCO) of the SOLO2 population who had a confirmed BRCAm and had previously received two lines of platinum-based chemotherapy is presented in Table 1.

At the time of the final DCO (3 February 2020), a total of [redacted] deaths ([redacted] in the olaparib arm and [redacted] in the placebo arm) had occurred in the second-line setting. This translates to a maturity of [redacted] for OS data in the second-line population ([redacted] and [redacted] in the olaparib and placebo arms, respectively).

Despite high rates of crossover to subsequent PARP inhibitor following disease progression in the placebo arm ([redacted] vs. [redacted] in the olaparib arm), a numerical benefit of 18.9 months in favour of olaparib as compared to placebo was demonstrated (median OS of [redacted] months vs. [redacted], respectively; hazard ratio [HR] = [redacted], 95% confidence interval [CI]: [redacted]; Figure 1.

Table 1: Unadjusted overall survival for olaparib vs. placebo (routine surveillance)

	Olaparib (N=110)	**Placebo (N=62)**
Events, n/N (%)	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]
HR (95% CI); *p* [2-sided]	[redacted]	

Figure 1: Overall survival Kaplan–Meier curve for olaparib vs. placebo (routine surveillance)

A.2. Incorporating the unadjusted overall survival data from SOLO2 in the economic analysis

In line with the Committee's request, a range of parametric distributions were fitted to the unadjusted dataset for overall survival: generalised gamma, lognormal, log logistic, Weibull, Gompertz, exponential and a flexible spline model (hazard 1-knot). The parametric distribution informing the base-case analysis was selected based on statistical goodness-of-fit, visual inspection and external clinical validation as described below.

The log cumulative hazards plot depicted in Figure 2 does not support the assumption of proportional hazards (PH). Furthermore, the Therneau and Grambsch's non-proportionality test demonstrated a p-value of 0.458 thereby rejecting the null hypothesis that PH holds at the 5% significance level. Following the NICE DSU process, independent models were therefore fitted which aligns with the approach in the original submission.

Figure 2: Log cumulative hazards vs. log-time plot for olaparib vs. placebo (routine surveillance)

A summary of the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) goodness-of-fit statistics for olaparib and the routine surveillance arms for OS in the second-line setting is provided in Table 2. The lognormal, log logistic, generalised gamma and spline models provided a good fit to the observed data with comparable AIC and BIC scores with a difference of 5 or less. The Weibull, Gompertz and exponential models, which had the highest AIC and BIC curves were considered the worst fit to the observed data for both olaparib and routine surveillance arms.

Table 2: Summary of the AIC and BIC goodness-of-fit data for the parametric overall survival analysis

	Olaparib		Placebo	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Generalised gamma	659.82	667.92	**381.92**	**388.31**
Spline	**658.06**	668.86	383.73	392.24
Lognormal	658.53	**663.93**	385.90	390.16
Log logistic	661.36	666.76	388.64	392.89
Weibull	664.00	669.40	393.80	398.05
Exponential	671.84	674.54	396.47	398.60
Gompertz	669.20	674.60	397.89	402.15

A plot of the survival functions is shown in Figure 3 and Figure 4 for visual assessment of fit to the observed data for both the olaparib and the routine surveillance arms, respectively. Consistent with the AIC and BIC scores, the lognormal, log logistic, generalised gamma and spline parametric models provided the most reasonable visual fit to the observed data, relative to that of the exponential, Weibull and Gompertz models for both arms.

Figure 3: Overall survival Kaplan–Meier curve and parametric functions for olaparib

Figure 4: Unadjusted overall survival Kaplan–Meier curve and parametric functions for routine surveillance

To clinically validate the choice of extrapolation, UK clinical experts with experience of treating patients with BRCAm relapsed ovarian cancer were consulted. Given the parametric extrapolations for the olaparib arm remained unchanged from the initial company submission, the expert feedback received remained consistent with prior consultations. The lognormal curve which produced the most consistent long-term OS estimates when compared with the observed data from SOLO2 at 3 and 5 years ([redacted] vs. [redacted] and [redacted] vs. [redacted], respectively) for olaparib was selected as the most plausible OS extrapolation. In relation to long-term survival beyond the follow-up period, clinical experts iterated that they would expect approximately [redacted] of patients to remain alive at 20 years following olaparib maintenance in the relapsed second-line setting (see Section A.7.1 of the company submission). As per the company submission, the lognormal curve which most closely aligns with these estimates was selected as the most plausible OS extrapolation for olaparib.

