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

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]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from AstraZeneca
2. **Clarification questions and company responses**
3. **SACT report**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. British Gynaecological Cancer Society
   b. Ovacome
   c. Ovarian Cancer Action
   d. Royal College of Pathologists
   e. Target Ovarian Cancer
5. **Evidence Review Group report** prepared by BMJ-TAG
6. **Evidence Review Group report – factual accuracy check**
7. **Technical engagement response from company**
8. **Technical engagement responses and statements from experts:**
   a. Florence Wilks – patient expert, nominated by Ovarian Cancer Action
   b. Rachel Downing, Head of Policy and Campaigns – patient expert, nominated by Target Ovarian Cancer
   c. Rebecca Bowen, Consultant Medical Oncologist – clinical expert, nominated by British Gynaecological Cancer Society
   d. Jonathan Ledermann, Professor of Medical Oncology and Consultant Medical Oncologist – clinical expert, nominated by AstraZeneca
9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ-TAG

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA620

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

Company evidence submission

27 June 2022

File name	Version	Contains confidential information	Date
ID3788_Olaparib_CDF review of TA620_Company evidence submission_ACICredacted	1	Yes	27 June 2022

Contents

Tables and figures

Executive summary

- In November 2019, the National Institute for Health and Care Excellence (NICE) published the Final Appraisal Document (FAD)[1] recommending olaparib use within the Cancer Drugs Fund (CDF). This recommended olaparib for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer patients with a breast cancer susceptibility gene mutation *(BRCAm)* who had two courses of platinum-based chemotherapy.[a]
- Since the recommendation was issued, poly(ADP-ribose) polymerase (PARP) inhibitors have been approved for use as maintenance treatment across all lines of therapy in ovarian cancer.[2,3] In the relapsed setting, their use has been restricted to patients who are PARP inhibitor-naïve only. UK clinical experts confirmed that although there is an increasing number of patients now receiving PARP inhibitors in the first-line setting, there is a diminishing, yet distinct unmet need for the minority of patients in the second-line relapsed setting, particularly in the short term.
- At the time of the original submission (November 2019), the cost-effectiveness estimates of olaparib for patients with a *BRCAm* who had two courses of platinum-based chemotherapy were considered uncertain due to immature overall survival (OS) data from SOLO2. The Committee determined that olaparib could be deemed cost effective for use in this population if further data confirm the long-term OS benefit estimated using the company's model.
- The final analysis of the SOLO2 trial has now been conducted, which provided over 6 years of follow-up (3 February 2020 final data cut-off [DCO]). The analysis showed that olaparib ultimately did improve survival, with a median OS benefit of 12.9 months compared with placebo observed in the intention-to-treat (ITT) population of patients with *BRCAm*, platinum-sensitive, relapsed ovarian cancer.[4] In the prespecified exploratory OS analysis that adjusted for subsequent PARP inhibitor therapy in the placebo group in the ITT population, the median OS benefit of olaparib increased to 16.3 months compared with placebo.[4] Furthermore, in the second-line setting (i.e., the relevant

[a]As part of the same guidance, NICE recommended olaparib for routine use as an option for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults whose disease has responded to platinum-based chemotherapy, only if they have a *BRCA1/2* mutation and they have had three or more courses of platinum-based chemotherapy. This indication is not relevant to this submission.

population in this submission), the analysis showed that olaparib provided an even greater median OS benefit than in the ITT population, with a median OS benefit of [redacted] months compared with placebo.[4] When adjusting for subsequent PARP inhibitor use, the OS data showed a clear benefit of [redacted] months in favour of olaparib versus placebo in the second-line maintenance setting.[5] Olaparib is the only PARP inhibitor to demonstrated meaningful long-term OS benefit in this population. In line with the population of interest discussed in the Terms of Engagement,[6] this submission focuses on the second-line population of SOLO2 only.

- Similarly, a clinically meaningful progression-free survival (PFS) benefit of [redacted] months in the olaparib arm compared with the placebo arm (median PFS = [redacted] and [redacted] months, respectively) was demonstrated in the second-line maintenance setting.[5]
- The long-term tolerability profile of olaparib reported in the final SOLO2 publication, was generally consistent with that reported previously.[4,5,7] There were no significant increases in treatment-emergent adverse events, dose modifications and treatment discontinuations with olaparib, despite the longer treatment duration. Across the clinical studies, the overall safety profile of olaparib has been associated with adverse reactions of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation.[8] Niraparib, the only PARP inhibitor routinely commissioned in the same population being considered in this review,[9,10] despite having a similar mechanism of action has been shown to have a different tolerability profile to olaparib with regards dose changes, interruptions, and treatment discontinuations.[11-16] Olaparib therefore offers the small minority of eligible patients with a BRCA1/2 mutation an alternative effective treatment option.
- As per the Terms of Engagement, the economic model has been updated with second line SOLO2 OS data from the final analysis (3 February 2020 DCO) to directly address the uncertainties highlighted in the original appraisal.
- Overall, the updated economic model demonstrates olaparib is a highly beneficial cost-effective therapy, producing an incremental cost effectiveness ratio (ICER) of [redacted] per quality-adjusted life-year (QALY), [redacted].
- Although the eligible population is expected to diminish over time, the budget impact highlights there remains a small minority (up to ~15 patients per year) who may potentially benefit from second-line maintenance olaparib in the short term.

A.1 Background

- Olaparib is recommended for use within the Cancer Drugs Fund (CDF) as an option for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults whose disease has responded to platinum-based chemotherapy only if:
    - They have a breast cancer susceptibility gene (*BRCA1* and/or *BRCA2*) mutation (*BRCAm*)
    - They have had two courses of platinum-based chemotherapy and
    - The conditions in the managed access agreement for olaparib are followed[17]
- Incremental cost effectiveness ratios (ICERs) originally presented to the Committee included a commercial agreement of [redacted].[b]
- The Committee's preferred ICER range for olaparib as a second-line treatment in patients who are *BRCAm* positive as detailed in the Final Appraisal Document (FAD) was [redacted] per quality-adjusted life-year (QALY) gained, depending on whether overall survival (OS) was estimated from progression-free survival (PFS) gain or directly from Study 19, respectively. The Committee noted that the lower end of the ICER range was within the range usually considered as a cost-effective use of National Health Service (NHS) resources.
- The Committee's key uncertainty was around the lack of long-term OS data for patients taking olaparib. It acknowledged that the SOLO2 trial was more relevant than Study 19 for the subgroup with a *BRCAm*. However, the OS data from SOLO2 were immature and could be used not at the time to inform the cost-effectiveness modelling.
- The Committee considered that, if mature long-term OS data from SOLO2 supported the survival estimates in the company's alternative model, then the ICERs in the second-line setting could be within the range normally considered to be cost effective. Therefore, it agreed that this provided the plausible potential for olaparib to be cost effective.

[b] [redacted]

A.2 Key Committee assumptions

The key Committee-preferred assumptions as per the Terms of Engagement,[6] dated September 2020, are detailed in Table 1.

Table 1: Committee preferred assumptions outlined in the Terms of Engagement

Area	Committee-preferred assumptions
Population	The Committee noted that olaparib was not cost effective compared with routine surveillance for the overall population or for patients without a *BRCAm*, but that patients with a *BRCAm* after three courses of platinum-based chemotherapy could be recommended within routine commissioning. The Committee concluded that patients with a *BRCAm* after two courses of platinum-based chemotherapy could be recommended within the CDF. **As such, patients with a *BRCAm* after two courses of platinum-based chemotherapy are the relevant population for this CDF review.**
Time horizon	A time horizon of 50 years should be used.
Progression-free survival	The company used data on time to first subsequent therapy to model time spent in the progression-free health state and considered this to be more clinically relevant for modelling clinical effectiveness than radiological disease progression. However, the ERG considered that time to treatment discontinuation would better reflect the timing of disease progression. The Committee considered time to first subsequent therapy not to be a reliable method to estimate progression-free survival. **The company should present progression-free survival estimates using radiological disease progression data as well as time to treatment discontinuation data from the SOLO2 trial.**
Overall survival	The company estimated overall survival by assuming a 1:2 ratio of mean progression-free survival gain to mean overall survival gain. The ERG preferred to use data directly from the Study 19 trial. At the time of the original appraisal the SOLO2 trial data were too immature. **The company should update the overall survival estimate using SOLO2 trial data.**
Most plausible ICER	The Committee concluded that the company's revised base case included its preferred assumptions as stated in the appraisal consultation document. The Committee considered that the most plausible ICER was in a range of [redacted][a] per QALY gained, depending on whether the overall survival was estimated using a 1:2 ratio of the mean progression-free survival gain or data from Study 19, respectively.
End of life	Olaparib does not meet the end-of-life criteria in patients with a *BRCAm* who had responded to two courses of platinum-based chemotherapy

[a] [redacted]

Abbreviations: *BRCAm,* breast cancer susceptibility gene mutation; CDF, Cancer Drugs Fund; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year Source: Terms of Engagement (2020)[6]

A.3 Other agreed changes

This CDF review submission is consistent with the agreed Terms of Engagement,[6] outlined in Section A.1, with minimal changes from the original evidence submission presented in the single technology appraisal (STA).[7] The updated OS data from the SOLO2 trial have been implemented for the relevant population, i.e., patients with a *BRCAm* after two courses of platinum-based chemotherapy. Investigator-assessed PFS data from SOLO2, determined using radiological disease progression and by time to treatment discontinuation (TTD), have also been implemented and remain consistent with data previously presented in the STA.[6,7] Minor additions include revising baseline characteristics and adjusting for subsequent treatment to ensure internal consistency with the presented analyses, while maintaining consistency with the Committee-preferred assumptions. Table 2 details how the updates made to the company model ensure alignment with the Committee's key preferred assumptions, as per the Terms of Engagement.[6]

Table 2: Company updates and alignment with the Committee-preferred assumptions

Area	Previous assumptions	Requested updates	Alignment with Terms of Engagement
Population	Patients with platinum-sensitive relapsed ovarian cancer, who are in response to platinum-based chemotherapy	Those with a *BRCAm* after two courses of platinum-based chemotherapy are the relevant population for the CDF review	Yes – The CDF submission has been updated with data from SOLO2 based on second-line patients with a *BRCAm*
Time horizon	30 years	A time horizon of 50 years should be used	Yes – Time horizon of 50 years was applied to the economic model
Definition of progression-free survival	Time to treatment discontinuation as proxy for progression-free survival	No proxy in the base case and present scenarios with time to first subsequent therapy and time to treatment discontinuation was applied	Yes – Investigator-assessed progression-free survival and time to treatment discontinuation data from SOLO2 have been included, along with a scenario analysis based on BICR-assessed progression-free survival
Progression-free survival	Progression-free survival data from Study 19	The company should present progression-free survival estimates using radiological disease progression data, as well as time to treatment discontinuation data from the SOLO2 trial	

Area	Previous assumptions	Requested updates	Alignment with Terms of Engagement
Overall survival	Overall survival data from Study 19	The company should update the overall survival estimate using SOLO2 trial data	Yes – Additional data collected for long-term overall survival in the SOLO2 trial during the CDF data collection period has been incorporated
Subsequent treatment usage	Based on Study 19	NA	NA – These have been updated with SOLO2 data to ensure internal consistency with the presented analyses

Abbreviations: BICR, blinded independent central review; *BRCAm*, breast cancer susceptibility gene mutation; CDF, Cancer Drugs Fund; FY, financial year; NA, not applicable
Sources: National Institute for Health and Care Excellence (2018);[7] Terms of Engagement (2020)[6]

A.4 The technology

Since the National Institute for Health and Care Excellence (NICE) recommended olaparib for use in the CDF in the FAD[1] in November 2019, poly(ADP-ribose) polymerase (PARP) inhibitors have been accepted for use earlier in the clinical pathway, including for first-line maintenance therapy.[2,3] Consequently, PARP inhibitors are now used routinely as first-line maintenance therapy in newly diagnosed ovarian cancer.

PARP inhibitors remain the only targeted therapeutic option in the relapsed setting; however, in the UK their use is restricted to only patients who are PARP inhibitor-naïve at relapse of their disease.[3,18] As a result, the eligible population of PARP inhibitor-naïve patients in the second-line is diminishing, with only a small number of relapse patients eligible to receive this therapy.

No changes in the technology have occurred since olaparib was recommended for use in the CDF.[1] An overview of the technology is presented in Table 3, originally available in the STA (Document B, Section B.1.2, page 7).[7]

Table 3: Technology being reviewed

UK approved name and brand name	Olaparib (Lynparza®)
Mechanism of action	• Olaparib is a potent, orally administered PARP inhibitor. PARP enzymes are essential for repairing commonly occurring DNA SSBs in human cells.[8] Olaparib works by trapping PARP enzymes at the site of SSBs, thereby preventing the repair pathway leading to the

	persistence of SSBs, and subsequently their conversion to more harmful DSBs during DNA replication.[19] • Normal cells can accurately repair these DNA DSBs through the high-fidelity HRR pathway. However, patients with a *BRCAm* are unable to accurately repair these breaks using the HRR pathway, leading to the accumulation of DNA damage and eventually cell death (or apoptosis).[19] This phenomenon, whereby the independent loss of two factors permits cell survival, but loss of both factors in combination results in cell death, is referred to as "synthetic lethality", and underpins the effectiveness of PARP inhibitors, such as olaparib.
Marketing authorisation/CE mark status	The EMA granted marketing authorisation for the olaparib tablet formulation for the maintenance treatment of adult patients with platinum-sensitive, relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy on 8 May 2018.
Ovarian cancer relevant indications and any restriction(s) as described in the SmPC	Olaparib as monotherapy is currently indicated for: • Maintenance treatment of adult patients with advanced (FIGO Stage III and IV) *BRCAm* (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. • Maintenance treatment of adult patients with platinum-sensitive, relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Olaparib in combination with bevacizumab is also indicated for the: • Maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD-positive status defined by either a *BRCAm* and/or genomic instability.
Method of administration and dosage	• Olaparib is available as 100 mg and 150 mg tablets. • The recommended dose of olaparib in monotherapy or in combination with bevacizumab is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction. <u>Olaparib monotherapy</u> • Patients with platinum-sensitive, relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy should start treatment with olaparib no later than 8 weeks after completion of their final dose of the platinum-containing regimen. <u>Olaparib in combination with bevacizumab</u> • When olaparib is used in combination with bevacizumab for the first-line maintenance treatment of high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer following completion of first-line platinum-based therapy with bevacizumab, the dose of bevacizumab

	is 15 mg/kg once every 3 weeks. Please refer to the full product information for bevacizumab.
Additional tests or investigations	• Patients should be evaluated for a *BRCAm* by a validated test to confirm deleterious or suspected deleterious germline and/or somatic mutations in *BRCA1/2*. • *BRCAm* status is routinely confirmed at earlier lines of therapy.
List price and average cost of a course of treatment	The list price for olaparib tablets is £2317.50 (56 x 150 mg tablets) per 14-day pack and £4635.00 per 28-day cycle (excluding VAT).
Commercial arrangement (if applicable)	A confidential commercial access agreement is in place for olaparib; the net price of olaparib for NHS hospitals in England is [redacted] per 28-day treatment regimen. This is based on a [redacted]
Date recommended for the CDF	November 2019, date of the Final Appraisal Document[1]
Data collection end date	• SOLO2 trial final analysis DCO: 3 February 2020 • PHE SACT data collection end date: October 2020

Abbreviations: *BRCA*, breast cancer susceptibility gene; *BRCAm*, breast cancer susceptibility gene mutation; CDF, Cancer Drugs Fund; DNA, deoxyribonucleic acid; DCO, data cut-off; DSB, double-strand break; EMA, European Medicines Agency; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; HRR, homologous recombination repair; NHS, National Health Service; PARP, poly(ADP-ribose) polymerase; PHE, Public Health England; SACT, systemic anti-cancer therapy; SmPC, summary of product characteristics; SSB, single-strand break; VAT, value added tax
Sources: AstraZeneca (2018);[8] National Institute for Health and Care Excellence (2019);[1] Public Health England (2020);[20] Data on file[5]

A.5 Clinical effectiveness evidence

In alignment with the Terms of Engagement,[6] the primary data source presented in support of the CDF review is the SOLO2 trial (NCT01874353). A secondary source of evidence included the Public Health England (PHE) systemic anti-cancer therapy (SACT) dataset.

A.5.1 *Primary source of clinical effectiveness evidence*

As detailed in Section A.1, the main data source presented in support of this review is the pivotal Phase 3 SOLO2 trial, in which long-term OS data were collected for olaparib in the maintenance setting of patients with a *BRCAm*, platinum-sensitive, relapsed ovarian, fallopian tube and peritoneal cancer.[1,6] Specifically, data from the second-line treatment setting were used to inform this CDF review.[21] Further details of the SOLO2 trial are provided in Table 4.

Table 4: Primary source of clinical effectiveness evidence

Study title	Olaparib tablets as maintenance therapy in patients with platinum sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21) NCT01874353

Study design	Double-blind, randomised, placebo-controlled, multicentre, international Phase 3 study
Population	Patients with platinum-sensitive relapsed HGSOC patients (including patients with primary peritoneal and/or fallopian tube cancer), who are in response (complete or partial) to platinum-based chemotherapy, and who have a confirmed *BRCAm*
Intervention(s)	Olaparib, 300 mg tablets BD (n=196)
Comparator(s)	Placebo, 300 mg tablets BD (n=99)
Outcomes collected that address Committee's key uncertainties	Overall survival
Reference to section in appendix	NA

Abbreviations: BD, twice daily; *BRCA*, breast cancer susceptibility gene; *BRCAm*, breast cancer susceptibility gene mutation; HGSOC, high grade serous ovarian cancer; NA, not applicable
Sources : Poveda et al. (2021);[4] Pujade-Lauraine et al. (2017);[22] Data on file[5]

Two key data cut-offs (DCOs) were scheduled in the analysis plan and provided primary evidence for this CDF review. The DCO for the primary analysis of PFS presented in the STA (19 September 2016) took place when 187 progression events had occurred (63.4% maturity), approximately 36 months after the first patient was enrolled. At this DCO, all efficacy, safety variables and patient-reported outcomes were analysed.

A further analysis was planned for when the OS data were approximately 60% mature, which was anticipated to occur approximately 72 months after the first patient was enrolled. The final DCO was 3 February 2020, which took place when 181 survival events had occurred (61% maturity), approximately 76 months after the first patient was enrolled on the trial.[4]

A.5.2 *Secondary source of clinical effectiveness evidence*

Per the managed access agreement, the SACT data collected by PHE were included in support of data collected from the SOLO2 trial. Details of the SACT cohort[20] are provided in Table 5.

Table 5: Secondary source of clinical effectiveness evidence

Study title	SACT data cohort
Study design	Analysis of SACT dataset
Population	Patients with platinum-sensitive relapsed HGSOC patients (including patients with primary peritoneal and/or fallopian tube cancer), who are in response (complete or partial) to second-line platinum-based chemotherapy, and who have a confirmed *BRCAm*

Intervention(s)	Olaparib, 300 mg tablets BD
Comparator(s)	NA
Outcomes collected that address Committee's key uncertainties	Due to the short data collection time, overall survival data were not reported
Reference to section in Appendix	A.13.1

Abbreviations: BD, twice daily; *BRCAm*, breast cancer susceptibility gene mutation; HGSOC, high-grade serous ovarian cancer; NA, not applicable; SACT, systemic anti-cancer therapy
Source: Public Health England (2020)[20]

The SACT dataset identified 15 unique patients during the reporting period (28 November 2019 to 27 February 2020).[20] Due to the short data collection time, there were no clinical outcomes reported in the SACT analysis (see Appendix A.13.1). Thus, the SACT dataset was not included in the updated economic model.

A.6 Key results of the data collection

The key uncertainty noted in the Terms of Engagement[6] was the lack of mature OS data from the SOLO2 trial at the time the FAD was published.[1,7] Despite Study 19 not being powered for OS, it provided a median duration of follow-up for OS of 6.5 years, and so was used in the primary analysis. Although Study 19 provided a reasonable alternative data source of long-term OS, the Committee's preference was to base decision making on the SOLO2 pivotal trial.[1,6] To address this, long-term OS data are presented from the SOLO2 trial; the median follow-up for OS at the final SOLO2 DCO was 65.7 months (interquartile range [IQR]: 63.6–69.3) with olaparib and 64.5 months (IQR 63.4–68.7) with placebo.[4]

Addressing the additional uncertainties noted in the Terms of Engagement,[6] such as the use of PFS and TTD from SOLO2, did not require additional data collection; over 50% of PFS events had occurred in each treatment group at the time of the primary analysis (63.4% maturity overall, 19 September 2016 DCO), in line with the statistical plan (Document B, Section B.2.6, page 64).[7] The median follow-up for PFS at the primary analysis was 22.1 months (IQR: 21.9–27.4) for patients treated with olaparib and 22.2 months (IQR: 8.3–27.5) for patients who received placebo.[4] The time horizon of the economic model was also updated. These endpoints have been updated to maintain consistency with the Committee-preferred assumptions (Sections A.1 and A.3).

As discussed in the original olaparib STA (Document B, Section B.2.3, page 39),[7] the SOLO2 trial was designed to investigate all patients (N=295) with platinum-sensitive

relapsed ovarian cancer, who were in response to platinum-based chemotherapy, and who had a confirmed *BRCAm*. However, in line with the population of interest discussed in the Terms of Engagement,[6] only the results for the second-line patient population (N=172) have been presented in this submission- from Section A.6.1 onwards.

For reference, detailed outcomes of the SOLO2 intention-to-treat population have been reported by Pujade-Lauraine et al (2017)[22], where the primary endpoint for PFS was met and Poveda et al (2021) for final OS analysis.[4]

A.6.1 *Overall survival*

A.6.1.1 Overall survival (unadjusted)

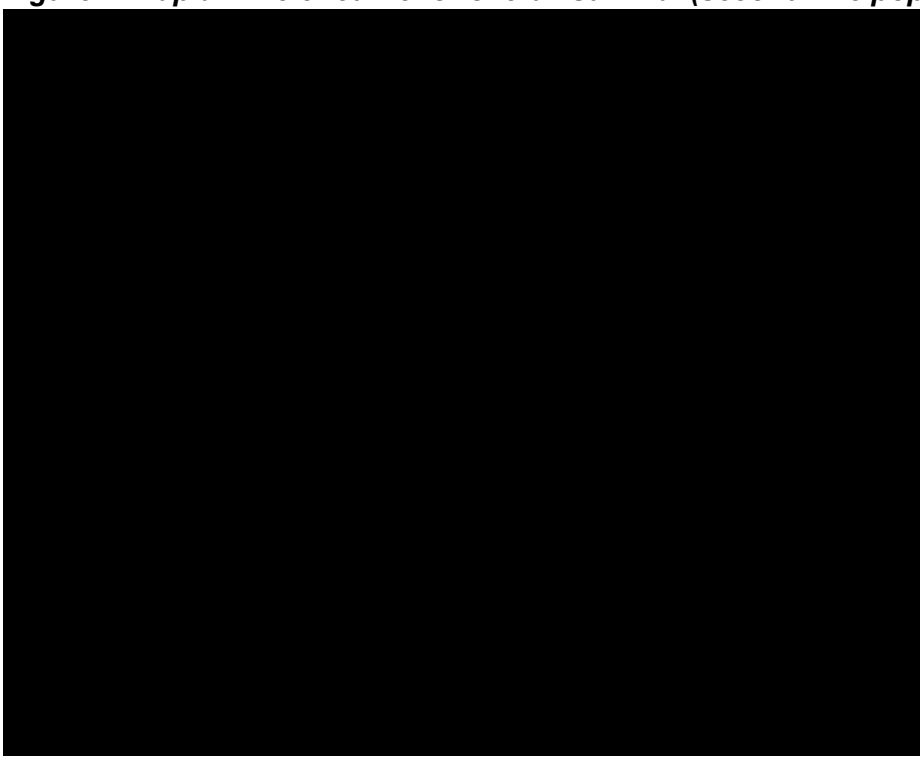
OS data from the SOLO2 population who had a confirmed *BRCAm* and had previously received two lines of platinum-based chemotherapy are presented in Table 6. At the time of the final DCO of SOLO2 (3 February 2020), a total of [redacted] ([redacted] in the olaparib arm and [redacted] in the placebo arm) had occurred in the second-line setting.[4] 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).[4] Despite high rates of crossover to subsequent PARP inhibitor therapy following disease progression in the placebo arm ([redacted] vs. [redacted] in the olaparib arm) (see Section A.6.1.2.1), the results show a clear benefit of [redacted] months in favour of olaparib versus placebo (median OS of [redacted] months vs [redacted], respectively; hazard ratio [HR] = [redacted], 95% confidence interval [CI]: [redacted]; Table 6 and Figure 1.[4]

Table 6: Overall survival (second-line population, unadjusted)

	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]	

Abbreviations: CI, confidence interval; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; OS, overall survival
Sources : Poveda et al. (2021);[4] Data on file[5]

Figure 1: Kaplan–Meier curve for overall survival (second-line population, unadjusted)



Abbreviation: bd, twice a day
Source: Data on file[5]

A.6.1.2 Overall survival (adjusted)

A.6.1.2.1 Treatment switching adjustment of SOLO2 OS data

Interpretation of the OS data is limited by the high rate of post-progression PARP inhibitor use which is not generalisable to current UK practice. While patients were not permitted to switch over to the opposite arm from which they were randomised in the SOLO2 trial, 20 (10%) of 196 patients in the olaparib group and 38 (38%) of 99 patients in the placebo group received subsequent PARP inhibitor following disease progression.[4] This included [redacted] olaparib-treated and [redacted] placebo-treated patients in the second-line setting. When switching occurs, particularly in the control group, the OS benefit of the new treatment will likely be underestimated.[23] In SOLO2, crossover to a PARP inhibitor impacts the placebo arm greater than the olaparib arm, as the magnitude of benefit is greater when switching from placebo to PARP inhibitor than with retreatment with olaparib. This limits the interpretation of the OS in patients randomised to the placebo arm.

The impact of crossover was anticipated during the SOLO2 study design hence, it was pre-specified in the statistical analysis plan that exploratory analysis of OS adjusting for treatment switching may be conducted if sufficient proportion of patients switch. To address

the OS confounding, treatment switching analyses were performed to estimate the relative treatment effect for olaparib compared with placebo on the OS endpoint, adjusting for the potential underestimation introduced by patients randomised to the placebo arm receiving olaparib or other PARP inhibitor as a subsequent treatment outside of the study.

The treatment switch adjustment is conducted using the method of rank preserving structural failure time (RPSFT) model.[24] This aligns with the treatment switch methodology presented in the Lancet publication of the final OS data for the overall SOLO2 population (see Appendix A.13.2).[4] The plausibility of the underlying assumptions of alternative methods such as the inverse probability of censoring weights (IPCW) and the two-stage method is assessed as follows. The IPCW methodology is not considered applicable because there would likely be insufficient data to robustly assess the time-dependent factors that affect the decision to switch, a key requisite for the IPCW. Similarly, the two-stage method is considered inappropriate due to the strong assumption of no time-dependent confounding between the time of disease progression and time of treatment, which is difficult to substantiate.

The RPSFT model utilises a causal framework to estimate counterfactual survival times, the survival time that would have been observed if patients had not received olaparib or other PARP inhibitor treatment. The causal model uses a single parameter, an acceleration factor, which models the relationship between duration of treatment and survival. The use of a single causal parameter requires the partitioning of survival into two states, time on placebo and time on PARP treatment. Unlike the two-stage method, the RPSFT model does not rely on the no unmeasured confounders assumption and identifies the treatment effect using only the randomisation of the trial, observed survival, and observed treatment history. The limitation of the RPSFT model is the assumption of a common treatment effect, which states that the relative treatment effect is the same for all participants regardless of when the treatment is received.[23] The primary analysis methodology also utilises re-censoring to ensure that the assumption of non-informative censoring – derived by standard survival analysis techniques (e.g., cox modelling, Kaplan–Meier methodology) – is not violated. The acceleration factor was not applied to the olaparib group, owing to the fact retreatment with a PARP inhibitor is not widely recommended as confirmed by UK ovarian cancer clinical expert consultations. This is due to the lack of data demonstrating the impact of PARP inhibitor retreatment on OS outcomes.[18] However, this was applied to patients in the SOLO2 placebo group, where the

OS benefit is likely overestimated. Furthermore, data based on the placebo arm of Study 19, where post-progression subsequent PARP inhibitor utilisation was relatively less compared to SOLO2, is presented within the economic model as an alternative scenario to estimate the OS.

Considering clinical practice in the UK, the treatment switching adjustment improves the generalisability of the SOLO2 trial. With the availability of PARP inhibitors in the first-line maintenance setting,[2,25] and the existing eligibility criterion for PARP inhibitor naïvety,[3] it is now increasingly unlikely that patients will receive a PARP inhibitor in the third-line setting in the UK. This is highlighted by UK clinicians, who report that majority of patients who are eligible for maintenance treatment with a PARP inhibitor will receive this after first-line treatment with chemotherapy. Moreover, clinical trial data support the implementation of PARP inhibitors in the earliest line of relapse possible, with the consistent aim of achieving the greatest possible benefit and to delay disease relapse for as long as possible.

A.6.1.2.2 Overall survival adjusted for subsequent PARP inhibitor therapy

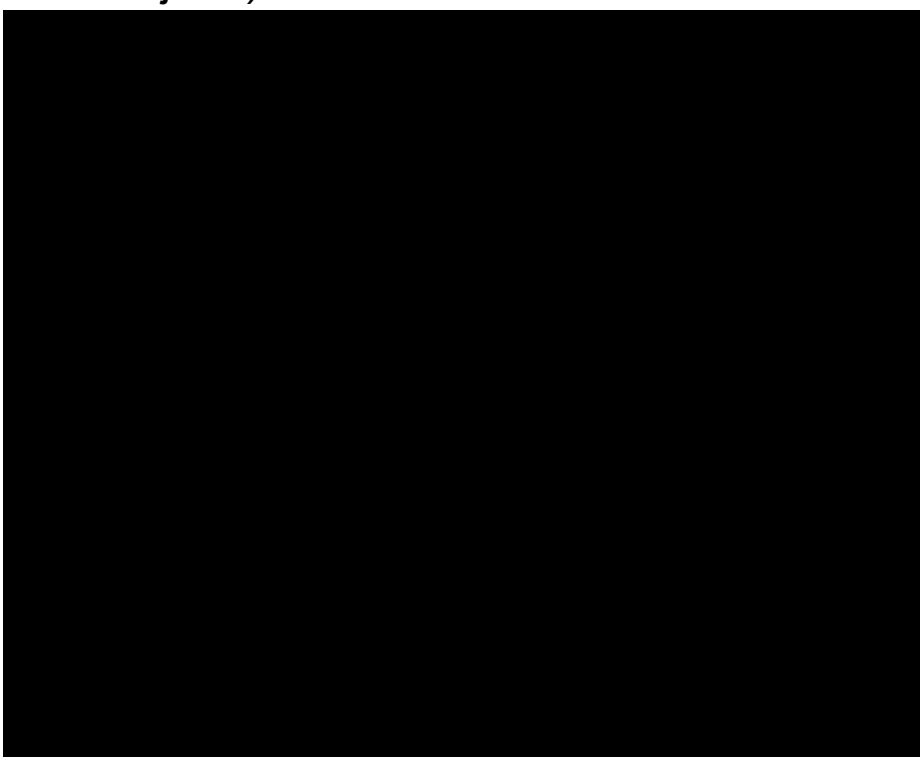
As outlined in Section A.6.1.1, the high rate of subsequent PARP inhibitor use in the SOLO2 placebo arm ([redacted]) relative to the olaparib arm ([redacted]) confounded the OS analysis therefore, the true OS benefit achieved with olaparib is likely to be underestimated. As discussed above, because retreatment 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 in the third line. Addressing the confounding bias observed in SOLO2 due to treatment switching therefore improves the generalisability of the SOLO2 study by aligning the subsequent treatments to better reflect UK clinical practice. When adjustment is carried out using the RPSFT model, the OS data for SOLO2 in the second line show a clinically meaningful benefit of [redacted] months in favour of olaparib versus placebo ([redacted] vs [redacted] months, respectively: Table 7 and Figure 2) and a reduction in risk by [redacted].

Table 7: Overall survival (second-line population, PARP inhibitor adjusted)

	Olaparib (N=110)	Placebo (N=62)
Events, n/N (%)	[redacted]	[redacted]
Median overall survival, months (95% CI)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; NE, not estimable; PARP, poly(ADP-ribose) polymerase
Source: Data on file[5]

Figure 2: Kaplan–Meier curve for overall survival (second-line population, PARP inhibitor adjusted)



Abbreviations: bd, twice a day; PARP, poly(ADP-ribose) polymerase
Source: Data on file[5]

A.6.2 *Progression-free survival*

PFS was evaluated at the primary analysis of the SOLO2 trial (19 September 2016 DCO) when the primary study endpoint was met. Unlike the OS endpoint, no further analysis on PFS was pre-planned for the SOLO2 study. As requested in the Terms of Engagement,[6] PFS estimates by radiological disease progression (Section A.6.2.1) and TTD (Section A.6.2.2), both from the SOLO2 study are presented in this submission.

A.6.2.1 Investigator-assessed progression-free survival

A total of [redacted] second-line patients ([redacted] in the olaparib arm and [redacted] in the placebo arm) experienced investigator-assessed PFS in the SOLO2 trial. Treatment with olaparib resulted in a median time to progression benefit of [redacted] months versus placebo (median PFS = [redacted] and [redacted] months, for olaparib and placebo, respectively; Table 8 and Figure 3).[21]

Table 8: Investigator-assessed progression-free survival (second-line population)

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

Abbreviations: CI, confidence interval; HR, hazard ratio; N, total number of patients; n, number of patients who experienced progression event; NE, not estimable
Sources: AstraZeneca (2017);[21] Data on file[5]

Figure 3: Kaplan–Meier curve for investigator-assessed progression-free survival (second-line population)

Abbreviation: bd, twice a day
Source: Data on file[5]

Sensitivity analysis for PFS was conducted using the blinded independent central review (BICR) methodology. A total of [redacted] second-line patients ([redacted] in the olaparib arm and [redacted] in the placebo arm) experienced PFS by BICR in the SOLO2 trial. Treatment with olaparib resulted in a median time to progression benefit of [redacted] months versus placebo (median PFS = [redacted] and [redacted] months, for olaparib and placebo, respectively; Table 9 and Figure 4). As seen from the HR, the analysis of PFS using the BICR data was consistent with the investigator assessment with respect to the benefit seen for olaparib versus placebo.

Table 9: Progression-free survival by blinded independent central review (second-line population)

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

Abbreviations: CI, confidence interval; HR, hazard ratio; N, total number of patients; n, number of patients who experienced progression event; NE, not estimable
Source: Data on file[5]

Figure 4: Kaplan–Meier curve for progression-free survival by blinded independent central review (second-line population)

Abbreviation: bd, twice a day
Source: Data on file[5]

A.6.2.2 Time to treatment discontinuation

A total of [redacted] second-line patients ([redacted] in the olaparib arm and [redacted] in the placebo arm) discontinued treatment in the second line only patient subgroup of the SOLO2 trial. Of the second-line patients randomised to the olaparib and placebo arms at the start of the study, [redacted] and [redacted] remained on treatment upon primary data analysis, respectively. Thus, treatment with olaparib resulted in a median time to event benefit of [redacted] months versus

placebo (median TTD = [redacted] and [redacted] months for olaparib and placebo, respectively; Table 10 and Figure 5).

Table 10: Time to treatment discontinuation (second-line population)

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

Abbreviations: CI, confidence interval; HR, hazard ratio; N, total number of patients; n, number of patients experiencing time to treatment discontinuation event
Source: Data on file[5]

Figure 5: Kaplan–Meier curve for time to treatment discontinuation (second-line population)

Abbreviation: bd, twice a day
Source: Data on file[5]

A.7 Incorporating collected data into the model

In TA620,[1] olaparib was deemed cost effective for patients with a *BRCAm* who have had three or more courses of platinum-based chemotherapy and was recommended for routine use in the NHS in this population. The Committee stated that the immaturity of the SOLO2 OS data generated uncertainty about the cost effectiveness of olaparib in patients with a *BRCAm* who have had two courses of platinum-based chemotherapy, but if mature OS data

from the SOLO2 trial supported the survival estimates in the company's alternative model, then the ICERs for olaparib use in this population could be within the range normally considered to be a cost-effective use of NHS resources, i.e. £20,000–30,000 per QALY gained (FAD, 3.14, page 14).[1]

To address this uncertainty, the ERG cost-effectiveness model at CDF entry has been updated with the final analysis of the SOLO2 trial (3 February 2020 DCO) in line with the Terms of Engagement.[6] Investigator-assessed PFS and TTD from SOLO2 have also been implemented and remain consistent with data previously presented in the STA.[6,7]

The model structure is identical to that previously submitted in the STA (Document B, Section B.3.2, page 113).[7] The updates made to the economic model are described in the following sections.

A.7.1 *Overall survival*

At the time of the original submission, SOLO2 OS data were considered immature, and hence were not used in the economic model. Following the final DCO in February 2020, mature OS are available from the SOLO2 study (3 February 2020), which informs the economic analysis in this submission. In line with the original submission,[7] the following independent parametric distributions are considered: generalised gamma, lognormal, log logistic, Weibull, Gompertz, exponential and a flexible spline model (hazard 1-knot). The parametric distributions that inform the analysis were selected based on statistical goodness-of-fit, visual inspection and external clinical validation.

A summary of the Akaike information criterion (AIC) goodness-of-fit statistic for each distribution explored for OS in the second-line setting is provided in Table 11. A plot of the survival functions is shown in Figure 6 for visual assessment of fit. The lognormal, log logistic, generalised gamma and spline models provided a good fit to the observed data with comparable AIC scores. The Weibull, Gompertz and exponential models were considered the worst fit to the placebo and olaparib groups.

Table 11: Summary of the Akaike information criterion goodness-of-fit data for the parametric overall survival analysis (second-line population)

Model	Olaparib	Adjusted Placebo
Generalised gamma	1041.74	992.2
Spline (1 knot scale = hazard)	1042.50	991.71
Lognormal	**1044.43**	**994.06**

Log logistic	1050.00	999.60
Weibull	1057.79	1006.39
Exponential	1067.09	1022.42
Gompertz	1068.32	1017.76

With consideration to outcomes in *BRCAm* relapsed ovarian cancer, the lognormal curve was considered the most plausible olaparib OS extrapolation based on statistical fit and UK clinical expert opinion. This was validated by UK ovarian cancer clinical experts who indicated around [redacted] of patients alive at 20 years was considered clinically plausible in the relapsed setting following olaparib maintenance which is consistent with the lognormal distribution. The lognormal curve also produced highly 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. For the routine surveillance arm, the adjusted placebo arm from SOLO2 was utilised for the base case. The lognormal curve was considered a reasonable fit by clinical experts to the adjusted placebo Kaplan–Meier data from SOLO2 (Figure 7) predicting [redacted] of patients managed under routine surveillance would remain alive at 3 years (vs. [redacted] from the SOLO2 adjusted placebo arm).

Despite being a reasonable fit over the observed period, the generalised gamma extrapolation projected clinically implausible outcomes over the long term for routine surveillance, with approximately [redacted] alive after 30 years and almost double the anticipated survival at the 20-year landmark ([redacted]). Similarly, the spline model fitted the observed Kaplan–Meier data well but produced implausible outcomes over the long term; approximately, [redacted] of patients were predicted alive at 15 years irrespective of whether they were actively treated with maintenance olaparib or managed by routine surveillance, which is clinically implausible particularly given the compelling data observed in the SOLO2 study. At 20 years, the spline model predicted no meaningful OS difference between patients managed by routine surveillance ([redacted]) and olaparib ([redacted]). When compared with the lognormal predictions at 20 years, which were deemed clinically plausible by UK ovarian cancer experts, the spline model potentially underestimates long-term survival for olaparib ([redacted], compared with [redacted] for lognormal), but overestimates this for routine surveillance in the relapsed setting ([redacted], compared with [redacted] for lognormal).

Given the above, the lognormal curve was selected in the base-case analysis for overall survival in both arms, scenario analysis using an alternative plausible distribution (log logistic) is also presented in Section A.11.

Figure 6: Overall survival Kaplan–Meier curve and parametric functions for olaparib overall survival (second-line population)

Abbreviations: KM, Kaplan–Meier; OS, overall survival

Figure 7: Overall survival Kaplan–Meier curve and lognormal curves for olaparib and adjusted-placebo (second-line population)

Abbreviations: KM, Kaplan–Meier; OS, overall survival; RS, routine surveillance

A.7.2 *Progression-free survival*

PFS was evaluated at the primary analysis of the SOLO2 trial (19 September 2016 DCO) when the primary study endpoint was met. Unlike the OS endpoint, no further analysis on PFS were pre-planned for the SOLO2 study.

In the original submission, the endpoint time to first subsequent treatment (TFST) was presented in the company base case as a proxy for PFS; however, the Committee considered TFST to be an unreliable method to estimate PFS. In alignment with the Terms of Engagement,[6] PFS is estimated directly from the SOLO2 PFS data for this submission.

A.7.2.1 Investigator-assessed progression-free survival

The following parametric distributions were considered in the PFS by investigator analysis: generalised gamma, log logistic, lognormal, Gompertz, exponential, Weibull, and a flexible spline model (hazard 1-knot). The parametric distributions that inform the base-case analysis were selected based on statistical goodness-of-fit, visual inspection and external clinical validation.

A summary of the AIC goodness-of-fit statistic for each distribution explored is Table 12. A plot of the PFS functions is shown in Figure 8, provided for visual assessment of fit. The log logistic, log normal, generalised gamma and spline distributions had the best goodness-of-fit, with comparable AIC scores. The Weibull, Gompertz and exponential models were considered the worst fit to the placebo and olaparib groups.

Table 12: Summary of the Akaike information criterion goodness-of-fit data for investigator-assessed progression-free survival (second-line population)

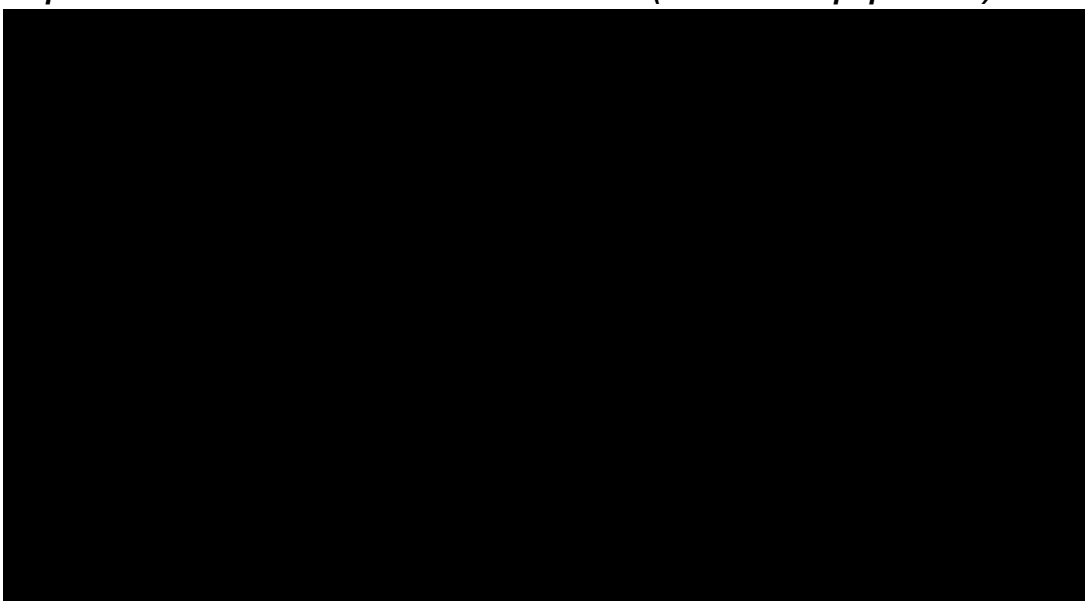
Model	Olaparib	Placebo
Spline (1 knot scale = hazard)	508.92	285.65
Generalised gamma	508.92	290.54
Log logistic	**507.00**	**302.83**
Lognormal	507.66	302.05
Gompertz	512.13	311.83
Exponential	512.25	315.67
Weibull	509.21	317.65

Similar to the OS extrapolation, the generalised gamma and flexible spline distributions offered a reasonable fit over the observed data period, but the shape of the curves over the long term was considered to be clinically implausible. Both the generalised gamma and spline models predict by 10 years the proportion of patients under routine surveillance who are progression free would exceed that of those treated with olaparib maintenance (Figure 8), which is not aligned with clinical expectations as validated by experts. The log logistic, was selected as the most plausible PFS extrapolation for olaparib and routine surveillance based on statistical fit (Figure 9) and expert opinion. Observed long-term estimates of PFS from the SOLO2 study also support the plausibility of the log logistic distribution. The log logistic curve produced consistent long-term OS estimates when compared to the observed data from SOLO2 at 1 and 2 years ([redacted] vs. [redacted] and [redacted] vs. [redacted], respectively) for olaparib and was therefore selected in the base-case analysis for both arms. Additional scenario analysis was conducted to determine the impact of alternative plausible distribution choices on the base case.

Figure 8: Progression-free survival Kaplan–Meier curve and parametric functions for olaparib (second-line population)

Abbreviations: KM, Kaplan-Meier; ola, olaparib; PFS, progression-free survival

Figure 9: Progression-free survival Kaplan–Meier curve and loglogistic curves for olaparib and routine surveillance from SOLO2 (second-line population)



Abbreviations: KM, Kaplan-Meier; ola, olaparib; PFS, progression-free survival; RS, routine surveillance

A.7.2.2 Time to treatment discontinuation

TTD estimated from SOLO2 was also presented as requested by the Terms of Engagement.[6] Consistent with the approach in the original submission, there is no active treatment in the routine surveillance (placebo) group because patients do not incur any treatment costs; therefore, TTD extrapolations for the routine surveillance arm are not

considered. The drug costs of olaparib are estimated based on the parametric models fitted to TTD data from SOLO2 in line with the assumption in the original submission.

The following parametric distributions were considered in the TTD analysis: spline (1 knot scale = hazard), generalised gamma, log logistic, lognormal, Gompertz, exponential and Weibull. The spline (1 knot scale = hazard) model, which had the lowest AIC, had the best goodness-of-fit (Table 13 and Figure 10).

Table 13: Summary of Akaike information criterion goodness-of-fit data for time to treatment discontinuation (second-line population)

Model	Olaparib	Placebo
Spline (1 knot scale = hazard)	**568.07**	**332.78**
Generalised gamma	568.07	337.48
Log logistic	565.82	342.26
Lognormal	568.72	342.32
Gompertz	567.03	350.53
Exponential	565.08	355.25
Weibull	566.55	357.22

Figure 10: Time to treatment discontinuation Kaplan–Meier curve and parametric functions for olaparib (second-line population)

Abbreviations: 1k, 1-knot; KM, Kaplan-Meier; Ola, olaparib; TTD, time to treatment discontinuation

Observed long-term estimates of TTD for olaparib from the SOLO2 study also supports the use of the flexible spline model for extrapolating TTD. Approximately [redacted] and [redacted] of patients treated with olaparib were on treatment in the SOLO2 study at 1 and 2 years, respectively; similarly, the spline model predicts [redacted] and [redacted] of patients remain on treatment at the 1- and 2-year timepoint, respectively.

The spline model was therefore selected in the base case extrapolation for TTD. Scenario analyses based on the generalised gamma and Weibull curves are also presented.

Figure 11: Time to treatment discontinuation Kaplan–Meier curve and flexible Spline curve for olaparib (second-line population)

Abbreviations: 1k, 1-knot; KM, Kaplan-Meier; Ola, olaparib; TTD, time to treatment discontinuation

A.8 Key model assumptions and inputs

Table 14: Key model assumptions and inputs

Model input and cross reference	Original parameter/ assumption	Updated parameter/ assumption	Source/justification
Overall survival source (Document B, Section B.3.3, page 119)	Evidence from Study 19	Evidence from the SOLO2 study	As per the terms of engagement
Progression-free survival source (Document B, Section B.3.3, page 125)	Evidence from Study 19	Evidence from the SOLO2 study	As per the terms of engagement
Time to treatment discontinuation source (Document B, Section B.3.3, page 131)	Evidence from Study 19	Evidence from the SOLO2 study	As per the terms of engagement
Baseline characteristics	Evidence from Study 19	Evidence from the SOLO2 study	Alignment with the source of efficacy data

Mean daily dose	Evidence from SOLO2 primary analysis	Evidence from SOLO2 final analysis	Alignment with the latest data available from SOLO2
Subsequent treatments	Evidence from Study 19	Evidence from SOLO2 final analysis	Alignment with the latest data available from SOLO2

A.9 Cost-effectiveness results (deterministic)

The key cost-effectiveness results considered by the Committee to demonstrate plausible potential for cost-effectiveness at entry to the CDF are presented in Table 15 (Document B, Section B.3.7, page 164).

The new company base case (Table 15) and sensitivity analyses presented in this section are based on the approved simple PAS for olaparib; Appendix A.13.3 outlines the cost-effectiveness results taking into account the existing managed access agreement for olaparib in the second-line maintenance setting.

The new company base-case results encompass the final OS data from SOLO2 plus any associated changes highlighted in the Terms of engagement. 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 a strategy of routine surveillance. The incremental cost per QALY gained for olaparib versus routine surveillance was [redacted]. The differences observed in the incremental costs and QALYs, for olaparib compared to routine surveillance at CDF entry versus the updated new company base case are primarily driven by the difference in the net prices for olaparib (See Appendix A.13.3) and the alignment of inputs in the model with the SOLO2 study.