For the routine surveillance arm, the OS estimates based on the unadjusted SOLO2 dataset as requested by NICE were considered in the clinical validation. As outlined in Section **Error! Reference source not found.** of the company submission, treatment switching to subsequent PARP inhibitor in the placebo arm ([redacted]) confounded the SOLO2 OS analysis introducing bias likely in favour of the routine surveillance arm. However, in order to reflect the clinical pathway at the point of CDF entry as requested by the Committee, the inclusion of subsequent olaparib benefit was implemented. Since PARP inhibitors are now available earlier in the pathway, the unadjusted dataset represents a historical clinical pathway necessitating retrospective clinical validation which was challenging.

The Weibull, Gompertz, spline and generalised gamma model predictions were ruled out in the first instance as clinically implausible estimations of OS in the routine surveillance arm. The Weibull and Gompertz extrapolations predicted [redacted] patients would be alive at 20 years which clinicians deduced to be overly pessimistic, particularly where [redacted] received subsequent PARP inhibitors following disease progression. The spline and generalised gamma models were excluded because they estimated at the 20-year timepoint, the proportion of people alive in the routine surveillance arm would exceed that of olaparib arm in the relapsed setting. Clinicians confirmed that it was highly unlikely that survival would be greater in the routine surveillance arm even within the context where some patients cross over to receive a

PARP inhibitor in subsequent lines of therapy. They explained that variation in overall survival outcomes are likely to be observed across treatment lines due to differences in prognostic factors, such as volume of residual disease and performance status hence the clinical emphasis on receiving PARP inhibitor maintenance as early as possible in the pathway. More importantly, response to platinum-based chemotherapy - a prerequisite for receipt of PARP inhibitor maintenance - sharply declines with each subsequent line due to cumulative toxicities and the onset of platinum resistance. Those who relapse within 6 months of receiving platinum chemotherapy are generally considered to have platinum-resistant disease and ineligible for platinum-based chemotherapy. Patients in the routine surveillance arm from SOLO2 study had a median investigator PFS of [redacted] months (vs. [redacted] months for olaparib); highlighting that more patients from the routine surveillance arm are likely to be considered as platinum resistant (as compared to the olaparib arm) and consequently ineligible for PARP inhibitor maintenance. Experts explained that the exclusion of platinum-based chemotherapy as a treatment option, with or without PARP maintenance in the relapsed setting negatively impacts prognosis due to limited efficacious non-platinum based subsequent therapies. Therefore, the feedback was that a survival benefit in favour of olaparib in those who received olaparib at the earliest opportunity would still be expected.

The lognormal model estimated that approximately [redacted] of patients remained alive at 20 years which aligned with clinicians' view that [redacted] may be a reasonable estimate considering the historical treatment pathway for routine surveillance. However, the lognormal overestimated survival during the observed period as compared to the optimised SOLO2 survival estimates (i.e., inclusive of subsequent PARP inhibitor benefits) for routine surveillance at 2 and 3 years [redacted] and [redacted] for lognormal vs. [redacted] and [redacted], observed in SOLO2, respectively). To avoid fitting vastly different functional forms to patients who have the same underlying disease, a pragmatic decision was taken to select the lognormal curve for the routine surveillance arm in order to maintain consistency with the preferred curve choice for the olaparib arm. However, the company would like to highlight that due to the confounding bias in favour of the routine surveillance arm, and the further overestimation of survival

during the observed period, the estimates based on the lognormal curve are conservative and likely represent the upper bound of the cost-effectiveness estimate.

Figure 5: Olaparib vs. Routine surveillance updated company analysis based on the unadjusted OS

The scenario analysis presented in the initial submission utilising the SOLO2 OS for olaparib and the Study 19 dataset for the routine surveillance arm demonstrates a more generalisable estimate of survival for routine surveillance that is also based on the historical pathway prior to PARP inhibitor use in earlier lines. The company acknowledge that this approach of using data from another clinical trial for the routine surveillance arm has limitations, however the intervention and comparator arms, and the population of interest (i.e., BRCAm relapsed patients) explored in Study 19 and SOLO2 studies are broadly consistent. This scenario was recently accepted by the Committee as a reasonable approach for decision making in the appraisal of niraparib in a similar setting [TA784] within the context of estimating survival for the routine surveillance arm. For the extrapolation of the placebo OS arm from Study 19, the spline model is selected to ensure consistency with the preferred curve choice as this is considered to represent the clinical pathway at the point of CDF entry. Updated cost-effectiveness results for this scenario, inclusive of the changes and evidence assessment group (EAG) corrections thus far are presented in Table 3.