Table 15: Cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER vs RS (£/QALY)
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry based on Study 19 *([redacted])*							
Routine surveillance	[redacted]	[redacted]	[redacted]	–	–	–	–
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness analysis 2: New company base-case incorporating clinical evidence from SOLO2 ***(based on [redacted] PAS)***							
Routine surveillance	[redacted]	[redacted]	[redacted]	–	–	–	–
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NA, not available; QALY, quality-adjusted life-year

A.10 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to assess the parametric uncertainty associated with the base-case model results in line with the approach in the original submission (Document B, Section B.3.8, page 165). Parameters where estimates of uncertainty were available were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques.

The PSA was run for 10,000 iterations for the base-case analysis. Results from the PSA are presented in Table 16. The probabilistic ICER is [redacted] per QALY gained, which is consistent with the deterministic analysis of [redacted].

Table 16: Average results based on probabilistic sensitivity analysis (10,000 iterations)

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

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

A.11 Key sensitivity and scenario analyses

A list of scenario analyses ran in the model is presented in Table 17. The results of the scenario analyses are presented in Table 18.

Consistent with the approach in TA784[10], scenario analysis based on the placebo arm of Study 19 (equivalent to routine surveillance) - where post-progression subsequent PARP inhibitor utilisation in the placebo arm was relatively less - is presented as an alternative scenario to the adjusted OS based on RPSFT model. As highlighted by the Committee in the original appraisal, the use of the SOLO2 OS data to directly estimate OS remains the primary and preferred approach for decision making. However, this analysis is presented as a useful scenario particularly because a relatively smaller proportion of patients with *BRCAm* in Study 19 received subsequent post-progression PARP inhibitors ([redacted] compared to SOLO2 ([redacted]). The curve selections for this scenario were kept consistent with the updated base case for TTD (spline), PFS (log logistic) and OS in the olaparib arm (log normal), given these endpoints are based on the SOLO2 data. For the extrapolation of the placebo OS arm from Study 19, the spline model is selected to ensure consistency with the preferred curves selected at the original appraisal for Study 19 placebo (routine surveillance) arm. The results in an ICER of [redacted] which, as anticipated, is higher than the new company base case due to subsequent PARP inhibitor therapy use inflating the OS in the placebo group of Study 19 thereby underestimating the OS gain for olaparib. Nevertheless, the direction of the result from this scenario is consistent, relative to the new company base case, indicating that the treatment-switching adjustment based on the RPSFT model is robust.

The scenario analyses indicate the alternative plausible model choice of log logistic to extrapolate OS resulted in a modest increase in the deterministic ICER by £1,635 ([redacted]). An alternative plausible curve selection of lognormal for PFS had a positive impact on the base case at an ICER of [redacted]. Changes to the choice of distribution for TTD based on the Weibull resulted in a decrease in the base case ICER to [redacted] and an increase to [redacted] when the generalised gamma distribution is selected.

Table 17: List of scenario analyses conducted

Parameter	Base case	Scenario	Comment
Survival extrapolations (PFS)	Log logistic	Alternative plausible extrapolation (based on AIC statistics, visual inspection, and expert opinion): Lognormal	Assess the impact of different extrapolation of PFS estimates
Survival extrapolations (OS)	Log normal	Alternative plausible extrapolations (based on AIC statistics, visual inspection, and expert opinion): Loglogistic	Assess the impact of different extrapolation of survival estimates
Survival extrapolations (TTD)	1-knot spline	Alternative plausible extrapolations (based on AIC statistics and visual inspection): Generalised gamma Weibull	Assess the impact of different extrapolation of treatment duration
PFS estimates	Investigator-assessed PFS	BICR-assessed PFS	Assess the impact of using an alternative source of PFS assessment
Placebo arm OS estimates	Adjusted placebo OS arm from SOLO2	Placebo arm from Study 19	Assess the impact of using alternative source of OS data for routine surveillance
Olaparib mean daily dose	SOLO2 final DCO	Aligned with estimates at the original submission	Assess the impact of maintaining the same assumption at CDF entry

Abbreviations: AIC, Akaike information criterion; BICR, blinded independent central review; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

Table 18: Results of scenario analyses (based on [redacted] PAS for olaparib)

Outcome	Scenario	Technology	Inc. costs	Inc. QALYs	ICER	Impact on base case (£)
New company base case ([redacted] *PAS*)					[redacted]	
PFS extrapolation	Lognormal	RS	–	–	–	–
		Olaparib	[redacted]	[redacted]	[redacted]	-£1,643
OS extrapolation	Log logistic	RS	–	–	–	–
		Olaparib	[redacted]	[redacted]	[redacted]	£1,635
TTD extrapolation	Generalised gamma	RS	–	–	–	–
		Olaparib	[redacted]	[redacted]	[redacted]	£2,998
	Weibull	RS	–	–	–	
		Olaparib	[redacted]	[redacted]	[redacted]	-£3,782
PFS estimates	BICR-assessed PFS	RS	–	–	–	–
		Olaparib	[redacted]	[redacted]	[redacted]	-£1,469
Placebo arm OS estimates	Placebo arm from Study 19	RS	–	–	–	–
		Olaparib	[redacted]	[redacted]	[redacted]	£8,727
Olaparib dosing	Original submission dosage	RS	–	–	–	–
		Olaparib	[redacted]	[redacted]	[redacted]	£177

Abbreviations: BICR, blinded independent central review; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; RS, routine surveillance; TTD, time to treatment discontinuation

A.12 Key issues and conclusions based on the data collected during the CDF review period

The SOLO2 trial provided 74-month follow-up data, which confirmed the long-term survival benefit of olaparib,[4] robustly addressing the key uncertainties outlined at the time of the FAD[1] and validating that use of olaparib for maintenance treatment is cost effective in patients with ovarian cancer with a *BRCAm* who have had two courses of platinum-based chemotherapy.

The key uncertainty noted in the Terms of Engagement[6] was addressed by collecting long-term OS data while olaparib was available in the CDF, with an additional ~40 months of follow-up data and an overall maturity of 61% provided at final DCO (3 February 2020). The final DCO analysis showed that olaparib provided a clinically meaningful median OS benefit of [redacted] months compared with placebo in the second-line maintenance setting.[4] When these data were adjusted for subsequent PARP inhibitor use, the OS data showed a clear benefit of [redacted] months in favour of olaparib versus placebo.[5] With PARP inhibitor use now commonplace in first-line maintenance setting,[2,25] and their use in the relapsed setting reserved for PARP inhibitor-naïve patients,[3] adjusting for subsequent PARP inhibitor use was warranted to reflect current UK clinical practice.

Due to the paucity of data for *BRCAm* patients in the second line setting, the OS estimate derived from the treatment switching analysis is difficult to externally validate against real-world outcomes. However, one real-world study based on a retrospective chart review published by Lord et al. in 2020[26] was identified, which included both *BRCAm* and non-*BRCAm* patients who had completed two courses of chemotherapy. The OS outcomes from this study suggests UK outcomes are potentially worse than demonstrated in the adjusted routine surveillance data from the SOLO2 study. Within the context of UK real-world outcomes, the adjusted OS for routine surveillance from SOLO2 therefore represents a conservative estimate of survival in the second-line relapsed setting.

As the PFS data at the time of the primary analysis already had an overall maturity of 63.4%, in line with the statistical plan (Document B, Section B.2.6, page 64), no additional PFS data collection was required.[7] However, in line with the Committee's request that PFS estimates using radiological disease progression and TTD data from the SOLO2 trial be presented, these have been implemented into the updated economic model. Of the second-line patients randomised to the olaparib and placebo arms at the start of the study, [redacted] and [redacted]

remained on treatment upon primary data analysis, respectively, resulting in a median time to event benefit of [redacted] months versus placebo (median TTD = [redacted] and [redacted] months for olaparib and placebo, respectively). Treatment with olaparib resulted in a median PFS (by investigator assessment) benefit of [redacted] months versus placebo.[21] Sensitivity analysis of PFS using the BICR data was consistent with the investigator assessment with respect to the benefit seen for olaparib versus placebo ([redacted] and [redacted] months, respectively).

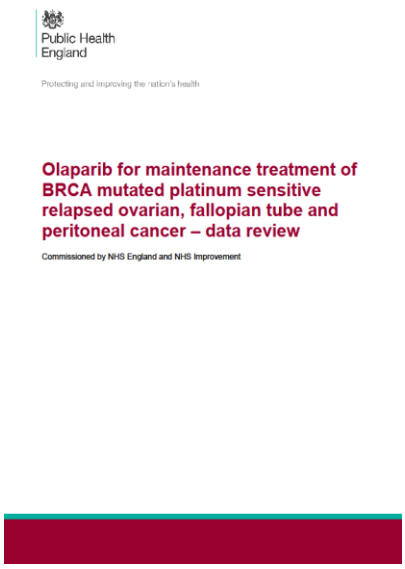
The new company base-case cost-effectiveness results were calculated by incorporating the final OS outcomes from the SOLO2 study, plus any associated changes highlighted by the Committee based on the appropriate ERG model at CDF entry. Over a 50-year time horizon, the incremental cost per QALY gained for olaparib versus routine surveillance was [redacted] (see Appendix **Error! Reference source not found.**).

Using olaparib in the second-line relapsed treatment setting would be a clinically important option in the treatment of ovarian cancer, due to the continued unmet need in the small minority of patients. Early use of PARP inhibitors has been shown to achieve the greatest benefits in this relapse setting.[4,27-29] Furthermore, the updated data clearly demonstrate olaparib is a cost-effective treatment option for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer patients with a *BRCAm* who had two courses of platinum-based chemotherapy.

A.13 Appendix

A.13.1 *Olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer – data review*

[Double click on link below to open the embedded PDF of the SACT dataset]


Public Health England

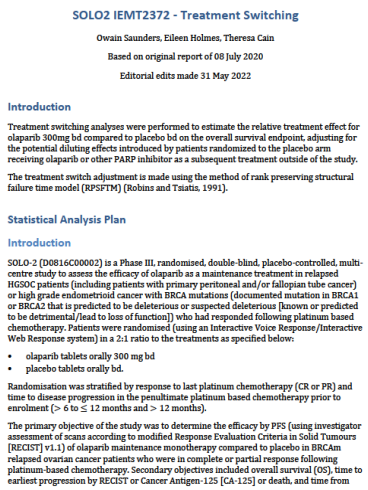
Protecting and improving the nation's health

Olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer – data review

Commissioned by NHS England and NHS Improvement

A.13.2 *Treatment switching*

[Double click on link below to open the embedded PDF of report on treatment switching for SOLO2]


SOLO2 IEMT2372 - Treatment Switching

Owain Saunders, Eileen Holmes, Theresa Cain

Based on original report of 08 July 2020

Editorial edits made 31 May 2022

Introduction

Treatment switching analyses were performed to estimate the relative treatment effect for olaparib 300mg bd compared to placebo bd on the overall survival endpoint, adjusting for the potential diluting effects introduced by patients randomized to the placebo arm receiving olaparib or other PARP inhibitor as a subsequent treatment outside of the study.

The treatment switch adjustment is made using the method of rank preserving structural failure time model (RPSFTM) (Robins and Tsiatis, 1991).

Statistical Analysis Plan

Introduction

SOLO-2 (D0816C00002) is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib as a maintenance treatment in relapsed HGSOC patients (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer with BRCA mutations (documented mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious [known or predicted to be detrimental/lead to loss of function]) who had responded following platinum based chemotherapy. Patients were randomised (using an Interactive Voice Response/Interactive Web Response system) in a 2:1 ratio to the treatments as specified below:

- olaparib tablets orally 300 mg bd
- placebo tablets orally bd.

Randomisation was stratified by response to last platinum chemotherapy (CR or PR) and time to disease progression in the penultimate platinum based chemotherapy prior to enrolment (> 6 to ≤ 12 months and > 12 months).

The primary objective of the study was to determine the efficacy by PFS (using investigator assessment of scans according to modified Response Evaluation Criteria in Solid Tumours [RECIST] v1.1) of olaparib maintenance monotherapy compared to placebo in BRCAm relapsed ovarian cancer patients who were in complete or partial response following platinum-based chemotherapy. Secondary objectives included overall survival (OS), time to earliest progression by RECIST or Cancer Antigen-125 [CA-125] or death, and time from

References

1. National Institute for Health and Care Excellence. *Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer - Final Appraisal Document*. 2019 Available from: https://www.nice.org.uk/guidance/ta620/documents/final-appraisal-determination-document-3.
2. National Institute for Health and Care Excellence. *Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer*. 2021 Available from: https://www.nice.org.uk/guidance/ta693/resources/olaparib-plus-bevacizumab-for-maintenance-treatment-of-advanced-ovarian-fallopian-tube-or-primary-peritoneal-cancer-pdf-82609438840261.
3. National Institute for Health and Care Excellence. *Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy - final appraisal document*. 2019 Available from: https://www.nice.org.uk/guidance/ta598/documents/final-appraisal-determination-document.
4. Poveda, A. et al., *Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial*. The Lancet Oncology, 2021. **22**(5): p.620-631.
5. AstraZeneca. *Data on File*. 2022.
6. National Institute for Health and Care Excellence. *Terms of engagement for CDF review (TA620)*. 2020.
7. National Institute for Health and Care Excellence. *Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy ID1296 - single technology appraisal*. 2018 Available from: https://www.nice.org.uk/guidance/ta620/documents/committee-papers.
8. European Medicines Agency. *Lynparza (tablet formulation): summary of product characteristics*. 2018 Available from: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf.
9. European Medicines Agency. *Zejula: summary of product characteristics*. 2017 Available from: https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf.
10. National Institute for Health and Care Excellence. *Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer*. 2022 [cited 2022 June]; Available from: https://www.nice.org.uk/guidance/ta784.
11. Valabrega, G. et al., *Differences in PARP inhibitors for the treatment of ovarian cancer: mechanisms of action, pharmacology, safety, and efficacy*. International Journal of Molecular Sciences, 2021. **22**(8): p.4203.
12. Mirza, M.R. et al., *Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer*. New England Journal of Medicine, 2016. **375**(22): p.2154-2164.
13. González-Martín, A. et al., *Niraparib in patients with newly diagnosed advanced ovarian cancer*. New England Journal of Medicine, 2019. **381**(25): p.2391-2402.
14. Arend, R.C. et al., *Utilization of poly (ADP-ribose) polymerase inhibitors in ovarian cancer: a retrospective cohort study of US healthcare claims data*. Advances in therapy, 2022. **39**(1): p.328-345.

15. Sackeyfio, A. et al., *Comparative efficacy and safety of olaparib 400 mg capsules BID and niraparib 300 mg tablets QD as maintenance treatment after response to chemotherapy in patients with platinum-sensitive relapsed non-germline BRCA-mutated ovarian cancer (PSROC)*. Value in Health, 2017. **20**(9): p.A412.
16. O'Malley, D.M. et al., *Real-world use, tolerability, and dose modifications of PARP inhibitors in ovarian cancer*. Poster presented at the American Society of Clinical Oncology (ASCO) 2022 Annual Meeting, held on June 3–7, 2022; Chicago, IL, USA.
17. National Institute for Health and Care Excellence. *Managed access agreement. Olaparib tablets for maintenance treatment of BRCAmutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer, after response to platinum-based chemotherapy [TA620]*. 2020 Available from: https://www.nice.org.uk/guidance/ta620/resources/managed-access-agreement-pdf-7025932189.
18. Tew, W.P. et al., *PARP inhibitors in the management of ovarian cancer: ASCO Guideline*. Journal of Clinical Oncology, 2020. **38**(30): p.3468-3493.
19. Morgan, R.D. et al., *PARP inhibitors in platinum-sensitive high-grade serous ovarian cancer*. Cancer Chemotherapy and Pharmacology, 2018. **81**(4): p.647-658.
20. Public Health England. *Olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer – data review*. 2020.
21. AstraZeneca. *A Phase III randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy - Clinical Study Report DCO1.* 2017.
22. Pujade-Lauraine, E. et al., *Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial*. The Lancet Oncology, 2017. **18**(9): p.1274-1284.
23. National Institute for Health and Care Excellence. *NICE DSU technical support document 16: adjusting survival time estimates in the presence of treatment switching*. 2014 Available from: https://eclass.uoa.gr/modules/document/file.php/MED1174/Lectures/Unit%207%20%28Missing%20data%20and%20non-compliance%29/TSD16_Treatment_Switching.pdf.
24. Robins, J.M. et al., *Correcting for non-compliance in randomized trials using rank preserving structural failure time models*. Communications in Statistics-Theory and Methods, 1991. **20**(8): p.2609-2631.
25. National Institute for Health and Care Excellence. *Olaparib for maintenance treatment of BRCA mutation positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy - Technology appraisal guidance*. 2019 Available from: https://www.nice.org.uk/guidance/ta598/resources/olaparib-for-maintenance-treatment-of-brca-mutationpositive-advanced-ovarian-fallopian-tube-or-peritoneal-cancer-after-response-to-firstline-platinumbased-chemotherapy-pdf-82607270456005.
26. Lord, R. et al., *Real world outcomes in platinum sensitive relapsed ovarian, fallopian tube, or peritoneal cancer treated in routine clinical practice in the United Kingdom prior to poly-ADP ribose polymerase inhibitors*. International Journal of Gynecologic Cancer, 2020. **30**(7).
27. Banerjee, S. et al., *Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a*

randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology, 2021. **22**(12): p.1721-1731.
28. Friedlander, M. et al., *Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial*. The Lancet Oncology, 2021. **22**(5): p.632-642.
29. Moore, K. et al., *Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer*. The New England Journal of Medicine, 2018. **379**(26): p.2495-2505.

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)

Clarification questions

July 2022

File name	Version	Contains confidential information	Date
ID3788 Olaparib CDF review clarification questions v1.0 [ACIC]	v1.0	Yes	July 18 2022

Section A: Clarification on effectiveness data

SOLO2

A1. Priority question: Please provide the baseline characteristics for the second line (2L) subgroup from SOLO2 (SOLO2 population who had a confirmed *BRCA*m and had previously received two lines of platinum-based chemotherapy [N=172]) which are informing the clinical data presented in the company submission.

Baseline characteristics for the second line (2L) subgroup from the SOLO2 study who had a confirmed *BRCA*m and had previously received two lines of platinum-based chemotherapy [N=172]) are outlined in Table 1 below.

Table 1: Baseline characteristics of SOLO2 population - 2L BRCAm subgroup

	Olaparib (N=110)	**Placebo (N=62)**
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
ECOG performance status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Primary tumour location, n (%)		
Ovary	[redacted]	[redacted]
Fallopian tubes or primary peritoneal	[redacted]	[redacted]
Histology type, n (%)		
Serous	[redacted]	[redacted]
Endometroid	[redacted]	[redacted]
Mixed, Epithelial	[redacted]	[redacted]
Other	[redacted]	[redacted]
Patients with >2 cm target lesions at baseline, n (%)	[redacted]	[redacted]
Response to previous platinum therapy, n (%)		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Platinum-free interval, n (%)		
>6 - 12 months	[redacted]	[redacted]
>12 months	[redacted]	[redacted]
Prior use of bevacizumab, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

A2. Priority question: Please provide the following olaparib dose information for the 2L subgroup of SOLO2 in the final data cut-off (DCO) presented in the company submission:

a) mean number of doses of olaparib (and standard deviation);
b) mean dose of olaparib received (and standard deviation);
c) median number of doses of olaparib received and interquartile range;
d) median dose of olaparib received and interquartile range,

Regarding Questions A2a and A2c, it is not possible to derive the mean or median *absolute number* of doses of olaparib. Olaparib is available in 100mg or 150mg tablets, for oral administration with a recommended dosage of 300mg per day. This equates to two 150 mg tablets - taken twice daily, resulting in the maximum number of four tablets per day. The 100mg tablets are available for the purposes of dose reductions.

In response to Question A2b and A2d, the mean and median daily dose recorded in the SOLO2 study based on the final data cut-off is provided in Table 2.

Table 2: Exposure by daily dose of SOLO2 population - 2L BRCAm subgroup (final DCO)

	Olaparib (N = 110)	**Placebo (N = 62)**
Daily dose in mg Mean (SD) Median (range)	[redacted]	[redacted]

A3. Priority question: Please provide the following detail on subsequent therapy for patients in the 2L subgroup of SOLO2:

a) the mean (with SD) number of lines of subsequent treatment received by treatment arm;

Table 3: Mean number of lines of subsequent regimens in SOLO2 population - 2L BRCAm subgroup (final DCO)

	Olaparib (N = 110)	**Placebo (N = 62)**
Mean number of lines of subsequent regimen **(SD)**	[redacted]	[redacted]

b) a breakdown of the types of subsequent treatment received in each treatment arm and the number of patients who received each treatment;

Table 4: Subsequent treatment received in SOLO2 population - 2L BRCAm subgroup (final DCO)

Subsequent regimen	Number of patients (%)		
	Olaparib (N = 110)	Placebo (N = 62)	Total (N = 172)
[redacted]			

c) the mean (and SD) duration of treatment (months) for each subsequent treatment in each treatment arm.

Table 5: Mean (SD) duration of subsequent treatment

Subsequent regimen Mean days (SD)	Olaparib (N = 110)	Placebo (N = 62)

[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]
[redacted]			[redacted]		[redacted]

A4. Priority question: Please provide the mean and standard deviation, and hazard ratio (HR), 95% confidence interval (95% CI) and p value [2-sided] for the 2L SOLO2 subgroup for the final data cut-off for the following outcomes:

a) investigator-assessed progression-free survival;

The primary study endpoint, PFS, the primary study endpoint, was evaluated and met at the primary analysis of the SOLO2 trial. Patients in both treatment arms had tumour assessments according to RECIST at baseline and every 12 weeks (+1 week) up to 72 weeks, and then every 24 weeks (+1 week) relative to the date of randomisation until objective radiological disease progression according to RECIST. Unlike overall survival, further analyses of PFS in subsequent data cut-offs were not planned given that the study had met its endpoint at the primary analysis. As pre-specified in the SOLO2 clinical study protocol (**see Appendix 2**), following disease progression, PFS assessments based on the RECIST criteria were not carried out for progression events determined at the final data cut-off. Instead, assessments of PFS were performed as per local clinical practice, leading to variation in the approach and timing of assessing disease progression. This represents a substantial limitation in the interpretation of PFS beyond the primary analysis, particularly given the SOLO2 trial was an international, multicentre study conducted across 123 sites in 16 countries. [redacted]

b) blinded independent central review assessed progression-free survival;

As outlined in Question A4, PFS was met at the primary analysis. Following this, central review of scans were no longer conducted as outlined in the SOLO2 study protocol (**see Appendix 2**) therefore it is not possible to produce point estimates for PFS based on BICR assessment at the final DCO.

c) overall survival; and

The hazard ratio for OS at the final DCO [redacted] a summary of OS at the final DCO based on SOLO2 is also presented in the company submission in Table 6 (Section A.6.1). Table 6 below provides mean OS, as requested.

Table 6: Restricted mean survival time for unadjusted OS (final DCO)

	Olaparib (N = 110)	Placebo (N = 62)
Restricted mean survival time (SE*)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value	[redacted]	

**Please note the standard error has been provided in lieu of the SD as requested by the EAG*

d) time to treatment discontinuation.

The hazard ratio for TTD at the final DCO is [redacted]; Table 7 below provides mean OS for TDT, as requested.

Table 7: Restricted mean survival time for TTD (final DCO)

	Olaparib (N = 110)	Placebo (N = 62)
Restricted mean survival time (SE*)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value	[redacted]	

**Please note the standard error has been provided in lieu of the SD as requested by the EAG*

Adjusted overall-survival analysis

A5. Priority question: Please provide the hazard ratio (HR), 95% confidence interval (95% CI) and p value [2-sided] for the adjusted overall survival analysis presented in Table 7 of the company submission for the 2L SOLO2 subgroup.

Table 8: Hazard ratio for adjusted OS – 2L BRCAm subgroup

	Olaparib (N = 110)	Placebo (N = 62)
Hazard ratio (95% CI)*	[redacted]	
p value	[redacted]	

**Following NICE DSU guidance on treatment switching, the 95% confidence intervals around the (log) hazard ratio estimate for the RPSFT corrected data were calculated by retaining the p-value from the "unadjusted" 2L analysis.*

A6. Priority question: Please conduct an exploratory analysis of OS with adjustment for treatment switching in both the placebo arm and the olaparib arm (to account for the [redacted] of patients who had subsequent PARPis) of

the 2L subgroup of SOLO2. Please provide the resulting mean and median OS with 95% CI for each treatment arm and hazard ratios with 95% CI and p value.