To conclude, the company believes that the cost-effectiveness estimates for olaparib in the subgroup of patients who have had two lines of platinum-based chemotherapy is therefore likely to be between the Study 19 scenario, and the unadjusted SOLO-2 analysis with the latter being most conservative estimate.

A.3. Cost-effectiveness results

The updated results presented in this section are fully aligned with the Committee's requests as follows:

- Overall survival in the routine surveillance arm is based on unadjusted data from SOLO2 and a range of OS extrapolations were explored in selecting the curves (See Section A.2)
- The analysis includes the approved costs for subsequent olaparib in the second and subsequent lines of therapy
- The analysis assumes that all subsequent PARP inhibitor use in SOLO2 is olaparib, the rate of patients receiving this has been derived from the latest SOLO2 dataset
- The duration of subsequent PARP inhibitor use is also derived from the latest SOLO2 dataset

A.3.1. Deterministic cost-effectiveness estimate based on the unadjusted dataset

The updated cost-effectiveness analysis (Table 3) and sensitivity analyses presented in this section are based on the approved simple PAS for olaparib.

Over a 50-year time horizon, treatment with olaparib was associated with a higher cost ([redacted]) and a higher number of life years ([redacted]) and QALYs ([redacted]) than routine surveillance. The resulting incremental cost per QALY gained for olaparib versus routine surveillance was [redacted].

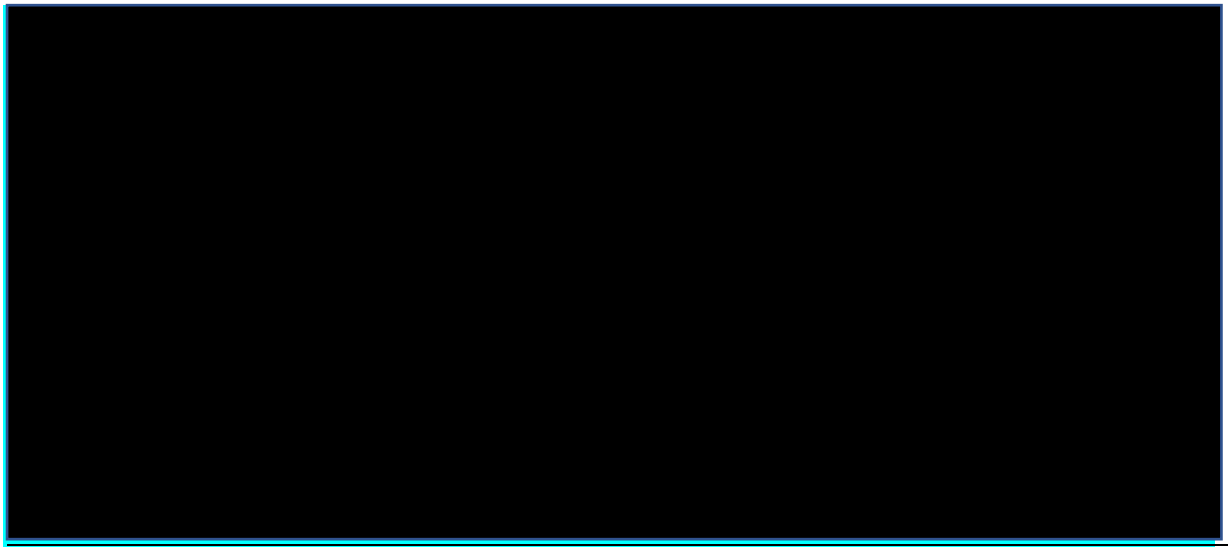
Table 3: Cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER vs RS (£/QALY)
Updated cost-effectiveness analysis incorporating unadjusted OS data from SOLO2 ***(based on [redacted] PAS for olaparib in the 2L)***							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Results of one-way sensitivity analysis

Parameter	Parameter value			Lower value (ICER)	Upper value (ICER)
	Lower value	Base-case value	Upper value		
Discount rate (outcomes)	0.0%	3.5%	6.0%	[redacted]	[redacted]
Cost per month: Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state utility - PF	0.650	0.812	0.974	[redacted]	[redacted]
Discount rate (cost)	0.0%	3.5%	6.0%	[redacted]	[redacted]
Health state utility - PD	0.60	0.755	0.91	[redacted]	[redacted]

Figure 6: Tornado diagram


[redacted]

A.3.2. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to assess the parametric uncertainty associated with the deterministic results in line with the approach in the original submission. Parameters where estimates of uncertainty were available were

assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Probabilistic estimates based on the requested unadjusted dataset were also captured within the PSA.