As discussed with NICE and the EAG during the clarification call, conducting a robust treatment switching adjustment for subsequent PARP inhibitor use in the olaparib arm based on the RPFST model is challenging due to limitations in deriving the appropriate acceleration factor (AF). This is primarily driven by the lack of validity and justification for the common treatment effect assumption, given the greater relative efficacy of PARP inhibitors in a PARP-naïve setting as compared to rechallenge. This is demonstrated in the randomised OReO study, where maintenance olaparib was investigated in patients with prior exposure to PARP inhibitors following 2 or more lines of chemotherapy. In the subgroup of patients with a BRCA1/2 mutation, rechallenge with a PARP inhibitor resulted in a 43% reduction in the risk of progression (HR=0.57 [95% CI, 0.37-0.87]), p= 0.022);[1] by contrast, in the SOLO2 study olaparib resulted in a 70% reduction in the risk of progression (HR=0·30 [95% CI, 0·22–0·41], p<0·0001) in patients who were PARP inhibitor naïve.[2] Thus, the treatment effect with rechallenge of a PARP inhibitor is likely lower than for de novo treatment (either at randomisation to olaparib, or upon switching to olaparib after progression on placebo). For this reason, it is highly unlikely that the common treatment effect assumption would be supported in the requested analysis for the [redacted] of patients in the olaparib arm who had subsequent PARP inhibitors.

Based on the EAG's suggestion, the company also considered a propensity score matching to explore the impact of PARP inhibitor retreatment. The propensity score weighting approach was unsuitable as it requires the availability of data for all patient characteristics that are prognostic of outcome, and the probability of re-treatment (otherwise known as the **"assumption of no unmeasured confounding"**). To provide reliable results, these data should be collected close to the point at which retreatment is administered; retreatment with a PARP inhibitor in the olaparib arm occurred at various lines of treatment, and throughout the post-discontinuation phase of the study. Because demographic and disease characteristic data were not routinely collected after discontinuation of treatment, a considerable time lag would exist between much of the available characteristic data (e.g., at baseline) and the time of retreatment, such that determining the covariates associated with the

probability of PARP inhibitor retreatment in the olaparib arm would be highly challenging, if not impossible. Furthermore, very few patients received a subsequent PARP inhibitor in the olaparib arm [redacted]. This dataset is likely insufficient to reliably determine the predictors of retreatment as part of any propensity analysis. To summarise, the assumption of no unmeasured confounders would therefore be highly questionable with the limited available data, meaning that the results of any propensity analysis would be at a substantial risk of bias.

Nevertheless, to demonstrate the impact of PARP inhibitor retreatment, the company explored two alternative exploratory analyses using the SOLO2 second-line data with the objective of determining whether the OS in the olaparib arm is likely confounded due to the receipt of subsequent PARP inhibitors in [redacted] of patients in the olaparib arm:

1. **Exploratory analysis 1:** Adjustment of the OS in those who received subsequent PARP inhibitor in the olaparib arm, using the equivalent AF from the RPSFT model, that was calculated and applied to the OS for *placebo-treated patients* who switched to PARP inhibitors following disease progression as per the original submission.

2. **Exploratory analysis 2**: Censoring of patients in the olaparib arm who received subsequent PARP inhibitor, at initiation of subsequent PARP inhibitor.

Exploratory analysis 1: Adjustment of OS in the olaparib arm based on the AF for treatment switching in the placebo arm

To explore the impact of PARP inhibitor-rechallenge, adjustment of the OS in the olaparib arm from SOLO2, second-line subgroup, was carried out using the equivalent AF applied to the placebo-treated patients who switched to PARP inhibitors as per the original NICE submission. The methodology followed to derive the AF applied to the placebo-treated patients is outlined in detail in Section A.6.1.2.1 in the company submission.

The company would like to highlight that this exploratory analysis represents an extremely conservative scenario because it implicitly assumes that the treatment

effect - and consequently the AF - derived by patients with prior exposure to PARP inhibitors is equivalent to that in patients who are PARP inhibitor naïve (i.e., at randomisation in SOLO2). As highlighted by clinical experts and in the OReO and SOLO2 studies, a greater and clinically meaningful benefit for olaparib is most likely to be observed when patients are PARP inhibitor naïve.

After adjustment of the [redacted] of patients who had subsequent PARP inhibitor in the olaparib arm based on this methodology, no meaningful change in the Kaplan-Meier estimates was observed when compared to the unadjusted olaparib arm (See Figure 1 below). This is reflective of the diminishing effectiveness of PARP inhibitor rechallenge and the relatively small proportion of patients receiving subsequent PARP inhibitor following olaparib in SOLO2. Likewise, no difference was observed in the HRs of [redacted] in the analysis where both olaparib and placebo arms from SOLO2 are adjusted, versus [redacted] where only the placebo OS arm is adjusted as per the company base case.

This demonstrates that even where an extreme and conservative approach is undertaken, retreatment with a PARP inhibitor following disease progression on olaparib in SOLO2 has no significant impact on the OS.

Figure 1: Kaplan-Meier plot comparing unadjusted olaparib arm vs. the adjusted olaparib arm based on the assumption of equivalence with the AF for the placebo-treatment switching analysis (2L population)

Exploratory analysis 2: Censoring of patients in the olaparib arm who received subsequent PARP inhibitor

In this exploratory analysis referred to as "the censored approach", the [redacted] of patients in the olaparib arm who switched to receive a PARP inhibitor following disease progression are censored at the point at which, they initiate subsequent treatment with a PARP inhibitor. This censored approach was adopted to explore the impact on OS in the SOLO2 second-line subgroup in a scenario where survival data after PARP inhibitor rechallenge is removed from the analysis set. Although this approach is likely prone to censoring-related selection bias, it is presented as an alternative to **"Exploratory analysis 1"** since it does not rely on the common treatment effect assumption.

The Kaplan-Meier plots depicted in Figure 2 highlight there are no significant differences in the data based on the censored approach when compared to the olaparib unadjusted arm inclusive of patients who switched to receive a PARP inhibitor following disease progression. This is reflective of the relatively small proportion of patients in the olaparib arm who crossed over to subsequent PARP inhibitor thus resulting in a negligible impact when censoring is applied. Consistent with the RPSFT model results in the company submission, and the exploratory olaparib-adjusted analysis above, the HR vs. the adjusted placebo arm based on the censored approach is [redacted].

Figure 2: Kaplan-Meier plot comparing unadjusted olaparib arm vs. the censored olaparib group who receieved subsequent PARP inhibitor (2L population)

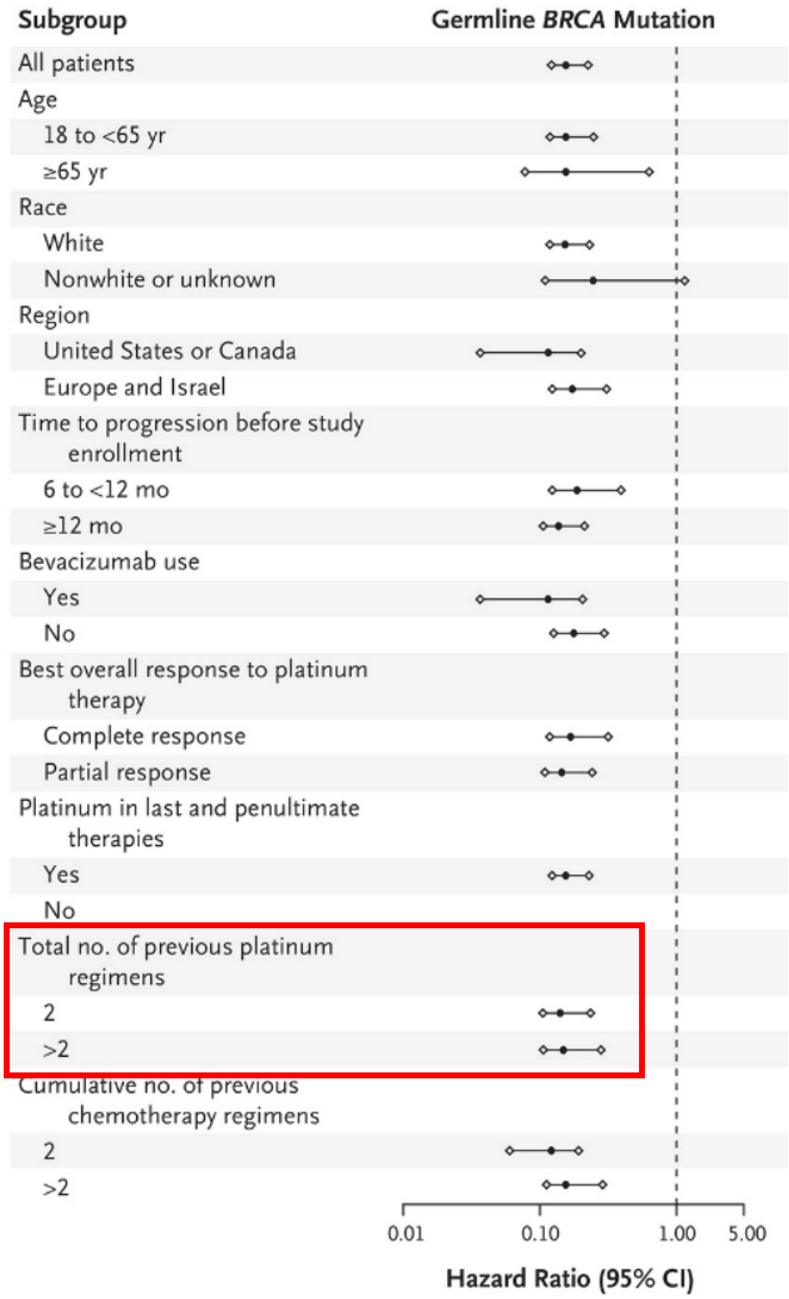
In summary, both exploratory analyses explored by the company demonstrate that even where conservative approaches are undertaken, retreatment with a PARP inhibitor in SOLO2 is unlikely to have any significant impact on the OS estimates of olaparib and is therefore unlikely to produce any meaningful conclusions to the cost-effectiveness of olaparib in the second-line setting. The company therefore maintains its base-case analysis where only the OS confounding pertaining to the [redacted] of placebo-treated patients who received subsequent PARP inhibitor in the SOLO2 study were adjusted.

A7. Priority question: Please comment on the likelihood that the common treatment effect assumption of the rank preserving structural failure time (RPSFT) model is met, and to what extent any violation of this assumption would affect the accuracy of the adjusted survival time estimates and associated hazard ratios.

The common treatment effect assumption between those receiving PARP inhibitor at randomisation (i.e., at 2nd line) and after progression in the placebo arm (i.e., at 3rd or later lines) was considered likely to hold based on the results of the subgroup analysis of PFS by number of chemotherapy lines prior to randomisation in the

SOLO2 and NOVA studies.[3, 4] In the SOLO2 subgroup analysis, patients that received olaparib after 2 lines of therapy of prior chemotherapy experienced a similar benefit versus placebo to those that had received 3 or more lines of chemotherapy ([redacted]), respectively).[3] Similarly, in the pivotal trial for niraparib, NOVA, patients with BRCAm treated with niraparib experienced consistent levels of benefit versus placebo (see **Figure 3**) in those that had received 2 lines of chemotherapy versus those that had greater than 2-prior lines. Together, these data suggest that PARP inhibitors provide similar levels of incremental benefit whether given at 2nd or later lines. This supports the use of the common treatment effect assumption across treatment lines in the RPSFT model analysis.

Figure 3: Subgroup analyses of PFS in BRCAm patients from the NOVA trial (niraparib vs. placebo)



Source: Mirza et al. 2016[4]

Nevertheless, to assess the impact of the "common treatment effect" assumption on results, sensitivity analysis were performed that assumed a proportional reduction in the efficacy of PARP inhibitor treatment in the placebo arm. The treatment effect (psi) of patients in the placebo arm who switched to olaparib was assumed equal to either 75% or 50% of the treatment effect observed in the olaparib arm. These

scenarios reflect extreme alternatives to the common treatment effect assumption (i.e., that 100% of the treatment effect applies). In this analysis, we report the point estimates for psi and the hazard ratio for olaparib versus placebo in the second line population. As in the base case RPSFT model, the p-value from the unadjusted analysis is maintained across scenarios.

The results of the sensitivity analysis show that the hazard ratio estimate for the adjusted second line population is robust to deviations from the common treatment effect assumption. Under the extreme scenario of a 50% reduction in the efficacy of PARP inhibitor after progression in the placebo arm, the with recensoring hazard ratio for OS comparing olaparib with placebo was [redacted] the base case that assumed a common treatment effect. A scenario assuming a 75% reduction in the efficacy of PARP inhibitor after progression in the placebo arm, results in no difference in the base case hazard ratio.

In summary, it is reasonable to assume the common treatment effect assumption holds based on evidence of a consistent treatment effect for PARP inhibitors versus placebo by the number of prior chemotherapies at baseline in SOLO2 and NOVA.[3, 4] The results of the sensitivity analysis assuming a lower effect for PARP inhibitors in the placebo arm shows that the analysis is robust to deviations from the common treatment effect assumption. These findings support the use of the RPSFT model for the treatment switching analysis.

A8. Please provide the estimates and 95% CIs for psi and the acceleration factor for the RPSFT model used for the 2L subgroup from SOLO2 used in the company submission.

Both psi and the acceleration factor reflect the treatment effect in the ITT population – in doing so, we assume a common treatment effect between 2L and 3L+ subgroups, as well as across arms (olaparib and placebo). A subset of this based on the 2L population was derived to give absolute estimates for the 2L only population.

Table 9: Psi and acceleration factor from the RPSFTM (adjusted placebo arm)

Proportional reduction in treatment effect applied to PARP use in the placebo arm	**With recensoring**

Psi	[redacted]
Acceleration factor	[redacted]

A9. Please provide the resulting median OS with 95% CI for each treatment arm and hazard ratio with 95% CI and p value for overall survival adjusted for subsequent PARP inhibitor therapy (using the RPSFT model) without re-censoring for:

a) the analysis presented in the company submission for the 2L SOLO2 subgroup (placebo arm adjusted); and

Table 10: Median adjusted OS placebo arm without recensoring

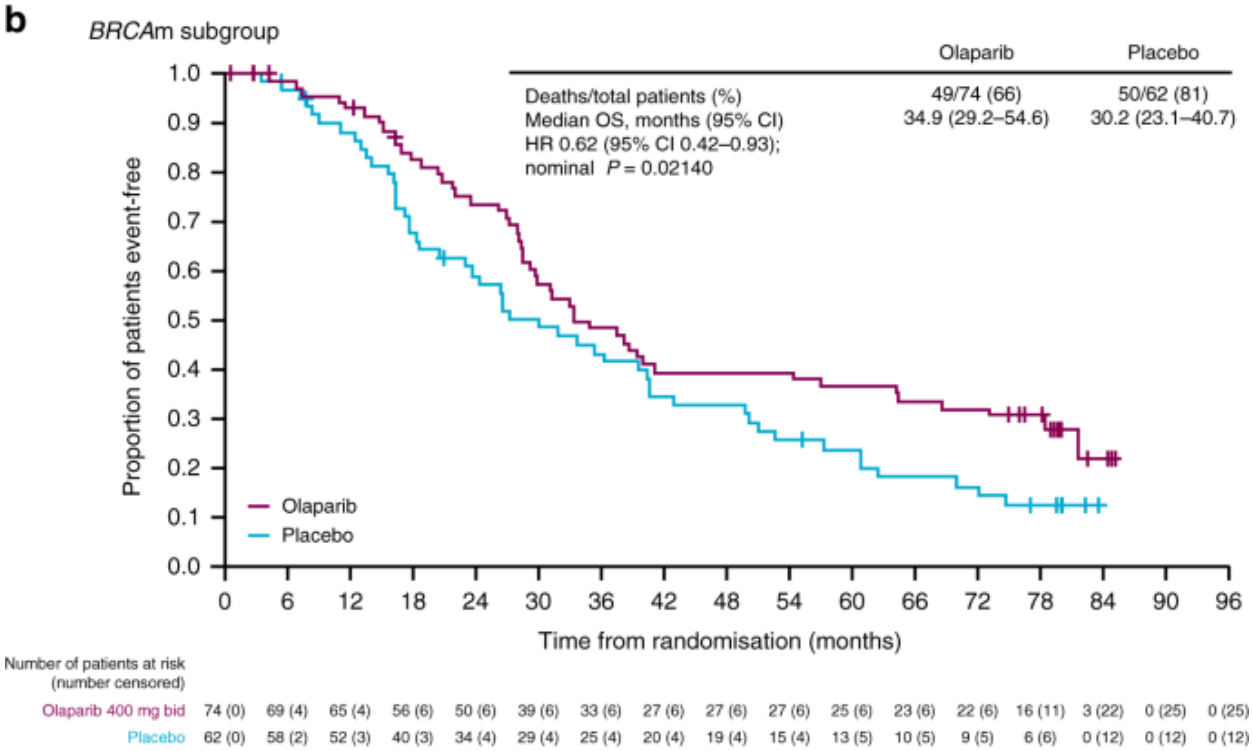
	Olaparib (N = 110)	**Placebo (N = 62)**
Median time to event **(95% CI)**	[redacted]	[redacted]
Hazard ratio	[redacted]	

The Kaplan-Meier plots for OS in the second line population according to the RPSFT treatment-switch adjustments, with and without recensoring are shown below in **Figure 4** and **Figure 5**. As expected, recensoring leads to a loss of follow-up in the placebo arm versus the analysis without recensoring. However, in the period of additional follow-up in the analysis without re-censoring (~month 42 onwards), the Kaplan-Meier plot shows a distinct flattening of the survival curve for the placebo arm. This implies a rapidly reducing hazard rate for death. This trend is inconsistent with data from Study 19 which provides long-term follow-up for placebo with low rates of crossover (**Figure 6**). The analysis without recensoring is likely impacted by informative censoring given that treatment switching decisions (i.e., use of PARP maintenance) are made based on response to subsequent chemotherapy and/or platinum sensitivity; both of which are prognostic for outcomes in platinum-sensitive relapsed ovarian cancer. Therefore, the analysis with recensoring has been adopted as the appropriate base case to minimise informative censoring bias.

Figure 4: Kaplan-Meier plot for adjusted OS placebo arm with recensoring

Figure 5: Kaplan-Meier for adjusted OS placebo arm without recensoring

Figure 6: Kaplan-Meier for OS, Olaparib vs. placebo in Study 19 trial (BRCAm subgroup)



b) the analysis requested in question A6 (olaparib and placebo arms adjusted).

Please see Table 10 and Figure 5 for the analysis in the placebo arm without recensoring. For the olaparib adjusted arm - please see the company response to Question 6.

A10. Please provide the resulting mean OS with 95% CI for each treatment arm and hazard ratio with 95% CI and p value for overall survival adjusted for subsequent PARP inhibitor therapy (using the RPSFT model) for:

a) the analysis presented in the company submission for the 2L SOLO2 subgroup (placebo arm adjusted) with re-censoring.

Table 11: Restricted mean adjusted OS placebo arm with recensoring

	Olaparib (N = 110)	**Placebo (N = 62)**
Restricted mean survival time (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value	[redacted]	

b) the analysis presented in the company submission for the 2L SOLO2 subgroup (placebo arm adjusted) without re-censoring.

Table 12: Restricted mean adjusted OS placebo arm without recensoring

	Olaparib (N = 110)	**Placebo (N = 62)**
Restricted mean (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value	[redacted]	

c) the analysis requested in question A6 (olaparib and placebo arms adjusted) with re-censoring; and

d) the analysis requested in question A6 (olaparib and placebo arms adjusted) without re-censoring.

Questions A10c and A10d are contingent on Question A6 which the company is unable to provide - please see the company response to Question 6.

Adverse events

A11. Priority question: Please provide details of the grade 3 or higher treatment emergent adverse events (AEs) that were reported by at least 3% of patients and the number of each event for each of the olaparib and placebo arms of SOLO2 at the final data cut-off for:

a) the full SOLO2 trial population; and

Table 13: Treatment emergent AEs of CTCAE ≥Grade 3 in at least 3% of patients (Safety analysis set)

	Olaparib (N = 195)	**Placebo (N = 99)**
Nausea	6 (3%)	0
Fatigue and asthenia*	11 (6%)	2 (2%)
Anaemia†	41 (21%)	2 (2%)
Vomiting	5 (3%)	1 (1%)
Abdominal pain	6 (3%)	3 (3%)
Constipation	0	3 (3%)
Leukopenia	7 (4%)	0
Neutropenia	14 (7%)	4 (4%)

Adverse-event data were collected up to the final data cut-off (Feb 3, 2020). The treatment-emergent adverse events were graded using CTCAE version 4.0. CTCAE=Common Terminology Criteria for Adverse Events.

b) the 2L subgroup from SOLO2.

Table 14: Treatment emergent AEs of CTCAE ≥Grade 3 in at least 3% of patients (2L BRCAm subgroup)

	Olaparib (N = 110)	Placebo (N = 62)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Adverse-event data were collected up to the final data cut-off (Feb 3, 2020). The treatment-emergent adverse events were graded using CTCAE version 4.0. CTCAE=Common Terminology Criteria for Adverse Events.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model. If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario. Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

Discrepancies between CDF and TA620 company base case

B1. Priority question: The EAG has identified some elements of the company's base case that were included in TA620 but have not been included in the CDF base. Please update the CDF base case for the following:

a) Include the costs of AEs in the model, using the same methodology as TA620, where grade 3 or higher AEs that were reported by at least 3% of patients in either treatment arm of SOLO 2 are included.

The model has now been updated to include the AEs consistent with the original submission in the base case analysis. The results of the updated base case are presented in the addendum to this response.

b) Include the cost of subsequent olaparib for routine surveillance patients, using the mean TTD for 3L patients from SOLO 2 (previously reported in TA620 as [redacted] months). Update the mean TTD from SOLO2 as necessary.

The model has now been updated to include the option to include subsequent olaparib costs for routine surveillance patients aligned with the original assumptions in TA620. The results of this scenario analysis are presented in Table 15 below. An alternative scenario based on SOLO2 final DCO has also been provided in which the subsequent treatment duration of olaparib is set to [redacted] months. The results of this scenario analysis are presented in Table 20 below.

However, as previously detailed (Company submission [CS], Section A.6.1.2.2), the base case cost-effectiveness analysis used the RPSFT model adjusted placebo arm from SOLO2 to ensure generalisability of subsequent treatments in UK clinical practice. This analysis was considered the most robust data for decision-making since retreatment with PARP inhibitors is not permitted in UK clinical practice; only a small and diminishing number of patients would be expected to be PARP inhibitor naïve and eligible to receive third line olaparib. By contrast, [redacted] of placebo-treated patients received subsequent PARP inhibitor in the SOLO2 study thereby limiting the generalisability of SOLO2 study to UK clinical practice and underestimating the OS benefit. This assumption was consistently validated by UK clinicians who highlighted that most patients who are eligible for maintenance treatment with a PARP inhibitor will receive this after first-line treatment with chemotherapy.

Furthermore, the decision to utilise the adjusted OS based on the RPSFT model in the base case analysis was also informed by data from AstraZeneca's internal commercial analytics function [redacted]

As a result, we maintain there is a strong justification to support the base case adjusted SOLO2 analysis and that it would be inappropriate and internally inconsistent to include the costs of subsequent olaparib here. Please see the company response to Question B3 where an alternative plausible scenario based on Study 19 is discussed.

Table 15: Results for scenario including costs for [redacted] months of subsequent olaparib treatment following routine surveillance

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER (£/QALY)
				Costs (£)	**LYG**	**QALYs**	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 16: Results for scenario including costs for [redacted] months of subsequent olaparib treatment following routine surveillance

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER (£/QALY)
				Costs (£)	**LYG**	**QALYs**	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Survival analysis

B2. Priority question: Please provide a scenario where adjusted OS data for olaparib (as requested in question A6) is used in the model.

For the reasons previously detailed in response to Question A6, this exploratory analysis has not been conducted, or included in the cost-effectiveness model.

B3. Priority question: As routine surveillance patients who relapse will be eligible for 3L olaparib in the NHS, the EAG considers that it is clinically plausible that OS for both olaparib and routine surveillance patients may potentially converge. As such, please provide a scenario using the 1 knot

spline for OS and inclusion of subsequent olaparib treatment costs for routine surveillance patients as requested in B1 (b).

This scenario has now been included as an option on the "Scenarios" tab of the model and can be selected in Cell B108. The results of this scenario analysis are presented in Table 17, below.

However, as previously indicated in the Company Submission (Section A.6.1.2.2) and in response to Question B1b, it is important to note that only a negligible number of patients in UK clinical practice will be PARP-inhibitor naïve and eligible to receive 3L treatment with olaparib following relapse on routine surveillance. This was confirmed by clinical experts consulted for the submission, and aligns with internal commercial analytics data from AstraZeneca,

[redacted]

The results of the one-knot spline model which do indeed converge predict no meaningful OS difference between patients managed by routine surveillance [redacted] and olaparib [redacted] after 20 years. Assuming an absence of long-term benefit represents an extremely conservative estimate of olaparib benefit in this setting. It is worth highlighting that the convergence in the spline model is observed within the context where the placebo arm from SOLO2 is adjusted to reflect clinical practice in the UK where PARP utilisation in the 3rd-line setting is seldom expected. As such, the results lack interval validity and should be interpreted with caution.