The PSA was run for 10,000 iterations for the updated analysis. Results from the PSA are presented in Table 5. The probabilistic ICER is [redacted] per QALY gained, which is consistent with the deterministic analysis of [redacted].

Table 5: Average results based on probabilistic sensitivity analysis (10,000 iterations)

Technologies	Total		Incremental		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

[redacted]

A.3.3. Key scenario analyses

Consistent with the approach in TA784, scenario analysis utilising the SOLO2 final OS for olaparib and Study 19 for the routine surveillance arm is presented below. The results in an ICER of £[redacted] inclusive of the EAG corrections and the duration and costs of subsequent olaparib aligned to estimates from Study 19. The cost-effectiveness results based on this scenario are less pessimistic than the

requested unadjusted analysis due less subsequent PARP inhibitor therapy use in the placebo group of Study 19.

Table 6: Results based on SOLO2 OS data for olaparib and Study 19 for the placebo arm

Technologies	Total		Incremental		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BMJ TAG

Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (CDF review of TA620) [ID3788]

EAG comments on company's post ACM scenario

February 2023

Source of funding
This report was commissioned by the NIHR Evidence Synthesis Programme as project number 131839.

1 Introduction

Following the first appraisal committee meeting of olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (Cancer Drugs Fund [CDF] review of TA620) on 13 December 2022, the committee requested the company to provide a scenario analysis using unadjusted overall survival (OS) data from SOLO2 for both olaparib and routine surveillance.

The committee considered that unadjusted OS data for routine surveillance from SOLO2 (that is, not adjusted for crossover) may best reflect NHS clinical practice at the point of entry to the CDF. Both the company and the Evidence Assessment Group (EAG) highlighted during the ACM the issues with the unadjusted OS data for routine surveillance, including the use of subsequent PARP inhibitor (PARPi) use in SOLO2 was not restricted to third-line olaparib maintenance treatment (which is what is currently available in routine commissioning in the NHS). Nonetheless, the committee's preferred assumptions for the unadjusted SOLO2 data were as follows:

- All subsequent PARPi use in SOLO2 is olaparib. The committee assumes that all PARPis have similar efficacy and tolerability.
- All subsequent PARPi use in SOLO2 is limited to third-line maintenance treatment only.
- The rate of subsequent PARPi use should be estimated based on SOLO2 data.

Section 2 provides an overview of the company's approach to the requested analysis along with the EAG's comments.

2 Company's SOLO2 unadjusted overall survival analysis

Survival analysis of unadjusted SOLO2 overall survival (OS) was performed by the company as per the methods outlined in the NICE Decision Support Unit Technical Support Document 14 (DSU TSD14).[1] The company explored the assumption of proportional hazards (PH) using log-cumulative hazard plots and concluded the assumption did not hold, thus independent models were fitted to each treatment arm.

Extrapolations of the Kaplan-Meier (KM) data were performed using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) and a flexible spline model (1-knot hazard). The company assessed the fit of each modelled curve against the observed KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the economic model.

Several of the distributions modelled (generalised gamma, Gompertz, 1-knot spline) estimated long-term OS of routine surveillance patients to exceed that of olaparib patients, which the company deemed as clinically implausible and this view was also shared by the clinical expert in attendance at the first appraisal committee meeting (ACM). Furthermore, in the Evidence Assessment Group (EAG) base case, OS for routine surveillance was capped to OS for olaparib, thus the EAG considers the company's approach to exclude extrapolations based on routine surveillance OS substantially exceeding olaparib OS is reasonable.

Of the remaining distributions (exponential, Weibull, lognormal and log-logistic), the company excluded the Weibull as OS at 20 years for both arms of the model was 0%, which the company's clinical experts considered was too pessimistic. Additionally, the EAG's clinical experts considered that at least 10% of routine surveillance patients would be alive at 20 years.

While not explicitly mentioned by the company, the EAG assumes the exponential and the log-logistic distributions were ruled out by the company based on statistical fit compared with the lognormal distribution. Thus, the lognormal distribution was selected for the company's scenario. The company highlighted that the lognormal was their preferred distribution for the original company base case, which utilised unadjusted OS data for the olaparib arm, and so their scenario is aligned with their original assumptions. However, the company noted that the lognormal distribution for the scenario is a conservative choice as extrapolated OS is overestimated compared

with observed data from SOLO2 between years two and three for routine surveillance. Figure 1 presents the company's lognormal extrapolation of unadjusted SOLO2 data.