Nevertheless, as part of the company submission, a scenario based on the placebo arm of Study 19 (equivalent to routine surveillance) where post-progression PARP inhibitor utilisation was relatively lower than observed in SOLO2, but non-zero was presented. This approach was recently accepted and formed the basis for decision making in a recent appraisal of niraparib [TA784] in a similar setting.[5] This analysis represents an alternative plausible scenario for assessing long-term OS, within a landscape where subsequent PARP inhibitor is accessed following relapse on routine surveillance in the third line. The landmark analysis from the Study 19 scenario shows that despite a small proportion of patients receiving subsequent PARP inhibitor at 3L in the placebo arm, an OS benefit with olaparib is still observed at 20 years. Approximately [redacted] in the olaparib arm and [redacted] in the placebo arm

remained alive which is notably consistent with the long-term OS expectations provided by ovarian cancer experts (see Section A.7.1 in the company submission).

Similarly, for the reasons detailed in response to Clarification Question B1b, the Company does not consider it to be appropriate to include the costs of subsequent olaparib treatment as requested, given that the adjusted placebo OS data are used in the base case cost-effectiveness analyses.

Table 17: Results for scenario with one-knot spline models for OS data

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER (£/QALY)
				Costs (£)	**LYG**	**QALYs**	
Routine surveillance	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B4. Priority question: in the model, TTD exceeds PFS between months 19 and 53. Please provide a scenario where either TTD is capped to PFS or use an alternative extrapolation of PFS or TTD that ensures TTD does not exceed PFS.

This scenario has now been included as an option on the "Scenarios" tab of the model and can be selected in Cell B110. The results of this scenario analysis are presented in Table 18, below.

Table 18: Results for scenario with TTD is capped to PFS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER (£/QALY)
				Costs (£)	**LYG**	**QALYs**	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Costs

B5. Priority question: Please justify why drug wastage was not included in the company base case as per the ERG's preferred assumptions in TA620. Please provide a scenario where drug wastage is included.

This option is already included in the model and can be selected in Cell B17 of the scenarios sheet. The company base case has now been updated to include drug wastage in the base-case analysis. The results of the updated base case are presented in the addendum to this document.

B6. Priority question: The EAG considers that the unit cost per pack of 3L olaparib in cells I24:J24, tab "Unit costs" includes a confidential discount of [redacted]?

[redacted]

Table 19: Summary of the [redacted]

Treatment	Discount from list	Discounted price 28-day pack
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Footnotes:

[redacted]

B7. Please confirm the formulations for the treatments listed in the 'Unit costs' sheet in the model (e.g., for 100mg etoposide there are 3 potential formulations; capsules, powder for solution or concentrate for solution).

The unit costs for the treatments were derived from the eMIT (2017), as detailed in the original NICE Submission Document B (Table 53, Page 146). Unfortunately, given that the eMIT 2017 spreadsheet is no longer available to access online, it has not been possible to cross-reference the costs in the model to confirm the specific formulations for each treatment.

However, AZ can confirm that these costs are aligned with the unit costs for these treatments that were used in the original submission and agreed on by the Company and the EAG, and this is unlikely to have an impact on the cost-effectiveness results.

Section C: Textual clarification and additional points

C1. **Priority question:** [redacted].

C2. Priority question: Please provide instructions or include an option in the model to replicate the CDF entry base case results in Table 15.

Following clarification questions, the economic model is set to the current company base case, with an ICER of [redacted], by default.

Please note that the base-case ICER at CDF entry presented in Table 15 and Table 19 in the company CDF exit submission are incorrect. The correct ICER at CDF entry is [redacted] as detailed in the terms of engagement and final appraisal document. To replicate the CDF entry base-case results, using the current company base case as a starting point, the following changes are required.

Scenario sheet

- Cell B17 = 1
- Cell B91 = 0
- Cell B106 = 1
- Cell B112 = [redacted]
- Cell B114 = 0
- Cell B116 = 1

Settings sheet

- Cell E12 = TDT
- Cell E19 = Study 19 2L

Drug costs sheet

- Cell E10 = SOLO2

Clinical data sheet

- Cell E29 = Spline 1 knot
- Cell E60 = Spline 1 knot
- Cell X60 = Spline 1 knot
- Cell E91 = Spline 1 knot
- Cell X91 = Spline 1 knot

Note in the original submission the unit cost per pack for olaparib 2L with PAS discount was rounded to [redacted] while in this version of the model, the unit cost per pack is [redacted]. This leads to a slight discrepancy in ICER – to recreate the original ICER precisely, Cell J25 should be overwritten to equal [redacted] exactly.

C3. Please present results of the one-way sensitivity analysis.

The results of the one-way sensitivity analyses, with respect to the Company's updated base case analysis, are presented in Section E.1 below.

Section D: Additional questions from NICE technical team

D1. Priority question: Has the updated commercial agreement discount of [redacted] been submitted to NHS England for approval?

The commercial arrangement of [redacted] has been approved as part of the existing managed access agreement for TA620.

D2. Priority question: Please supply a redacted version of the cost-effectiveness model or supply a version which uses dummy values in place of confidential information.

As agreed with NICE during the clarification call, AstraZeneca will supply a redacted model version following technical engagement.

References

1. Pujade-Lauraine E, Selle F, Scambia G, et al. LBA33 Maintenance olaparib rechallenge in patients (pts) with ovarian carcinoma (OC) previously treated with a PARP inhibitor (PARPi): Phase IIIb OReO/ENGOT Ov-38 trial. Annals of Oncology 2021;32:S1308-S1309.

2. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274-1284.

3. Penson R, Kaminsky-Forrett MC, Ledermann J, et al. Efficacy of olaparib maintenance therapy in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) by lines of prior chemotherapy: Phase III SOLO2 trial (ENGOT Ov-21). Annals of Oncology 2017;28:v331.

4. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. New England Journal of Medicine 2016;375:2154-2164.

5. National Institute for Health and Care Excellence (NICE). Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer [TA784]. Available at https://www.nice.org.uk/guidance/ta784 [accessed 18 July 2022].

Appendix 1: Updated company base case results

E1. Details of changes to the Company base case

In response to Clarification Questions, AstraZeneca have updated their base-case cost-effectiveness analysis, to incorporate the following changes:

- AEs reported by at least 3% of patients in either treatment arm of SOLO-2 have been included, based on the final DCO of SOLO2 (as detailed in Question B1a).
- Drug wastage has been included.
- The dosage of olaparib tablets (3L+) was previously set to 688 mg consistent with the original submission based on the capsule formulation. However, the recommended dosage of olaparib tablets is 600 mg/day which is now updated in the model.

E2. Company base case results (based on [redacted]% PAS for olaparib)

Table 20: Updated base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			ICER (£/QALY)
				Costs (£)	**LYG**	**QALYs**	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 21: Average results based on PSA (10,000 iterations)

Technologies	Total costs (£)	Total QALYs	Incremental		ICER (£/QALY)
			Costs (£)	QALYs	
Routine surveillance	[redacted]	[redacted]			
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 7: Cost-effectiveness plane

Figure 8: Cost-effectiveness acceptability curve

Table 22: Results of deterministic 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]

Abbreviations: ICER, incremental cost-effectiveness ratio; PD, progressed disease; PF, progression free.

Figure 9: Tornado diagram

Only includes parameters which lead to >1% variation around the base case.

Table 23: Results of scenario analyses (based on [redacted] PAS for olaparib)

Outcome	Scenario	Technology	Inc. costs	Inc. QALYs	ICER	Impact on base case (£)
				Company base case ([redacted] *PAS*)	[redacted]	
PFS extrapolation	**Lognormal**	**RS**				–
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
OS extrapolation	**Log logistic**	**RS**	[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
TTD extrapolation	**Generalised gamma**	**RS**	[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	**RS**	[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
PFS estimates	**BICR-assessed PFS**	**RS**	[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
Placebo arm OS estimates	**Placebo arm from Study 19**	**RS**	[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib dosing	**Original submission dosage**	**RS**	[redacted]	[redacted]	[redacted]	[redacted]
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: [a] Drug wastage is incorporated in the Company's revised base case, meaning that the results of this scenario analysis are identical to the base case.
Abbreviations: BICR, blinded independent central review; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; RS, routine surveillance; TTD, time to treatment discontinuation

E3. Updated company base case results with proposed commercial offer ([redacted]% PAS for olaparib)

Table 24: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental			**ICER (£/QALY)**
				Costs (£)	**LYG**	**QALYs**	
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 25: Average results based on PSA (10,000 iterations)

Technologies	Total costs (£)	Total QALYs	Incremental		ICER (£/QALY)
			Costs (£)	QALYs	
Routine surveillance	[redacted]	[redacted]			
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 10: Cost-effectiveness plane

[redacted]

Figure 11: Cost-effectiveness acceptability curve

Table 26: Results of deterministic 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]

Abbreviations: ICER, incremental cost-effectiveness ratio; PD, progressed disease; PF, progression free.

Figure 12: Tornado diagram

Appendix 2: SOLO2 Clinical Study Protocol

[Double click on link below to open the embedded PDF of clinical study protocol for SOLO2]

Statistical Analysis Plan

Drug Substance	Olaparib
Study Code	D0816C00002
ENGOT Study Code	ENGOT-Ov21
Edition Number	3
Date	22 April 2016

A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed *BRCA* Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

Public Health England

Protecting and improving the nation's health

Olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer – data review

Commissioned by NHS England and NHS Improvement

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

Published October 2020
PHE publications
gateway number: GW-1583

PHE supports the UN
Sustainable Development Goals

Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of olaparib tablets for maintenance treatment of Breast Cancer gene (BRCA) mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended commissioning of olaparib through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection from the SOLO-2 trial to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of olaparib in the CDF population during the managed access period. This report presents the results of the use of olaparib in clinical practice, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis of data for the full patient population, with 100% of patients reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 28 November 2019 and 27 February 2020, 22 applications for olaparib were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 15 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

Fifteen (100%) unique patients with CDF applications were reported in the SACT dataset.

Patient characteristics from the SACT dataset show that of patients receiving olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer, most were aged between 40 and 69 years (87%, N=13) and 87% (N=13) of patients had a performance status between 0 and 1 at the start of their regimen with two patients having a missing performance status.

Conclusion

This report analyses SACT real world data for patients treated with olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer in the CDF. This report presents patient characteristics in SACT and clinical characteristics from Blueteq.

Introduction

Ovarian, fallopian tube and peritoneal cancer accounts for 5% of all cancer diagnoses in England amongst women. In 2017, 6,751 women were diagnosed with ovarian, fallopian tube or peritoneal cancer (ICD-10: C48, C56, C57)[2].

Olaparib is recommended for use within the CDF as an option for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults whose disease has responded to platinum-based chemotherapy only if:

- they have a BRCA1 or BRCA2 mutation
- they have had 2 courses of platinum-based chemotherapy and
- the conditions in the managed access agreement for olaparib are followed.

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England NHS Improvement and PHE's ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using SACT data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the CDF during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From the 29th July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical and cost effectiveness. During this period of managed access, ongoing data collection is used to answer the uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE will analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer [TA620].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of olaparib (AstraZeneca) for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer [TA620] and published guidance for this indication in January 2020[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning olaparib through the CDF for a period of seven months, from November 2019 to June 2020.

During the CDF funding period, results from ongoing clinical trials evaluating olaparib in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. The ongoing trial to support the evaluation of olaparib is SOLO-2[7]. Data collected from the SOLO-2 clinical trial would be the primary source of data collection.

Analysis of the SACT dataset would provide information on real-world treatment patterns and outcomes for olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer in England, during the CDF funding period. This would act as a secondary source of information alongside the results of the SOLO-2[7] trial.

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **overall survival data**

Results for the clinical uncertainty mentioned above will come from the SOLO-2 clinical trial. PHE has presented patient characteristics in this report due to the short data collection time.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (AstraZeneca) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of olaparib. It also detailed the eligibility criteria for patient access to olaparib through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for olaparib, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications - identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the EU General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of EU GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS E & I do not have an exemption to the Common Law Duty of Confidentiality, NHS E & I cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

olaparib clinical treatment criteria

- patient has a proven histological diagnosis of predominantly high grade serous or endometrioid ovarian, fallopian tube or primary peritoneal carcinoma.
- patient has had germline and/or somatic (tumour) BRCA testing.
- patient HAS a documented deleterious or suspected deleterious BRCA mutation(s) in the germline or in the tumour or in both. Please specify:
    - in the germline only
    - in the tumour (somatic tissue) only
    - in both germline and somatic tissue.
- patient HAS a documented deleterious or suspected deleterious BRCA 1 or BRCA 2 mutation(s). Please specify:
    - BRCA 1 mutation
    - BRCA 2 mutation
    - both BRCA1 and BRCA 2 mutations.
    - Note: Patients without a deleterious or suspected deleterious BRCA mutation are not eligible to receive olaparib but they are potentially eligible to receive niraparib (form NIR4) or rucaparib (form RUC2).
- patient had disease which was sensitive to initial (first line) platinum-based chemotherapy i.e. the recent FIRST relapse has occurred after a response to initial (first line) platinum-based chemotherapy.
- patient has recently completed a SECOND platinum-based chemotherapy and has received a minimum of 4 cycles of platinum-based treatment.
- patient has responded to the recently completed SECOND platinum-based chemotherapy and has achieved a partial or complete response to treatment according to the definitions given below and there is no evidence of progressive disease on the post-treatment scan or a rising CA125 level. Please specify:
    - achieved a complete response at the end of the 2nd platinum-based chemotherapy i.e. has no measurable or non-measurable disease on the post-chemotherapy scan and the CA125 is normal
    - achieved a partial response at the end of the 2nd platinum-based chemotherapy i.e. has had a ≥30% reduction in measurable or non-measurable disease from the start of to the completion of the 2nd platinum-based chemotherapy or the patient has a complete remission on the post-chemotherapy CT scan but the CA125 has not decreased to within the normal range.
- patient is currently less than 8 weeks from the date of the last infusion of the last cycle of the 2nd platinum-based chemotherapy.
- patient has not previously received any PARP inhibitor unless either niraparib or rucaparib via the CDF has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression or olaparib tablets have been received as part of an early access scheme and the patient meets all the other criteria listed here. Please specify which of the four scenarios applies to this patient:

    - the patient has never previously received a PARP inhibitor
    - the patient has previously received niraparib via the CDF and this has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression
    - the patient has previously received rucaparib via the CDF and this has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression
    - the patient has previously received olaparib tablets via an early access scheme and the patient meets all the other criteria listed here.
- olaparib tablets will be used as monotherapy.
- patient has an ECOG performance status of either 0 or 1.
    - Note: a patient with a performance status of 2 or more is not eligible for olaparib.
- olaparib is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment.
    - Note: this open treatment duration is different to that of maintenance olaparib tablets after FIRST line platinum-based chemotherapy in which treatment duration beyond 2 years is only allowed for certain patients (as outlined in forms OLAP1a and 1b).
- a formal medical review as to whether maintenance treatment with olaparib should continue or not will be scheduled to occur at least by the start of the third cycle of treatment.
- no treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or intercurrent comorbidities to improve).
- olaparib in its tablet formulation is to be otherwise used as set out in its Summary of Product Characteristics.

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

- If two trusts apply for olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

- If two trusts apply for olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

- If two applications are submitted for olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

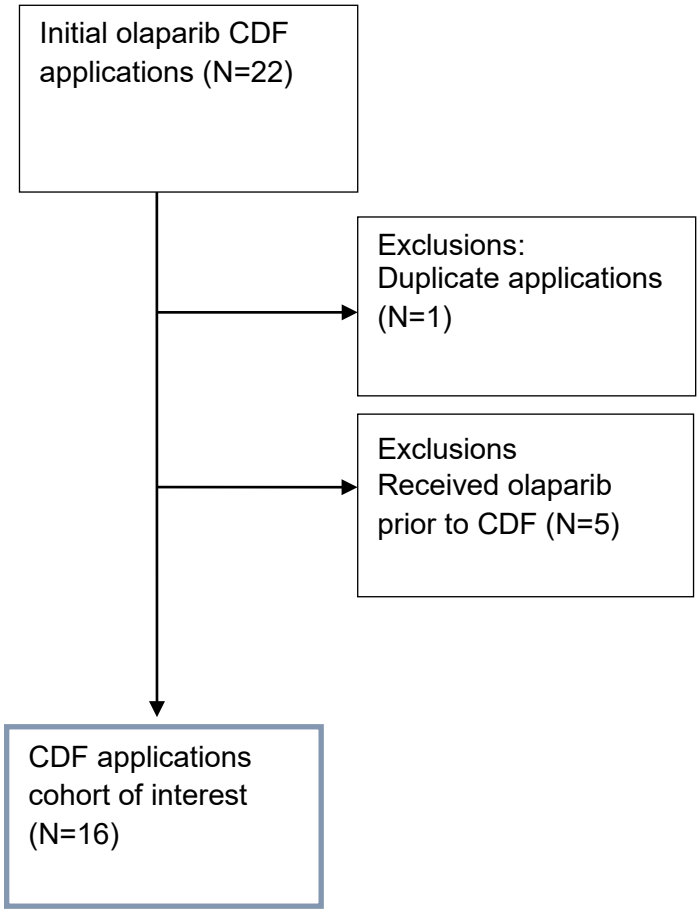
The analysis cohort is limited to the date olaparib entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the pharmaceutical company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 28 November 2019 to 27 February 2020. A snapshot of SACT data was taken on 6 June 2020 and made available for analysis on 12 June 2020. The snapshot includes SACT activity up to 29 February 2020. Tracing the patients' vital status was carried out on 29 July 2020 using the personal demographics service (PDS)[1].

There were 22 applications for CDF funding for olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer between 28 November 2019 and 27 February 2020 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 21 unique patients.

Five patients were excluded from these analyses as they appeared to have received olaparib prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer between 28 November 2019 and 27 February 2020



Linking CDF cohort to SACT

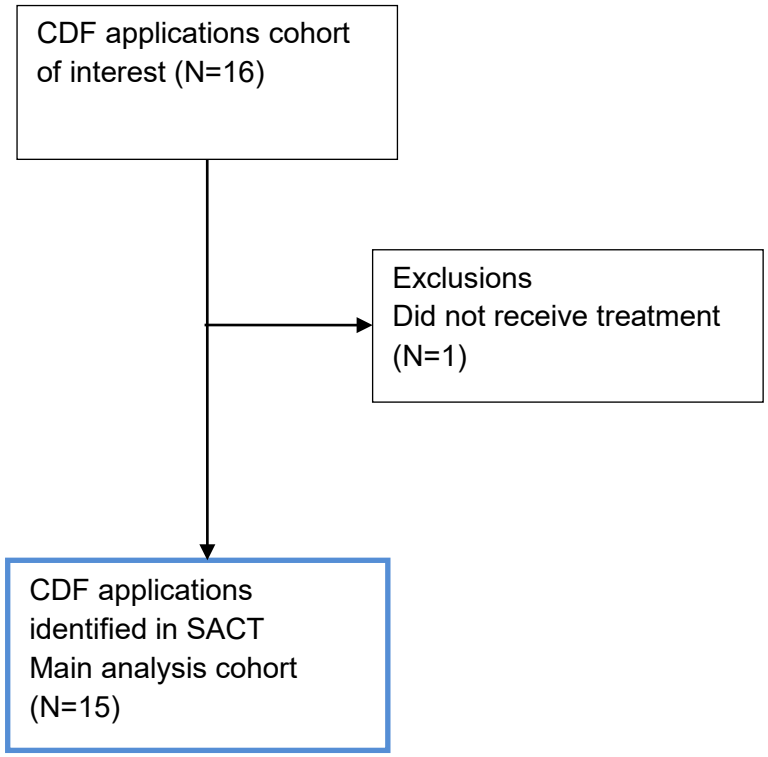
NHS numbers were used to link SACT records to CDF applications for olaparib in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Results

Cohort of interest

Of the 16 new applications for CDF funding for olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer, one patient did not receive treatment[a] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer between 28 November 2019 and 27 February 2020



A maximum of 15 olaparib records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 100% (15/15) of these applicants for CDF funding have a treatment record in SACT.

[a] The one patient that did not receive treatment was confirmed by the relevant trust by the PHE data liaison team.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 87% complete.

Table 1: Completeness of key SACT data items for the olaparib cohort (N=15)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	87%

A patient's outcome summary details the reason why treatment was stopped. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with olaparib in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, no patients have been identified as completing treatment, no outcomes are expected in the SACT dataset.

Completeness of Blueteq key variables

Table 2 presents the completeness of key data items required from Blueteq, all of which are 100% complete.

Table 2: Blueteq data items (N=15)

Variable	Completeness (%)
Type of BRCA test	100%
BRCA 1 and BRCA 2 mutation	100%
Response assessment	100%
PARP inhibitor	100%

Patient characteristics

The median age of the 15 patients receiving olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer was 55 years.

Table 3: Patient characteristics (N=15)

Patient characteristics[b]		N	%
Sex	Female	15	100%
Age	<40	0	0%
	40-49	3	20%
	50-59	7	47%
	60-69	3	20%
	70-79	2	13%
	80+	0	0%
Performance status	0	5	33%
	1	8	53%
	2	0	0%
	3	0	0%
	4	0	0%
	Missing	2	13%

[b] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 4: Distribution of type of test in Blueteq (N=15)

Type of BRCA test	N	%
In the germline only	14	93%
In both germline and somatic tissue	1	7%
Total	**15**	**100%**

Table 5: Distribution of BRCA mutation in Blueteq (N=15)

BRCA 1 and BRCA 2 mutation	N	%
BRCA 1 mutation	10	67%
BRCA 2 mutation	5	33%
Total	**15**	**100%**

Table 6: Distribution of response assessment in Blueteq (N=15)

Response assessment	N	%
Achieved a partial response at the end of the 2nd platinum-based chemotherapy i.e. has had a =30% reduction in measurable or non-measurable disease from the start of to the completion of the 2nd platinum-based chemotherapy or the patient has a complete remission on the post-chemotherapy CT scan but the CA125 has not decreased to within the normal range	10	67%
Achieved a complete response at the end of the 2nd platinum-based chemotherapy i.e. has no measurable or non-measurable disease on the post-chemotherapy scan and the CA125 is normal	5	33%
Total	**15**	**100%**

Table 7: Distribution of PARP inhibitor in Blueteq (N=15)

PARP inhibitor	N	%
The patient has never previously received a PARP inhibitor	13	87%
The patient has previously received niraparib via the CDF and this has had to be stopped within 3 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression	2	13%
Total	**15**	**100%**

Conclusions

Fifteen patients received olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer [TA620] through the CDF in the reporting period (28 November 2019 and 27 February 2020), all 15 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 100%. An additional patient with a CDF application did not receive treatment, this was confirmed by the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that of patients receiving olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer, most were aged between 40 and 69 years (87%, N=13) and 87% (N=13) of patients had a performance status between 0 and 1 at the start of their regimen with two patients having a missing performance status.

References

1. The Personal Demographics Service (PDS) [Internet]. NHS Digital: 2019 [cited 2020 Aug]. Available from: https://digital.nhs.uk/Demographics

2. Office for National Statistics. Cancer Registration Statistics, England: 2017. 2019 [cited 2020 Aug. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland

3. National Institute for Health and Care Excellence: 2020 [cited 2020 Aug]. Available from: https://www.nice.org.uk/guidance/ta620/chapter/1-Recommendations

4. Cancer Drugs Fund. [Internet]. NHS England and NHS Improvement: 2017 [cited 2020 Aug]. Available from: https://www.england.nhs.uk/cancer/cdf/

5. Appraisal and funding of Cancer Drugs. NHS England and NHS Improvement: 2016 [cited 2020 Aug]. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf

6. National Institute for Health and Care Excellence: 2020 [cited 2020 Aug]. Available from: https://www.nice.org.uk/guidance/ta620/chapter/3-Committee-discussion

7. SOLO-2 clinical trial: 2019 [cited 2020 Aug] Available from: https://clinicaltrials.gov/ct2/show/NCT01874353

NICE National Institute for Health and Care Excellence

Professional organisation submission

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]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]

2. Name of organisation	**British Gynaecological Cancer Society (BGCS)**
3. Job title or position	**Consultant Medical Oncologist and BGCS Medical Oncologist Representative**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	BGCS is the group for multidisciplinary healthcare providers working and researching the area of gynaecological cancers. We represent trainees, nurses, unit leads, oncologists, pathologists and radiologists and as such can discuss and formulating policy on gynaecological cancer research and treatment. The society is made up of a membership who must be introduced to and approved by the council and who pay an annual membership fee.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Yes. AstraZeneca are one of a number of pharmaceutical companies who provide sponsorship for the BGCS annual educational meetings eg Cheltenham 2021

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**none**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	This is an oral maintenance treatment following response to platinum-base chemotherapy aiming to slow progression and delay the time to need further intravenous systemic anti-cancer treatment. This is not a curative intervention.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Significant progression-free and overall survival advantage without reduction in quality of life

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are a number of unmet needs in advanced ovarian cancer but the delivery of oral maintenance PARPi in the platinum-sensitive population as per this indication is a significant advance in the treatment of relapsed disease
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently maintenance PARP inhibitor therapy is standard of care for women who have benefitted from platinum-based chemotherapy for relapsed disease and who have not received prior PARP inhibitor therapy
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE: relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults, only if they have a germline BRCA mutation and have had 3 or more courses of platinum-based chemotherapy (NICE pathways – Managing Advanced Ovarian Cancer)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Yes. Well established treatment pathway defined and in England it is limited by funding but choice of individual PARPi may vary from centre to centre with individual preference where funding may allow the option of more than one PARPi

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It has had a big impact on the pathway of care since introduced and as an oral therapy, during the COVID-19 pandemic, maintaining women on outpatient treatment with remote consultations and delaying the need for intravenous chemotherapy has been invaluable.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	yes
• How does healthcare resource use differ between the technology and current care?	n/a
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care within specialist outpatient clinics
• What investment is needed to introduce the technology? (For	Already running as standard

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Maintenance olaparib in this setting provides clinically meaningful benefits compared with no maintenance treatment
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is greater benefit with PARPi maintenance for those with a BRCA1 or BRCA2 mutation (germline or somatic) and for those with non-BRCA HRD (homologous recombination defects) but all patients who have responded to platinum-based therapy can benefit even those who have homologous recombination proficient disease (approx. 50%) albeit to a lesser extent.

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Already running as standard of care. If not offering oral maintenance therapy as standard of care there is a requirement for monthly blood tests and clinical review which might otherwise have been approximately 3 monthly if receiving no maintenance therapy. However blood tests can be performed in the community and medications sent to patients alongside virtual clinic appointments to minimise hospital attendances for patients
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment is continued until unacceptable toxicity or disease progression

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	yes
• Is the technology a 'step-change' in the management of the condition?	yes

• Does the use of the technology address any particular unmet need of the patient population?	Improves outcomes for patients with relapsed disease responding to platinum-based chemotherapy
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Olaparib is well-tolerated and side effects are rarely severe, occuring predominantly in the first few cycles of treatment and can be readily managed with dose adjustments and supportive medications and clinical trials have repeatedly confirm that it does not impact negatively on quality of life
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	Real world studies suggest benefit in the real populations mirror that in clinical trials
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression-free and overall survival with maintenance of quality of life

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	none
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA620]?	No

21. How do data on real-world experience compare with the trial data?	Directly comparable
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use	

of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Established standard of care for PARPi-naïve relapsed ovarian cancer, following response to platinum-based chemotherapy
- Well tolerated oral therapy delaying time to subsequent line of intravenous chemotherapy
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient organisation submission

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]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

<table>
<tr><td>2. Name of organisation</td><td>Ovacome Ovarian Cancer Charity</td></tr>
<tr><td>3. Job title or position</td><td>Head of Support Services</td></tr>
<tr><td>4a. Brief description of the organisation (including who funds it). How many members does it have?</td><td>Ovacome is the national UK ovarian cancer charity focused on providing support and information to anyone affected by ovarian cancer. This includes people who have either been diagnosed with the disease or think that they might be at risk, as well as their friends and family and healthcare professionals.
We currently have over 4,000 members and each year we support around 18,000 people.
We have 12 full time members of staff and 5 part-time members of staff.
We are funded through charitable donations, trusts and foundations donations, community fundraising and donations.</td></tr>
<tr><td>4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]</td><td>
<table>
<tr><th>Company</th><th>Amount Received</th><th>Date received money</th><th>Funding for:</th></tr>
<tr><td>GSK</td><td>£1,500.00</td><td>11/08/2021</td><td>Second payment for a further 25 hours dedicated to the Give Her Time project</td></tr>
<tr><td>Astra Zeneca</td><td>£366.22</td><td>23/12/2021</td><td>Ovacome attendance at OC Summit on 14 October 2021</td></tr>
<tr><td>GSK</td><td>£3,000.00</td><td>30/03/2022</td><td>Ovacome - Ovarian Cancer awareness campaign - Give Her Time extra payment</td></tr>
<tr><td>GSK</td><td>£270.00</td><td>09/06/2022</td><td>Ovacome - Nurse webinar speaker services</td></tr>
<tr><td>Total</td><td>£5,136.22</td><td></td><td></td></tr>
</table>
<table>
<tr><th>Name of Grant/Foundations</th><th>Amount Received</th><th>Date received money</th><th>Funding for:</th></tr>
<tr><td>Sanofi</td><td>£2,573</td><td>18/11/2021</td><td>Grant to support Ovacome's Older people project</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>If so, please state the name of manufacturer, amount, and purpose of funding.</td><td>
<table>
<tr><td>GSK</td><td>£15,000</td><td>06/05/2022</td><td>Grant to support Ovacome’s education programme for clinicians and medical students</td></tr>
<tr><td>Total</td><td>£17,573</td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?</td><td>No.</td></tr>
<tr><td>5. How did you gather information about the experiences of patients and carers to include in your submission?</td><td>Knowledge and experience from 26 years providing support to those affected by ovarian cancer. Feedback from members collected through My Ovacome online forum.</td></tr>
<tr><td colspan="2">Living with the condition</td></tr>
<tr><td>6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?</td><td>Ovarian cancer has a significant impact on quality of life. The majority are diagnosed at Stage III when it has already spread outside of the pelvis. This means treatment is aimed at minimising the burden of the disease and maximising periods of wellness between treatments. As treatment lines are exhausted, those diagnosed fear being told there is no more treatment available to manage their ovarian cancer.

The surgery undertaken is most usually a total abdominal hysterectomy and bilateral salpingo-oophorectomy. This operation can have long term effects on abdominal organs and particularly the bowel with associated continence issues. This may mean having manage a stoma, either short or long term. Associated issues include fatigue and changes to body image and function affecting sexuality.</td></tr>
</table>

	Those diagnosed live with the anxiety of possible recurrence. The time after treatment whereby they are under routine surveillance can be psychologically very hard to cope with. Having a choice of maintenance therapy to extend progression free survival and continued input from oncology teams offers significant psychological as well as health benefits. For both those living with ovarian cancer and their carers, ovarian cancer can be very isolating, due to its comparative rarity they may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	They are concerned that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative symptom control only. The development of biological therapies is offering hope when there had been no new chemotherapy options for many years.
8. Is there an unmet need for patients with this condition?	Currently no PARP inhibitors are routinely available second line. At the point of recurrence, those diagnosed are advised that their cancer is incurable and they will face further recurrences with diminishing treatment choices. Olaparib's efficacy has been established through its use as maintenance treatment for BRCA-mutated disease and clinical trials. Patients are aware that having a BRCA mutation makes their disease more likely to respond to PARP inhibitors and are keen to access this treatment. It is vital that those who did not have the opportunity of PARP treatment first line have this option available second line, where appropriate. Having a PARP inhibitor available that offers a longer period of feeling well and delaying the need for further lines of treatment for as long as possible, confers an additional psychological benefit as well as a physical one. This is further enhanced for patients on follow-up who find maintenance therapy and continued input from oncology teams offers significant psychological as well as health benefits compared to routine surveillance.

	Olaparib as an oral medication offers patients greater choice and flexibility regarding location of treatment as hospital attendance is not necessary for administration.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is expanding routine availability of PARP inhibitors. It is a treatment that offers increased progression free and overall survival without debilitating side effects, enabling a good quality of life. They are aware that the side effects are generally manageable and non-cumulative. Comments from members of our forum who have taken olaparib include: 'I have a CA125 of below 3 and a really good quality of life which enables me to remain productive, working full time etc and living life to the full.' And 'I am so thankful that I can lead a normal life.'
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	While they are aware of a drug's side effects they are prepared to manage these for increased survival. Studies such SOLO2 suggest that the side effects of olaparib are such that they do not adversely affect quality of life.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding maintenance therapies for this group of patients is vital.
- The health benefit of olaparib is established through its availability to those with BRCA-mutated ovarian cancer and there are additional psychological benefits of expanding treatment options by having a PARP inhibitor made routinely available at second-line.
- For patients on follow-up knowing their cancer is likely to be incurable and require further systemic therapy in the future, continued input from oncology teams offers significant psychological as well as health benefits compared to routine surveillance.
- Olaparib as an oral medication offers patients greater flexibility and convenience regarding location of treatment, minimising detrimental impact on quality of life.

Thank you for your time.

NICE National Institute for Health and Care Excellence

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

NICE National Institute for Health and Care Excellence

Patient organisation submission

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]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Ovarian Cancer Action
3. Job title or position	Head of Policy and Research
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovarian Cancer Action was founded in 2005 to raise awareness, to fund much needed research, and to give a voice to all those affected by the disease. We have been working ever since, driven by a clear vision – a world where no woman dies of ovarian cancer. We're committed to funding research to accelerate progress in three main areas: prevention, diagnosis and treatment. And while our scientists are busy in the lab, we're on the ground campaigning for change and raising awareness of the disease, so that every woman and healthcare professional knows the signs to look out for. Together, these priorities will help women survive ovarian cancer. Fundamentally we demand that every woman should have the best treatment available. To date, we've funded a grand total of £12.3 million in medical research. The charity is funded through a range of sources that includes trust funding and individual donations. We have a full time equivalent of 18 employees in our office, supported by regular administrative volunteers.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Funding received in the last 12 months: AstraZeneca – none Comparator product manufacturers GlaxoSmithkline - £10,000 – donation to support national clinical service improvement policy work Clovis – none

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Many years of experience in direct consultation with ovarian cancer patients and their families. Previous direct consultation of patients on Olaparib for other NICE and SMC reviews. NB – the extremely short timeframe in which to turn around this submission meant it was not possible to carry out a patient consultation specific to this CDF review. Instead we have used previously held evidence and insight.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of ovarian cancer can be devastating, significantly affecting the quality of life of patients. Women not only suffer from the consequences of the disease but also have to live with the long-term impact of its treatment and the uncertainty of whether the disease will return. Most women diagnosed with ovarian cancer are diagnosed at stage 3 or 4, and so the majority of women diagnosed with ovarian cancer have a poor prognosis. This has a significant impact emotionally with patients experiencing high levels of fear and anxiety. Even after a seemingly successful course of treatment there is still fear and anxiety due to the possibility of a recurrence, as recurrence rates for ovarian cancer are around 70%. This

	creates a sense of uncertainty about the future and this is difficult for many women to live with. This fear and anxiety is not just experienced by patients but family and friends too. In addition to the emotional impact of ovarian cancer, patients experience a number of physical symptoms that result from the disease itself (ascites, bloating, abdominal pain) and side effects from its treatment. Surgery used in the treatment of ovarian cancer often leads younger women to go into premature menopause, with its resulting effects. Chemotherapy causes a number of short and long term effects that impact quality of life. For an ovarian cancer patient, their condition affects every aspect of their life – their relationships, work, family life and social life. And, in many cases there can be additional challenges due to stigma, cultural insensitivity, a feeling of isolation and in some cases unaddressed psychosexual issues. Furthermore family members and carers are also impacted by all of these issues. Many of our patient group members have experienced a recurrence and this is a very difficult time for them. Some patients do experience severe side effects with chemotherapy with one carer stating “I was witness to the heavy side effects. The side effects were even worse the second time around”. From one of our supporters: “To live with OC is like learning to ride a bike through a bog of mud. It is a journey that you don’t want to have to make - or push upon those you love. But there is little choice in the matter and one way or another you find the path that works for you. For me personally after the initial diagnosis and first lot of treatment I thought there is just no way I can do that again. Chemotherapy is so tough. You have the trauma of knowing it is most likely coming back.” The husband of a lady who sadly died from the disease in 2017 said: “Life for both the patient and carer becomes totally consumed by the disease – when the next hospital appointment will be, managing side effects, organising childcare, sleepless nights – it is a vicious circle that never seems to end.” A patient who first developed ovarian cancer at the age of 37 and is currently being treated for platinum resistant recurrence said “When you have ovarian cancer you are not yourself - life revolves around the disease and in the very worst moments you have no interest in your family, friends and general life outside of the disease and what it is putting your body and mind through.”

	"An ovarian cancer diagnosis turns the entire family's life upside down." Was a quote from a patient diagnosed at the age of 67 and recently finished her last round of chemo. A patient who has been having treatment over the course of the last seven years said "Quality of life is poor – reasonable at best when on treatment. There is a desire to cram as much into life as possible due to not knowing what is going to happen next but being bound by the horrific side effects such as complete exhaustion, severe pain, nausea and vomiting and mouth ulcers that make it almost impossible to eat."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The main concern that patients and carers have about treatment is the worry is that the high recurrence rate means current treatment is not effective, and they live with the anxiety that they will have to repeat chemotherapy, and experience its side effects, again and again. Many experience severe side effects and their treatment schedule is intense, requiring regular hospital visits and so the prospect of repeating this is a huge worry.
8. Is there an unmet need for patients with this condition?	There remains a huge unmet need for more effective therapies for patients with ovarian cancer. While researchers continue efforts towards preventing recurrence and treatment resistance, there are ultimately no curative treatments. Maintenance therapies offer precious time in the recurrent setting. With widespread approval of PARP inhibitors now available for firstline patients, this review will benefit a small number of women who missed out on access when first diagnosed. It is extremely important that these women are able to have the same opportunities to access a PARP as their counterparts. This review offers a safety net to scoop up the few remaining women who were diagnosed too late to receive a PARP in first line, but have not yet had a recurrence and offer them treatment.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The benefits that patients appreciate with olaparib are: • They feel these drugs are targeted specifically at their disease. This means that they can be immediately offered a treatment that is known to be the best option for their condition. • It improves progression free survival providing more hope to patients • It improves overall survival and gives them more time with their family and friends • Generally patients in clinical trials have found its side effects to be acceptable; the main side effects have been anaemia, fatigue, nausea and vomiting. • Olaparib is taken orally which makes is an easy and convenient drug to administer From one of our supporters: “The main advantage would be to delay the disease coming back. And that it is less gruelling that chemotherapy. Patients can live a much more ‘normal’ life.” From another supporter: “Huge extensions of life, the last chemo (4th time) didn't get rid of all the disease, so without Olaparib I very much doubt I would be here. It is most probably my last chance for any real extension of life. This obviously has massive implications for my friends and family. So far I've been on Olaparib 20 months. The most amazing 20 months. It brings incredible HOPE. Data shows that 20% of women are on the drug for 5 years plus. That is my target. So what difference on a daily basis....apart from the first three months which was tough (side effects such as really bad nausea/fatigue etc.). I live a wonderful, manageable life. I can do the things to lead a great life. I still have to manage the fatigue, and stress of living with cancer, but can plan short term things like holidays and trips with my family. I play tennis, I paint. I am able to celebrate important life events of my children ie my son going to Uni, plan adventures with them. Share another Christmas. Build more memories with my children. Try and become a better person. Use my experiences of cancer and help others. Be more empathetic and compassionate....it goes on and on....what do we all want out of life?” From another of our supporters: “I have been very lucky with the treatment I have received. I have had chemotherapy 4 times, as well as 2 major surgeries, Avastin 2 1/4 years, and currently Olaparib for the last 3 years. My care has been outstanding. I can’t thank them enough. I would obviously have preferred

	to have been able to access olaparib after first line treatment, which might have kept me well for a considerable time- as opposed to having chemo for the 2nd time 18 months after the first lot. Olaparib is a massive game changer. Without it I believe I simply wouldn't be here now. My family and I literally owe my life to the scientists who came up with the drug, and NICE for allowing me to access it, 3 years under other circumstances I would simply not have had."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Ovarian Cancer Action has received numerous anecdotal comments and concerns regarding side effects of treatments. We assert that adverse effects of treatment and health-related quality of life should certainly be considered as significant in any outcome assessments. Patients are concerned about any short and long term side effects of the treatments, as key for them is that the time are living with this disease is of good quality and enjoyable. Patients have reported to us however that compared to chemotherapy, the side effects of Olaparib are easier to deal with. We are told the side effects are annoying, rather than incapacitating. One of our supporters tells us: "My Mum has BRCA [mutation] and was fortunate to go onto Lynparza [Olaparib] tablets. My Mum was on Lynparza for 18 months, wow they were amazing, they gave her her life back. She actually felt well for the first time since her diagnosis in 2013, stage 3/4. Her cancer can't be cured only controlled with treatment. Lynparza [olaparib] makes a huge difference, chemo strips everything, even good cells it makes you feel ill, whereas tablets don't, they give you your life back, it only takes away bad cells, you can live again, see family, see places, eat what you desire, don't lose your hair, they are a medical miracle When on chemo you can't see anyone each time for 10 days because of the risk and fear of infection, tablets are not like this. You don't have to have constant picc line in as that in its self is another fear as can cause problems. These tablets made her feel in control of her own life again, as her daughter it was wonderful to see my Mum back again as she was, it was like she hadn't been diagnosed with the c word."

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- There are no curative treatments for advanced ovarian cancer, therefore maintenance drugs to give patients more time between recurrences is vital and significantly improves mental health also.
- Compared to chemotherapy, the side effects of Olaparib are easier to deal with. Patients can live a “normal” life.
- This review offers a safety net to scoop up the few remaining women who were diagnosed too late to receive a PARP in first line but have not yet had a recurrence and offer them treatment. It is vital that this group of women are not left behind.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Professional organisation submission

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]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]

2. Name of organisation	**Imperial College London**
3. Job title or position	**Professor of Practice in Histopathology**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Affiliates, and trainees, supported by the staff who are based at the College's London offices.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Olaparib is used as a drug for the maintenance treatment of adult patients with BRCA-mutated advanced ovarian cancer with the aims of delaying disease progression and prolonging survival.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Decrease in recurrent tumour burden and prolonged progression free survival.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Tumour recurrence post chemotherapy is one of the biggest challenges in management of ovarian cancer. Effective targeted therapy with less side effects compared to conventional chemotherapy is a much needed addition.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Ovarian cancer is principally treated by surgery and chemotherapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes - there are guidelines issued by national and international professional bodies such as the British Gynaecological Cancer Society.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The new current standard of care for recurrent platinum-sensitive ovarian cancer is platinum-based chemotherapy (usually platinum doublet combinations or carboplatin with one of paclitaxel, pegylated liposomal doxorubicin or gemcitabine). In those who respond (by CA125 and/or CT), chemotherapy is followed by PARP inhibitor maintenance until disease progression or unacceptable toxicity for patients who have not received a PARP inhibitor previously. This is universal with no difference in opinion between professionals.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	There are two other PARP inhibitors licenced in this indication – Niraparib and Rucaparib. These two drugs are also licenced in patients without BRCA1/2 mutations. Olaparib would be added to the list but be limited to those with BRCA1/2 mutation (either germline or somatic).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	This is an addition to current protocols of management for patients with recurrent disease.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment should be used in specialist gynaecological cancer centres.
• What investment is needed to introduce the technology? (For	Funding for making the drug available to patients. Sustained adequate funding to support the role of Diagnostic Histopathologists and Histopathology Laboratories for their work on patient sample selection and preparation for genomic testing and funding for

example, for facilities, equipment, or training.)	the genomic testing, the results of which are essential for determining eligibility for the prescription of the drug.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The drug can play a role in improvement of progression free survival for patients with recurrent BRCA-mutated ovarian cancer.
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, as it plays a role in progression free survival.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The treatment is most effective for ovarian cancer patients who have BRCA-mutated cancer.

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The oral administration of the drug means that its use does not require a hospital setting. The usual follow up the patients are offered would cover the requirements for the use of the drug without specific additional requirements. Hence other than the cost of the drug, and requirements for genomic testing (including professional time of personnel involved) no significant additional burden is expected on the healthcare system as compared to usual care for these patients.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Start: patients will need to have responded to platinum-based chemotherapy given immediately prior. Patients need to have received at least 4 cycles. In addition, patients must not experience disease progression in the weeks between completing chemotherapy and starting Olaparib.

	Stopping: disease progression (by CT criteria – CA125 progression alone should not cause treatment to be stopped) or unacceptable toxicity or patient request.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Studies show the drug has potential to significantly improve progression free survival in patients with advanced ovarian cancer. This with the facts that the drug is used with oral administration and has relatively tolerable side effects present improvements to current practice.

• Is the technology a 'step-change' in the management of the condition?	Yes. This is one example of targeted therapy and personalised medicine which is the current and future direction for cancer therapy.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, it is an additional potentially effective tool in management of recurrent disease.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The common side effects for the drug are not significantly more than those of conventional chemotherapy. The more serious and perhaps long term side effects such as bone marrow and lung problems can affect the patient's quality of life and lead to death and would be an indication to stop treatment.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression-free survival – yes this was measured. Overall survival – critical secondary outcome that was measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Time to second subsequent treatment – used as a surrogate for OS and this is acceptable.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No - the risk of MDS/AML was well-documented in the trials
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology	

appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	Real world data support the trial findings
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Recurrence is a significant challenge in management of ovarian cancer patients
- Targeted personalised therapy is a requirement in management of the disease
- PARP inhibitors such as Olaparib represent a significant addition in management of BRCA-mutated advanced ovarian cancer
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Patient organisation submission

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]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Target Ovarian Cancer
3. Job title or position	Head of Policy and Campaigns
4a. Brief description of the organisation (including who funds it). How many members does it have?	Target Ovarian Cancer is the UK's leading ovarian cancer charity. We work to: • improve early diagnosis • fund life-saving research • provide much needed support to women with ovarian cancer We are the only national charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. We are the authority on ovarian cancer. We work with women, family members, and health professionals to ensure we target the areas that matter most for those living and working with Target Ovarian Cancer is funded through voluntary donations and we have been in receipt of some limited funding from manufactures which are outlined below
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Yes GSK £10,000 Nov 2021 - The grant was for the running of Target Ovarian Cancer's nurse-led Support Line AstraZeneca £20,000 March 2021 - The grant for the running of Target Ovarian Cancer's nurse-led support line and online support to women as part of our response to the coronavirus pandemic GSK June 2022 £300 honorarium for a speaking engagement

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• Anecdotal feedback from patients and their families. • Patient survey on access to cancer drugs. • Calls to the Target Ovarian Cancer support line, questions submitted to our Ask the Experts forum and questions/comments posted on social media.
Living with the condition	
6. What is it like to live with the condition? What do carers	Around 6,900 women are diagnosed with ovarian cancer in England each year; many women face a delayed diagnosis and currently just a third are diagnosed at an early stage (stage I or II) when the disease is easier to treat. Survival rates for ovarian cancer trail those for many other cancers. Overall five-year survival is 37 per cent for women with ovary, fallopian tube and primary peritoneal carcinomas.[1]

[1] Ovarian Cancer audit feasibility pilot(2020), disease profile in England: incidence, mortality. stage and survival for ovary, fallopian tube and primary peritoneal carcinomas. Available at: digital.nhs.uk/ndrs/our-work/ncras-partnerships/ovarian-cancer-audit-feasibility-pilot-ocafp---disease-profile-in-england/contents

experience when caring for someone with the condition?	Standard treatment involves surgery and chemotherapy, with chemotherapy either post-surgery or neoadjuvant. In the majority of cases the disease returns after first line treatment. At this point treatment is no longer curative and each further recurrence and subsequent round of platinum based chemotherapy a woman goes through increases her chance of becoming platinum resistant; at which point very few treatment options remain and prognosis is extremely poor. The prospect of recurrence casts a shadow over the lives of many women. Fears around recurrence are compounded by the knowledge that there are few treatment options for ovarian cancer. *"I feel now and when I was going through my treatment that ovarian cancer is the poor relation of women's cancers. No screening programme, reduction in research funding, with a high recurrence. Having ovarian cancer doesn't fill you with high hopes by the time you are diagnosed*." Woman with ovarian cancer. An ovarian cancer diagnosis can have a negative impact on many aspects of an individual's life. Perhaps most notably are the practical implications of debilitating treatments rendering individuals unable to work or take part in regular day-to-day life.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	*"The latest drugs offer hope and the chance that women with progressive disease can enjoy a better quality of life and longer survival. If new drugs are not made available, the current survival rates will continue to be dire in comparison with other cancers and this has to change. Women with ovarian cancer should be given the same right to life as those with other, more widely supported, cancers."* Woman with ovarian cancer Platinum-based chemotherapy is effective in maintaining stable disease, and helping alleviate the impact of ovarian cancer symptoms. However, platinum-based chemotherapy will cause some side effects which

	women find difficult to manage, including tiredness and fatigue, hair loss, nausea and vomiting, and tingling and numbness in the fingers and toes. Women are keen to consider options that may extend their life or the interval between recurrences. 73 per cent of women with ovarian cancer said they felt it was important to take part in clinical trials so knowledge and treatment can advance. And 66 per cent of women with ovarian cancer wanting to take part in clinical trials were prepared to travel to another hospital to do so.[2]
8. Is there an unmet need for patients with this condition?	In order to maximise the benefits of platinum-based chemotherapy it is crucial to increase the time intervals between chemotherapy cycles, this works to reduce the risk of the ovarian cancer developing platinum-resistance and the individual developing an allergic reaction. If sensitivity to platinum chemotherapy is maintained women can expect to be effectively treated with this regimen for multiple recurrences, however, most women will eventually become platinum resistant. This is why progression free survival (PFS) is hugely important to women who have had a recurrence *'Very limited options, with limited success new treatments are urgently needed*" Woman with ovarian cancer

[2] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	In the last few months, we have asked those had taken olaparib specifically about their experience of taking the treatment and this is what they told us: *The treatment was easy to take and the side effects were not as bad as chemotherapy* *I tested BRCA2 so was told that I'd be put on olaparib. Found olaparib easy with minimal random side effects.* *Excellent. First few days of mild nausea then absolutely fine since (last 9 months)* *Olaparib was fine until it stopped working 2 years later. I was on Carbo Taxol which failed. I'm now on Caeylex* *Initial Olaparib dose of 600mg was too high and gave me chronic stomach pain and fatigue. I also suffered from a bitter taste in my mouth throughout the day. Now the dose has been reduced to 300mg it is much better and the previous symptoms have all but disappeared.* *I was concerned about side effects but was actually ok* *Olaparib was good, very little side effects. Originally, I was told I would be on this long term. It was upsetting when I was told guidelines had changed and they were being stopped after 2 years* *I have been taking this for 20 months. No side effects at all.* Overall, the following themes emerged as advantages: • The potential to increase the time between chemotherapy treatments. The drug is given as tablets that the patient can take at home without the need for hospital visits. Reducing visits to the hospital

	reduces the financial burden on the patient in terms of travel time to the hospital and family and carers potentially taking unpaid leave from work to attend appointments. • The potential to take a treatment that has manageable side effects and, in some cases, milder side effects than chemotherapy
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	A major consideration for patients and carers when choosing to start a new treatment is the impact of the treatment. They want to be clear about the potential side-effects and the possible impact on their quality of life. The extent to which side effects may impact in a woman's quality of life cannot be predicted in advance, however, there are a range of approaches that a woman can discuss with her clinical team to reduce the impact of the side-effects while continuing to benefit from the treatment. We asked patients who had taken olaparib their experience of side effects: *I've only on the olaparib about 3 monthsTo date my main side effect has been fatigue and mild indigestion.* *Olaparib causing joint aches and tired otherwise completely manageable.* *Dose was reduced after 1st month due to exhaustion and fatigue - no side effects since.*

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Platinum-based chemotherapy is the primary treatment for recurrent platinum-sensitive ovarian cancer. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited. Maintenance treatments like olaparib give patients and clinicians a valuable opportunity to extend the progression free survival period and therefore the interval between chemotherapy treatment. This can prolong the efficacy of standard platinum-based chemotherapy, delaying the onset of platinum drug resistance
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points

- **Quality of life impact:** the threat of recurrent disease looms large over the lives of women with ovarian cancer, the emotional, practical and physical implications for women and their family are significant. This makes it hard for women to plan events and activities that would have a positive impact on their quality of life.
- **Limitations of current treatment:** platinum-based chemotherapy is the primary treatment for recurrent platinum-sensitive ovarian cancer. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited.
- **Benefits of new treatment:** olaparib has the potential to extend the time between chemotherapy treatments and therefore potentially prolong the use of platinum-based chemotherapy. This gives women and their families more opportunity to focus on emotional and physical recovery.
- **Mode of delivery:** olaparib is given in tablet form allowing women to easily continue treatment in their own home and greatly reducing hospital visits. It also reduces the need for women to live their life around their hospital appointments and treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

.....

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 technology appraisal 620)

Cancer Drugs Fund Review

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 131839T.

Title:	Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (CDF review of technology appraisal 620)
Produced by:	BMJ Technology Assessment Group (BMJ TAG)
Authors:	Steven J Edwards, Director of Health Technology Assessment, BMJ-TAG, London Victoria Wakefield, Principal Clinical Evidence Analyst, BMJ-TAG, London Tracey Jhita, Health Economics manager, BMJ-TAG, London Benjamin Farrar, Senior Clinical Evidence Analyst, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.
Date completed:	27/07/2022
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number 13/18/39T.
Declared competing interests of the authors	Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Professor Nicholas Reed (Consultant Clinical Oncologist, Beatson Oncology Centre, Glasgow) and Professor Gordon Rustin (Consultant Medical Oncologist, Mount Vernon Cancer Centre, Middlesex) for providing clinical advice throughout the project.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Wakefield V, Jhita T, and Farrar B. Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (CDF review of technology appraisal 620): A Cancer Drugs Fund Review. BMJ Technology Assessment Group, 2022.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; and provided feedback on all versions of the report. Guarantor of the report
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and drafted the summary, background and clinical results sections
Benjamin Farrar	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and assisted with drafting the background and clinical results sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE	Adverse events
AF	Acceleration factor
AIC	Akaike information criterion
ADP	Adenosine diphosphate
BD	Twice daily
BIC	Bayesian information criterion
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
BRCAm	Breast cancer susceptibility gene mutation
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CMU	Commercial medicines unit
CQ	Clarification question
CTCAE	Common Terminology Criteria for Adverse Events
CS	Company submission
DCO	Data cut-off
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EAG	Evidence Review Group
HGSOC	High grade serous ovarian cancer
HR	Hazard ratio
IA	Investigator assessed
ICER	Incremental cost effectiveness ratio
ITT	intention-to-treat
KM	Kaplan Meier
Mg	Milligrams
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
OS	Overall survival
OWSA	One-way sensitivity analyses
PARP	Poly (ADP-ribose) polymerase
PAS	Patient access scheme
PFS	Progression-free survival
PH	Proportional hazards
PHE	Public Health England
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial

RECIST	Response evaluation criteria in solid tumors
RPSFT	Rank preserving structural failure time
SACT	Systemic anti-cancer therapy
SAE	Serious adverse event
SAS	Safety Analysis Set
SD	Standard deviation
SE	Standard error
SmPC	Summary of product characteristics
TSD	Technical support document
ToE	Terms of Engagement
TTD	Time to treatment discontinuation

1 Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides a critique of the adherence to committee's preferred assumptions from the Terms of Engagement (ToE) in the company's submission. Section 1.2 provides an overview of the key issues. Section 1.3 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.4 and 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute of Health and Care Excellence (NICE).

1.1 Critique of the adherence to committees preferred assumptions from the Terms of Engagement in the company's submission

Overall, the company has adhered to the committee's preferred assumptions from the Terms of Engagement (ToE). However, the EAG has identified some key issues with the implementation of overall survival (OS) in the model and the implication of long-term survival for routine surveillance patients which are outlined in the below sections.

1.2 Overview of the EAG's key issues

Table 1 presents a summary of the EAG's key issues on the evidence submitted on the clinical and cost effectiveness of olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy.

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Extrapolation of OS in the model	4.1.3.1
2	Costs of subsequent olaparib for routine surveillance patients	4.1.4.1
3	TTD not capped to PFS	4.1.6.1

Abbreviations: ADP, adenosine diphosphate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival; TTD, time to treatment discontinuation.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are around the extrapolation of overall survival in the model to account for improved

survival of relapsed routine surveillance patients who, in the NHS, would be eligible for subsequent olaparib maintenance treatment and inclusion of the associated costs of treatment.

1.3 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing progression-free survival (PFS) and overall survival (OS).

Overall, the technology is modelled to affect costs by:

- Its higher unit price compared with the cost of routine surveillance in the NHS.

The modelling assumptions that have the greatest effect on the ICER are:

- Choice of extrapolation for OS;
- Inclusion of subsequent olaparib maintenance costs for routine surveillance patients; and

1.4 The clinical and cost-effectiveness evidence: summary of the EAG's key issues

Table 2. Issue 1: Extrapolation of OS

Report section	4.1.3.1
Description of issue and why the EAG has identified it as important	In the model, patients on routine surveillance are PARP inhibitor naïve and thus, when they relapse, they will be eligible for third-line olaparib maintenance treatment after another course of platinum-based chemotherapy (as recommend in TA620). Additionally, relapsed olaparib BRCAm patients would only receive routine surveillance as maintenance in the NHS as they are no longer PARP inhibitor naïve. As accepted in TA620, third-line olaparib maintenance treatment is associated with improved survival outcomes for BRCAm patients who would have otherwise received routine surveillance as maintenance.
What alternative approach has the EAG suggested?	The EAG considers that over time, the OS curves for second-line olaparib and routine surveillance may eventually converge. In their assessment of extrapolations for OS, the company identified that the 1-knot spline resulted in converging curves. Consequently, the EAG considers the 1-knot spline to produce clinically plausible estimates of survival given survival for relapsed routine surveillance patients is likely to improve, while for relapsed olaparib patients, survival is likely to decline. Additionally, the 1-knot spline had a better statistical fit and better visual fit to the placebo arm than the lognormal used for the base case.
What is the expected effect on the cost-effectiveness estimates?	Using the 1-knot spline for the extrapolation of OS increases the company's corrected ICER from [redacted] to [redacted]. Additionally, the EAG explored a scenario using the inverse of the unadjusted OS HR to estimate unadjusted OS for routine surveillance, which resulted in an ICER of [redacted].
What additional evidence or analyses might help to resolve this key issue?	Survival analysis using unadjusted OS data for placebo from the 2L subgroup of SOLO2. However, it is not clear if subsequent PARP inhibitor use in SOLO2 was limited to third-line maintenance treatment and thus there may be limitations with the interpretation of the analysis. As such, the EAG considers that no one approach to account for improved survival for routine surveillance patients is more robust than others, but it is important for the committee to consider which approach best accounts for improved survival for routine surveillance.

Abbreviations: 2L, second-line; BRCAm, breast cancer susceptibility gene mutation; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PARP, poly (ADP [adenosine diphosphate] -ribose) polymerase.

Table 3. Issue 2: Costs of subsequent olaparib for routine surveillance patients

Report section	4.1.4.1
Description of issue and why the EAG has identified it as important	In TA620, the company included the costs of subsequent third-line olaparib maintenance treatment for routine surveillance patients but has opted to omit this in the updated model. The company stated that in current UK practice a small and diminishing number of patients will be PARP inhibitor naïve at third-line and retreatment with a PARP inhibitor is not recommended in the NHS. However, at the time of the publication of TA620 there were no second-line PARP inhibitor maintenance treatments recommended by NICE for routine use in the NHS, thus the current CDF review needs to consider the treatment pathway as it was then.
What alternative approach has the EAG suggested?	The EAG considers that relapsed routine surveillance patients who are PARP inhibitor naïve in the NHS would receive third-line olaparib maintenance treatment and are likely to have improved survival outcomes. Thus costs of subsequent olaparib maintenance treatment for routine surveillance patients should be included in the cost-effectiveness analysis.
What is the expected effect on the cost-effectiveness estimates?	At the request of the EAG, the company supplied a scenario including the costs of subsequent olaparib maintenance treatment. The company's corrected ICER reduced from [redacted] to [redacted] when using the final DCO for TTD from SOLO2 ([redacted] months)
What additional evidence or analyses might help to resolve this key issue?	None. The scenario resolves the issue.

Abbreviations: CDF, cancer drugs fund; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PARP, poly (ADP [adenosine diphosphate] -ribose) polymerase.

Table 4. Issue 3: TTD capped by PFS

Report section	4.1.6.1
Description of issue and why the EAG has identified it as important	According to the summary of product characteristics (SmPC) for olaparib, treatment should be continued until progression of the underlying disease or unacceptable toxicity. In the company's base case, TTD was not capped by PFS. Consequently, extrapolated TTD exceeds PFS between months 19 and 53 in the company's base case
What alternative approach has the EAG suggested?	The EAG considers TTD should not exceed PFS. Upon request of the EAG, the company supplied a scenario capping TTD to PFS.
What is the expected effect on the cost-effectiveness estimates?	Inclusion of the TTD capped by PFS reduces the company corrected ICER from [redacted] to [redacted]
What additional evidence or analyses might help to resolve this key issue?	None. Scenario resolves the issue.

Abbreviations: EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; TTD, time to treatment discontinuation.

1.5 Other key issues: summary of the EAG's view

The EAG notes that there is a discrepancy in the data cut-off (DCO) used for the PFS data compared with the OS and TTD data presented in the CS. The DCO used for the PFS analyses is from the primary analysis, whereas the final DCO is used for the analyses of TTD and OS. The company

reported that because the primary endpoint was met at the primary analysis of the SOLO2 trial, there were no further planned analyses of PFS. Patients who remained in the study following the primary analysis were followed up for disease progression according to local clinical practice, with timings and assessments likely to have varied between study sites. In addition, [redacted] The EAG therefore considers it a limitation of the available data and notes that there is thus a discrepancy in the DCO used for the analyses of PFS compared with that of the analyses of OS and TTD from SOLO2. The EAG notes that in the primary analysis the PFS maturity for the overall SOLO2 population was 63.4%.

Lastly, in the company base case, TTD is not capped to PFS and the company's selected extrapolation of TTD results in estimates exceeding PFS between months 19 and 53. According the summary of product characteristics (SmPC) for olaparib, treatment should be continued until progression of the underlying disease or unacceptable toxicity. As such, the EAG considers TTD should not exceed PFS and it is methodologically appropriate to include a cap on TTD, which is included this in the EAG base case.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 5 presents the EAG preferred assumptions as well as the EAG deterministic base case ICER. The EAG were unable to produce a probabilistic base case ICER as, due to a paucity of time, the EAG's scenario capping OS for routine surveillance to olaparib when using the 1-knot spline could not be appropriately linked to the probabilistic sensitivity analysis (PSA).

The company have an approved patient access scheme (PAS) discount of [redacted] and all results presented in this report are inclusive of the discount.

Table 5. EAG preferred assumptions and base case ICER ([redacted] PAS discount)

Scenario	Incremental costs	Incremental QALYs	Deterministic ICER (£/QALY)	Cumulative ICER (£/QALY)
Corrected company base case post clarification	[redacted]	[redacted]	[redacted]	[redacted]
1-knot spline for extrapolation of OS + routine surveillance OS cap	[redacted]	[redacted]	[redacted]	[redacted]
Third-line olaparib maintenance costs using the final DCO for TTD ([redacted] months)	[redacted]	[redacted]	[redacted]	[redacted]
TTD capped to PFS	[redacted]	[redacted]	[redacted]	[redacted]

EAG's preferred base case (deterministic)	[redacted]	[redacted]	-	[redacted]

Abbreviations: EAG, evidence review group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; TTD, time to treatment discontinuation.

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.2.

2 Introduction and background

2.1 Introduction

High-grade epithelial ovarian, fallopian tube or peritoneal cancer are rare cancers that are often fatal. In 2017 there were 6,236 newly registered cases of ovarian cancer in England,[1] and there were 3,472 registered deaths in England and Wales.[2] Ovarian cancer patients are most often treated by platinum-based chemotherapy, and a patient's cancer is labelled platinum sensitive if they progress more than six months after chemotherapy. Maintenance therapies, including poly (ADP [adenosine diphosphate] -ribose) polymerase (PARP) inhibitors, are given between different lines of chemotherapy to extend progression free survival (PFS) and sustain platinum sensitivity.

Olaparib (brand name Lynparza®, AstraZeneca) is a PARP inhibitor that inhibits PARP enzyme-mediated repair of DNA single-strand breaks. This leads to chromosomal instability in tumour cells and eventual apoptosis.[3] PARP inhibitors may be especially effective in patients with breast cancer susceptibility gene (BRCA) BRCA1 or BRCA2 mutations (BRCAm), as BRCAm status is associated with homologous recombination repair deficiencies.[4]

Olaparib was recommended for use within the Cancer Drugs Fund (CDF) in November 2019 for the maintenance treatment of people who have relapsed, BRCAm, platinum sensitive high-grade epithelial ovarian, fallopian tube or peritoneal cancer that is in complete or partial response to the second course of platinum-based chemotherapy (TA620).[5, 6] In this setting, the appraisal committee deemed there was the plausible potential for olaparib to be cost-effective compared to routine surveillance. However, the committee considered there to be outstanding clinical uncertainty for the overall survival (OS) benefit for this patient population and that the uncertainty was likely to be resolved by further data collection from the SOLO2 trial.[5] In the current submission, the company present mature survival data from the *post hoc* subgroup analysis of patients who had a confirmed BRCAm and had previously received two lines of platinum-based chemotherapy (the second-line [2L] BRCAm subgroup [N=172]) in the Phase 3 SOLO2 randomised controlled trial (RCT)[7, 8] in an updated economic model. The evidence assessment group (EAG) considers the 2L BRCAm subgroup from SOLO2 appropriately reflects the population specified in the NICE final scope[9] but considers it important to highlight that it represents a *post hoc* subgroup.

2.2 Background

In this submission, the company positions olaparib as a maintenance therapy for BRCAm patients with relapsed, platinum sensitive high-grade epithelial ovarian, fallopian tube or peritoneal cancer

that is in complete or partial response to the second course of platinum-based chemotherapy. The EAG believes the positioning of olaparib by the company to be appropriate and to adhere to the terms of engagement (ToE) for this CDF review.[10]

The EAG notes that olaparib and other PARP inhibitors are now available for first-line maintenance therapy of advanced ovarian cancer through the CDF.[11, 12] Due to this earlier availability of olaparib in the treatment pathway, only a small number of patients are expected to be eligible for olaparib as second-line (2L) maintenance therapy in the future, something which was highlighted by both the company (Section A.4, page 9), and by the EAG's clinical experts. The EAG's clinical experts highlighted the following cohorts of patients as being potentially eligible to receive olaparib as 2L maintenance therapy:

- Patients who had first-line treatment before any PARP inhibitor was available as a first-line maintenance therapy;
- Patients who were treated with a PARP inhibitor, other than olaparib, as first-line maintenance, but who discontinued this early due to toxicity;
- Patients who chose not to have a PARP inhibitor as a first-line maintenance therapy.

The EAG notes that in TA620 Study 19, a study not powered for OS but with a median duration of follow-up for OS of 6.5 years was used in the primary analysis due to the lack of mature OS data from the SOLO2 trial.[5, 13] However, the committee's preference was for data from SOLO2 to be used for decision making and the CS presents the now mature OS data from the SOLO2 trial.[5, 10]

2.3 Further data collection

The Terms of Engagement (ToE) requested further follow-up from SOLO2 to provide longer-term progression-free survival (PFS) and overall survival (OS) data. Additionally, the ToE required real-world data to be collected within the CDF by Public Health England (PHE) to help support the generalisability of the SOLO2 data. The EAG notes that the company has presented and used in the updated economic model:

- OS data from the 2L BRCAm subgroup of SOLO2;
- Investigator-assessed PFS and time to treatment discontinuation (TTD) from the 2L BRCAm subgroup of SOLO2 .

In addition, the company present the baseline characteristics of [redacted] patients from the PHE systemic anti-cancer therapy (SACT) dataset, although no outcome data for these patients were available at the time of the SACT dataset report (6 June 2020).

2.4 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

Table 6 outlines how the company has addressed the preferred assumptions from the ToE and the EAG's critique of this. In general, the EAG believes that the company has adhered to the ToE, although the EAG notes that the company has:

- adjusted the OS of placebo patients in the SOLO2 to account for PARP inhibitor use after progression in this group; and
- updated the baseline characteristics in the model to be those of the 2L *post hoc* subgroup from SOLO2.

The EAG considers that when patients on routine surveillance who are PARP inhibitor naïve (which is the modelled population for this CDF review) relapse, they will potentially be eligible for third-line olaparib maintenance treatment after another course of platinum-based chemotherapy (as recommended in TA620). However, the EAG considers it unclear where in the treatment pathway the subsequent PARP inhibitors were given in the placebo arm of SOLO2. Additionally, relapsed olaparib patients would only receive routine surveillance as maintenance in the National Health Service (NHS) as they are no longer PARP inhibitor naïve. The EAG thus requested at clarification that the company also conduct an analysis to adjust for subsequent PARP inhibitor use in the olaparib arm. Further detail on the method of adjustment used in the company's placebo adjusted analyses of OS and the EAG critique of the method of this adjustment is provided in Section 3.2.1.

The EAG considers it reasonable to update the baseline characteristics used in the model to match those of SOLO2, although the EAG's clinical experts reported some differences between the baseline characteristics of patients in SOLO2 and the patients likely to be eligible for olaparib as 2L maintenance therapy for ovarian cancer in England. This is discussed further in Section 3.1.1.

As requested in the ToE, the company have used radiologically-assessed PFS data in the model as PFS in SOLO2 was determined using [redacted]. However, the ToE did not specify whether the investigator assessed (IA) or blinded independent central review (BICR) PFS should be used. The company has used the IA data in the model and presented a scenario analysis using BICR. The EAG considers the IA data likely to be less

confounded due to the potential of informative censoring causing an overestimation of PFS using BICR, as discussed in the original EAG report.[13] Briefly, when a patient is deemed to progress by IA they are taken off-treatment and they are considered censored at this timepoint for the BICR analysis if no event has been detected by BICR. As patients who have IA progression are more likely to progress at the (hypothetical) next BICR assessment than patients who do not have IA progression, this censoring is informative and will cause an overestimation of the median survival time in the BICR analysis.[14-16] Moreover, insofar as treatments tend to extend PFS, patients in treatment groups will have more radiologic assessments than patients in placebo groups, and therefore more opportunity for incongruencies between the time of IA- and BICR-determined progression.[14] In-line with this, at the time of the PFS analysis in SOLO2 there were [redacted] events reported in the IA analysis than the BICR analysis in the olaparib arm, [redacted] events reported in the IA analysis than the BICR analysis in the placebo arm. The EAG thus recommends caution in drawing conclusions from the BICR PFS from SOLO2.

Table 6. Preferred assumptions from Terms of Engagement (Adapted from CS, Table 2)

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	EAG comment
Population	Those with BRCA mutation after 2 courses of platinum-based chemotherapy are the relevant population for the CDF review.	Yes.	NA	The population used in the economic model matches that set out in the ToE.
Time Horizon	A time horizon of 50 years should be used.	Yes.	NA	The economic model uses a time horizon of 50 years.
Progression-free survival	The company should present PFS estimates using radiological disease progression data as well as TTD data from the SOLO2 trial.	Yes.	NA	The company has used the investigator assessed radiological disease PFS data and TTD data from the SOLO2 trial in the model, with a scenario analysis using BICR-assessed PFS.
Overall Survival	The company should update the OS estimate using SOLO2 trial data.	Yes. The company uses the adjusted OS estimates from the SOLO2 trial data.	Subsequent PARP inhibitor use in the placebo arm would lead to an overestimate of overall survival for patients only treated with placebo.	The EAG considers it reasonable to adjust for subsequent PARP inhibitor use in the survival data but notes that the company only adjusted for subsequent PARP inhibitor use in the placebo arm of SOLO2 in the estimates of OS used in the company base case. In response to clarification the company also conducted exploratory analyses to account for subsequent PARP inhibitor use in the olaparib arm of SOLO2. Further details and EAG critique on the

				analyses of OS can be found in Section 3.2.1.
End of life	Olaparib does not meet the end-of-life criteria.	Yes.	NA	The company has not submitted for end-of-life.

Abbreviations: BICR, blinded independent central review; CDF, cancer drugs fund; EAG, evidence assessment group; PARP, poly (ADP-ribose) polymerase; PFS, progression free survival; OS, overall survival; ToE, terms of engagement; TTD, time to treatment discontinuation

3 Clinical effectiveness

3.1 Critique of new clinical evidence

3.1.1 SOLO2

The SOLO2 trial was a randomised controlled trial (RCT) designed to investigate patients (N=295) with platinum-sensitive relapsed ovarian cancer, who were in response to platinum-based chemotherapy, and who had a confirmed breast cancer susceptibility gene mutation (BRCAm). However, as discussed in Section 2, the evidence assessment group (EAG) considers the clinical evidence from the *post hoc* subgroup of patients who had a confirmed BRCAm and had previously received two lines of platinum-based chemotherapy (the second-line [2L] subgroup [N=172]) in the Phase 3 SOLO2 RCT[7, 8] to be of the most relevance to this review 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 technology appraisal 620).

The EAG notes that the data cut-off (DCO) for the progression-free survival (PFS) and overall survival (OS) data presented in the company submission (CS) differ due to the timing of analyses in SOLO2:

- the primary analysis of PFS (19 September 2016) took place when 187 progression events had occurred (63.4% maturity), approximately 36 months after the first patient was enrolled;
- analysis of OS was planned for when the OS data were approximately 60% mature, and this was the final DCO (3 February 2020). The final DCO took place when 181 survival events had occurred (61% maturity) and occurred approximately 76 months after the first patient was enrolled on the trial.[17]

The EAG requested the company provide updated PFS and time-to-treatment discontinuation (TTD) data using the final DCO during the clarification question stage. The company provided TTD results using the final DCO (Section 0) but reported that they were unable to provide either investigator assessed (IA) PFS or blinded independent central review (BICR) PFS results. The company reported that because the primary endpoint was met at the primary analysis of the SOLO2 trial, there were no further planned analyses of PFS. Patients who remained in the study following the primary analysis were followed up for disease progression according to local clinical practice, with timings and assessments likely to have varied between study sites. In addition, [redacted]

[redacted] The EAG therefore considers it a limitation of the available data and notes that there is thus a discrepancy in the DCO used for the analyses of PFS compared with that of the analyses of OS and TTD from SOLO2. A summary of the key features of SOLO2 is provided in Table 7 and baseline characteristics of the 2L BRCAm subgroup are presented in Appendix 8.1 (Table 29). The EAG's clinical experts reported that the baseline characteristics of the 2L BRCAm SOLO2 subgroup are broadly representative of patients in clinical practice in England, although the baseline performance status is potentially [redacted] than might be expected.

The results for the 2L BRCAm subgroup of SOLO2 are discussed in Section 3.2.

Table 7. Summary of SOLO2 trial (Adapted from CS, Table 4)

Study title	Olaparib tablets as maintenance therapy in patients with platinum sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21) NCT01874353
Study design	Double-blind, randomised, placebo-controlled, multicentre, international Phase 3 study
Population	Patients with platinum-sensitive relapsed HGSOC patients (including patients with primary peritoneal and/or fallopian tube cancer), who are in response (complete or partial) to platinum-based chemotherapy, and who have a confirmed BRCAm
Intervention(s)	Olaparib, 300 mg tablets BD (n=196)
Comparator(s)	Placebo, 300 mg tablets BD (n=99)
Outcomes collected that address Committee's key uncertainties	Overall survival

Abbreviations: BD, twice daily; BRCA, breast cancer susceptibility gene; BRCAm, breast cancer susceptibility gene mutation; HGSOC, high grade serous ovarian cancer; mg, milligram; NA, not applicable.

Sources : Poveda *et al.* 2021;[17] Pujade-Lauraine *et al.* 2017;[18] Data on file[8]

3.1.1.1 Subsequent therapies

In response to clarification, the company provided a breakdown of subsequent treatments received by patients in each arm of the 2L BRCAm subgroup of SOLO2 (clarification question [CQ] response, Table 4) and the EAG provides a summary of those received by >5% of patients in either treatment arm (Table 8). The EAG notes that the most frequently received subsequent treatments in the olaparib arm were [redacted] (Table 8). Subsequent therapies in the placebo arm also included high usage of [redacted] (Table 8).

In the CS it is reported that [redacted] of the 2L patients in the olaparib arm of SOLO2 received subsequent PARP inhibitor following disease progression and there were [redacted] rates of crossover to subsequent PARP inhibitor therapy following disease progression in the placebo arm ([redacted] patients) of the 2L BRCAm subgroup of SOLO2.[17] The EAG is concerned that relapsed olaparib patients [redacted]. In addition, the EAG considers it unclear whether the subsequent PARP inhibitor use in the placebo arm of SOLO2 is reflective of clinical practice in England. The EAG's concerns around this are discussed further in Section 3.2.1.

The EAG notes from the company response to clarification question A3 that the mean number of lines of subsequent treatment in the olaparib arm of the 2L BRCAm subgroup of SOLO2 ([redacted]) was [redacted] than the mean number received by patients in the placebo arm ([redacted]).

Table 8. Subsequent treatments received by >5% of patients in either arm of the 2L BRCAm subgroup of SOLO2 at final DCO (Adapted from CQ response A2, Table 4)

Subsequent regimen	Number of patients (%)		
	Olaparib (N = 110)	Placebo (N = 62)	Total (N = 172)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

3.1.2 SACT data

The CS included a summary of the SACT data[19] collected by Public Health England (PHE) during the managed access period, although the EAG notes that the reporting period for the SACT data was limited to 28 November 2019 to 27 February 2020. As a results of the short data collection period for the SACT cohort, there were no outcome data available from the SACT dataset.

A summary of the SACT data[19] is provided in Table 9 and the baseline characteristics of patients are presented in Appendix 8.1. The EAG considers it important to highlight that the SACT cohort comprises of [redacted] patients and therefore the EAG is unsure of how representative it is of patients in England who would potentially receive olaparib for this indication. The EAG's clinical experts did however consider the SACT cohort characteristics to be broadly representative of patients likely to receive 2L maintenance olaparib in clinical practice in England.

Table 9. Summary of SACT data (Adapted from CS, Table 5)

Study title	SACT data cohort
Study design	Analysis of SACT dataset
Population	Patients with platinum-sensitive relapsed HGSOC patients (including patients with primary peritoneal and/or fallopian tube cancer), who are in response (complete or partial) to second-line platinum-based chemotherapy, and who have a confirmed BRCAm
Intervention(s)	Olaparib, 300 mg tablets BD
Comparator(s)	NA
Outcomes collected that address Committee's key uncertainties	Due to the short data collection time, overall survival data were not reported

Abbreviations: BD, twice daily; BRCAm, breast cancer susceptibility gene mutation; HGSOC, high-grade serous ovarian cancer; NA, not applicable; SACT, systemic anti-cancer therapy

Source: Public Health England (2020)[19]

3.2 SOLO2 results

3.2.1 Overall survival

The company reported that there were high rates of crossover to subsequent PARP inhibitor therapy following disease progression in the placebo arm ([redacted]% patients) of the 2L BRCAm subgroup of SOLO2 that they considered limited the interpretation of the OS data from SOLO2. In addition, the EAG notes that [redacted] of the 2L patients in the olaparib arm of SOLO2 received subsequent PARP inhibitor following disease progression.[17] The company highlighted that the post-progression PARP

inhibitor use in SOLO2 is not generalisable to current UK practice. Additionally, the company reported that they consider the OS benefit of olaparib is likely to be underestimated as a result of treatment switching and that it is likely to have a greater impact on the placebo arm compared to the olaparib arm as the placebo arm will be switching from placebo to a PARP inhibitor whereas the olaparib arm have already received a PARP inhibitor (olaparib).

The SOLO2 statistical analysis plan for OS included a pre-specified exploratory analysis of OS to adjust for treatment switching and the company presented results for both unadjusted and adjusted analyses of OS for the 2L BRCAm subgroup of SOLO2 in the CS.

The EAG notes that PARP inhibitors are now available in the first-line maintenance setting via the CDF,[11, 20] and that the eligibility criteria for PARP inhibitor use are that patients should be treatment naïve to PARP inhibitors.[21] The company and EAG's clinical experts agree that the majority of patients who are eligible for maintenance treatment with a PARP inhibitor will now receive this after first-line treatment with chemotherapy and therefore patients are unlikely to receive PARP inhibitors at 2L or beyond. However, the EAG considers that when patients on routine surveillance who are PARP inhibitor naïve (which is the modelled population for this CDF review) relapse, they will potentially be eligible for third-line olaparib maintenance treatment after another course of platinum-based chemotherapy (as recommended in TA620). Additionally, relapsed olaparib patients would not generally receive further PARP inhibitor maintenance therapy in the NHS as they are no longer PARP inhibitor naïve.

The EAG considers it unclear where in the treatment pathway subsequent PARP inhibitors have been given in the unadjusted placebo-arm of SOLO2 and whether it is reflective of clinical practice in the NHS. Additionally, the EAG is concerned that the use of subsequent PARP inhibitors in the olaparib arm of SOLO2 is not likely to be reflective of clinical practice. The EAG therefore considers adjustment for subsequent PARP inhibitor use in both the placebo and the olaparib arms of SOLO2 should be explored, or evidence presented to demonstrate the minimal impact of subsequent PARP inhibitor use on OS for patients in the olaparib arm of the 2L BRCAm subgroup of SOLO2. The EAG thus requested the company conduct an analysis of OS where treatment switching in both the olaparib and placebo arms is adjusted for but the company reported that this was not possible due to limitations in deriving the acceleration factor (AF) for olaparib, although they provided two exploratory analyses which are discussed below. The company's argument included that there is a lack of validity and justification for the common treatment effect assumption because there is

evidence to suggest a greater relative efficacy of PARP inhibitors in a PARP-naïve setting as compared to rechallenge. The company cited the randomised OReO study, where patients with a BRCA1/2 mutation and prior exposure to PARP inhibitors following 2 or more lines of chemotherapy had a 43% reduction in the risk of progression following rechallenge with a PARP inhibitor (HR 0.57, 95% CI: 0.37 to 0.87; p= 0.022).[22] The company also highlighted that in SOLO2, olaparib resulted in a 70% reduction in the risk of progression (HR 0.30, 95% CI: 0·22 to 0·41; p<0·0001) in patients who were PARP inhibitor naïve.[17]

3.2.1.1 Methods

The company conducted the treatment switch adjustment in the analysis of OS using the method of rank preserving structural failure time (RPSFT) model.[23] The company also reported that they considered other methods such as the inverse probability of censoring weights (IPCW) and the two-stage method but these were deemed unsuitable. Details of the RPSFT model and approach taken by the company to adjust for PARP inhibitor use in the placebo arm are reported in Section A.6.1.2.1 of the CS.

The EAG notes that the RPSFT model assumes a common treatment effect, i.e. that the treatment effect is the same irrespective of when it is received (e.g. at 2nd line or at a later treatment line).[24] In response to clarification question A7, the company provided further justification for the suitability of the use of the RPSFT model and confirmation that it is reasonable to assume the common treatment effect assumption holds. The company reported that evidence of a consistent treatment effect for PARP inhibitors versus placebo regardless of the number of prior chemotherapies at baseline was demonstrated in both the SOLO2 (olaparib) and NOVA (niraparib) trials.[25, 26] In addition, the company conducted sensitivity analyses assuming a lower effect for PARP inhibitors in the placebo arm, and the results demonstrated that the analysis is robust to deviations from the common treatment effect assumption.

In addition, the EAG notes that the company base case includes re-censoring in the adjusted OS analysis and the rationale for the re-censoring was that it minimises informative censoring. The EAG notes that the re-censoring leads to a loss of follow-up in the placebo arm versus the analysis without re-censoring but agrees with the company that re-censoring helps to address the likely informative censoring bias in the analysis of OS. Hence, the EAG believes the model with re-censoring should be preferred, even if such models may lead to slight overestimation of treatment

effects.[27] Results from the placebo-adjusted OS analyses are presented both with re-censoring and without re-censoring in Section 3.2.1.2.

As discussed above, the AF was only applied to patients in the SOLO2 placebo group and the results of the adjusted OS analysis are discussed in Section 3.2.1.2. In response to clarification question A6 the company conducted two exploratory analyses, one of which involved applying the placebo AF to both the placebo and olaparib arms of SOLO2 (exploratory analysis 1) to account for the patients who switched to PARP inhibitors/a subsequent PARP inhibitor following disease progression.

Exploratory analysis 2 involved the censoring of patients in the olaparib arm who received subsequent PARP inhibitors, with the censoring being at initiation of subsequent PARP inhibitor. Further details on the exploratory analyses and their results are provided in Sections 3.2.1.2.2 and 3.2.1.2.3.

The EAG notes that OS data based on the placebo arm of Study 19 is also presented as a scenario analysis within the economic model and that post-progression subsequent PARP inhibitor utilisation was [redacted] in the placebo arm of Study 19[13] compared to in SOLO2 (13.5% versus [redacted]%, respectively).

3.2.1.2 Results

3.2.1.2.1 Unadjusted OS and placebo adjusted OS

At the final DCO of SOLO2 (3 February 2020), the median follow-up for OS was 65.7 months (interquartile range [IQR]: 63.6 to 69.3) with olaparib and 64.5 months (IQR 63.4 to 68.7) with placebo for the full trial population and OS maturity was [redacted]% in the 2L population ([redacted]% and [redacted]% in the olaparib and placebo arms, respectively).[17]

The unadjusted results for median OS demonstrated a benefit of [redacted] months in favour of olaparib versus placebo, [redacted] (median OS of [redacted] months vs [redacted], respectively; hazard ratio [HR] [redacted], 95% confidence interval [CI]: [redacted]; p = [redacted] [Table 10 and Figure 1]).[17]

The results of the placebo adjusted OS for the 2L BRCAm subgroup of SOLO2 demonstrate a median OS benefit of [redacted] months in favour of olaparib versus placebo ([redacted] vs [redacted] months, respectively: Table 10 and Figure 2). The EAG notes that the adjusted median OS results in a [redacted] month greater benefit for olaparib versus placebo when compared with the unadjusted median OS ([redacted] months vs [redacted] months, respectively). However, the EAG notes that while the HRs for median OS

favour olaparib, [redacted]; Table 10).

In response to clarification questions A4 and A10, the company provided the restricted mean survival time for OS and the EAG notes that [redacted] (Table 11).

Table 10. OS from 2L BRCAm subgroup of SOLO2 (Adapted from CS, Table 6 & Table 7, CQ response A5, Table 8 and CQ response A9, Table 10)

OS analysis	Statistic	Olaparib (N=110)	Placebo (N=62)
Unadjusted OS	Events, n/N (%)	[redacted]	[redacted]
	Median OS, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); *p* [2-sided]	[redacted]	
Adjusted OS (placebo arm) with re-censoring	Events, n/N (%)	[redacted]	[redacted]
	Median OS, months (95% CI)	[redacted]	[redacted]
	HR (95% CI)*; *p* [2-sided]	[redacted]	
Adjusted OS (placebo arm) without re-censoring	Median time to event (95% CI)	[redacted]	[redacted]
	Hazard ratio	[redacted]	

*Following National Institute for Health and Care Excellence (NICE) decision support unit (DSU) guidance on treatment switching, the 95% confidence intervals around the (log) hazard ratio estimate for the rank preserving structural failure time (RPSFT) model corrected data were calculated by retaining the p-value from the "unadjusted" 2L analysis.

Abbreviations: 2L, second-line; CI, confidence interval; HR, hazard ratio; N, total number of patients; n, number of patients who experienced survival event; NE, not estimable; OS, overall survival.

Sources : Poveda *et al.* 2021;[17] Data on file[8]

Table 11: Restricted mean survival time for OS for the 2L BRCAm subgroup of SOLO2 using the final DCO (Adapted from CQ response A4, Table 6, and CQ response A10, Tables 11 and 12)

Analysis	Statistic	Olaparib (N = 110)	Placebo (N = 62)
Unadjusted OS	Restricted mean survival time (SE)	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
	p value	[redacted]	
Adjusted OS placebo arm with re-censoring	Restricted mean survival time (SE)	[redacted]	[redacted]

	95% CI	[redacted]	[redacted]
	p value	[redacted]	
Adjusted OS placebo arm without re-censoring	Restricted mean (SE)	[redacted]	[redacted]
	95% CI	[redacted]	[redacted]
	p value	[redacted]	

Abbreviations: CI, confidence interval; DCO, data cut-off; OS, overall survival; SE, standard error.

Figure 1. Kaplan–Meier curve for unadjusted OS from 2L BRCAm subgroup of SOLO2 (Reproduced from CS, figure 1)

[redacted]

Figure 2. Kaplan–Meier curve for OS from the 2L BRCAm subgroup of SOLO2 - placebo arm adjusted for subsequent PARP inhibitor use and with re-censoring (Reproduced from CS, figure 2)

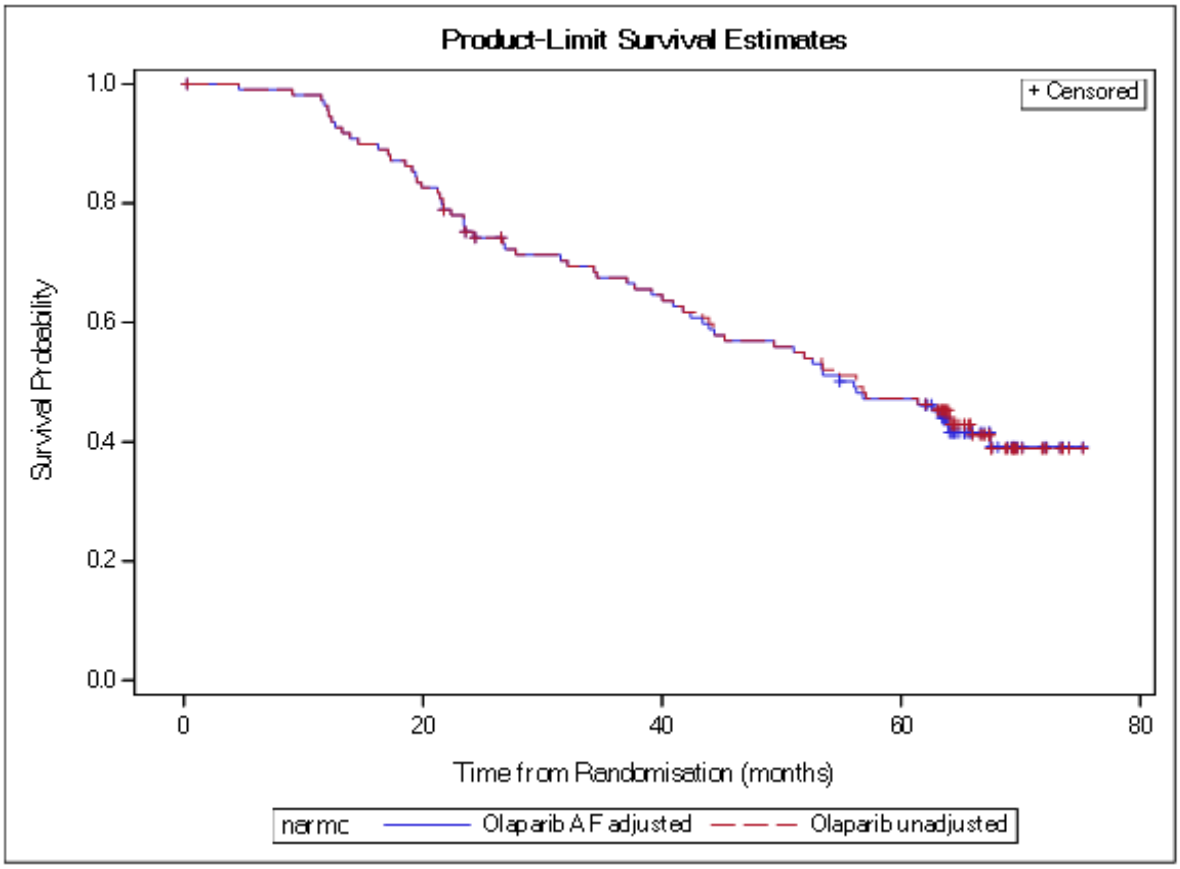
3.2.1.2.2 Exploratory analysis 1: Adjustment of OS in the olaparib arm based on the AF for treatment switching in the placebo arm

In Exploratory analysis 1, the AF applied to the placebo arm of SOLO2 in the placebo adjusted analysis of OS was also applied to the olaparib arm, to adjust for the [redacted] of patients who had subsequent PARP inhibitor in the olaparib arm. The EAG notes that the company consider this exploratory analysis to be conservative because it assumes that the treatment effect and the AF derived by patients with prior exposure to PARP inhibitors is equivalent to that in patients who are PARP inhibitor naïve. The company also reported that their clinical experts and the OReO and SOLO2 studies suggest a greater benefit for olaparib is most likely to be observed when patients are PARP inhibitor naïve.

The Kaplan-Meier plot for the unadjusted olaparib OS is similar to the plot for the adjusted olaparib OS (

Figure 3). Additionally, there is no difference in the HRs for this analysis where both olaparib and placebo are adjusted (HR [redacted]) compared to the placebo only adjusted analysis of OS (HR [redacted] although the EAG notes there is a small difference in the 95% CIs.

Figure 3. Kaplan-Meier plot comparing unadjusted olaparib arm vs the adjusted olaparib arm based on the assumption of equivalence with the AF for the placebo-treatment switching analysis in the 2L population of SOLO2 (Reproduced from response to clarification question A6, figure 1)

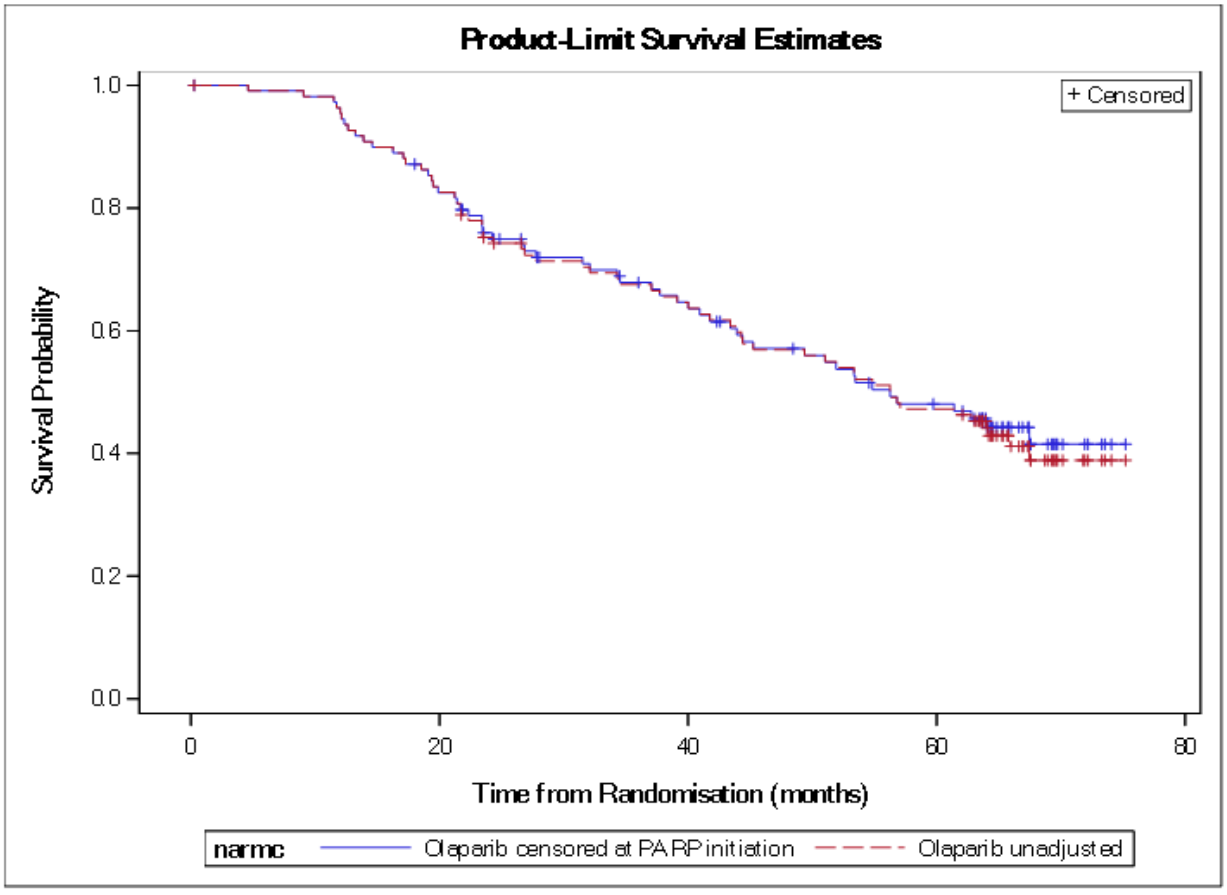


3.2.1.2.3 Exploratory analysis 2: Censoring of patients in the olaparib arm who received subsequent PARP inhibitor

In exploratory analysis 2 (censored approach), the [redacted] of patients in the olaparib arm who switched to receive a PARP inhibitor following disease progression are censored at the point at which they initiate subsequent treatment with a PARP inhibitor. The EAG agrees with the company that this creates a censoring-related selection bias but note it was presented as an alternative to *"Exploratory analysis 1"* since it does not rely on the common treatment effect assumption.

The Kaplan-Meier plot for the olaparib OS from the censored approach (exploratory analysis 2) is similar to the unadjusted olaparib OS until beyond 60 months where there is heavy censoring in the tails of both curves (Figure 4). The EAG notes that the HR and 95% CI for olaparib versus placebo (adjusted placebo arm with re-censoring) using the censored approach is identical to that from the RPSFT model for the adjusted OS (placebo arm) with re-censoring analysis (HR [redacted]).

Figure 4. Kaplan-Meier plot comparing unadjusted olaparib arm vs the censored olaparib group who received subsequent PARP inhibitor in the 2L population of SOLO2 (Reproduced from response to clarification question A6, figure 2)



3.2.2 *Progression-free survival*

PFS was evaluated at the primary analysis of the SOLO