Figure 1. Lognormal extrapolation of unadjusted OS SOLO2 (Figure 5 of the company's response to NICE requested analysis)

The deterministic and probabilistic (10,000 iterations) results of the company's scenario are presented in Table 1 and includes the company's post-technical engagement base case assumptions of time-to treatment discontinuation (TTD) capped to progression-free survival (PFS) and adverse event data (AE) derived from the final data cut from SOLO2, in addition to the scenario specific assumptions of inclusion third-line olaparib maintenance costs based on a mean TTD of [redacted] months from SOLO2 for the subgroup of patients on third-line olaparib.

Results of the analysis include a [redacted] patient access scheme discount (PAS) for second-line olaparib and [redacted] PAS discount for third-line olaparib tablets. Confidential discounts are available for subsequent treatments included in the analysis. The source of the confidential prices for subsequent treatments is the commercial medicines unit (CMU). As such, the EAG has produced a confidential appendix to this document. All results presented in this document are replicated in the confidential appendix.

Table 1. Company's base case post-technical engagement and unadjusted OS from SOLO2 scenario

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/QALY)
Company's base case post-technical engagement - deterministic							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted OS from SOLO2 using lognormal extrapolation scenario - deterministic							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted OS from SOLO2 using lognormal extrapolation scenario - probabilistic							
Routine surveillance	[redacted]	-	[redacted]	-	-	-	-
Olaparib	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life years; OS, overall survival; QALY, quality-adjusted life-years

The EAG considers that the company's scenario is mostly appropriate and aligned with the committee preferences and highlights that the company's results are in line with the scenario the EAG performed using the inverse of the unadjusted OS hazard ratio (HR) to produce an unadjusted OS curve for routine surveillance (scenario 2, Table 29 of the EAG report). The EAG's scenario estimated an incremental cost-effectiveness ratio (ICER) of [redacted]. As a reminder, the EAG's base case ICER was estimated to be [redacted] and was based on a 1-knot spline extrapolation of adjusted OS data for routine surveillance from SOLO2, which converged with OS for olaparib, and inclusion of third-line olaparib costs.

The EAG considers that the company overlooked an aspect of the committee's request, which was to assume all PARP inhibitor (PARPi) use in SOLO2 was olaparib. In the placebo arm of SOLO2, [redacted] and these data were not included in the company's scenario. However, the EAG considers inclusion of other PARPis from SOLO2, assuming the costs and mean TTD of third-line olaparib, will only modestly improve the ICER in favour of olaparib. Nonetheless, the EAG has corrected the company's scenario to align with the committee preferences and results are presented in Table 2. The corrected company scenario can also be considered as a scenario around the EAG's original base case, as it only changes the main assumptions of choice of OS extrapolation and estimation of third-line olaparib costs.

Table 2. Corrected company scenario using unadjusted OS from SOLO2 scenario

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/QALY)
Unadjusted OS from SOLO2 using lognormal extrapolation scenario - deterministic							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted OS from SOLO2 using lognormal extrapolation scenario - probabilistic							
Routine surveillance	[redacted]	-	[redacted]	-	-	-	-
Olaparib	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life years; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life-years

Table 3 presents the range of deterministic and probabilistic ICERs (where available), with the different assumptions for committee consideration.

Table 3. ICER ranges for different overall survival assumptions

Scenario	Assumptions	Deterministic ICER (£/QALY)	Probabilistic ICER (£/QALY)
Company base-case post-technical engagement	Unadjusted OS for olaparib, adjusted OS for routine surveillance extrapolated using the lognormal distribution. Exclusion of third-line olaparib costs	[redacted]	[redacted]
EAG preferred base case	Unadjusted OS for olaparib, adjusted OS for routine surveillance extrapolated using the 1-knot spline. Inclusion of third-line olaparib costs.	[redacted]	N/A - spline not linked to PSA (see Section 6.3 of the EAG report)
Corrected company unadjusted OS scenario	Unadjusted OS for olaparib and routine surveillance extrapolated using the lognormal distribution. Inclusion of third-line olaparib costs.	[redacted]	[redacted]

Abbreviations: EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; N/A, not available; OS, overall survival; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-years

3 References

1. NICE DSU. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data, 2013. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf.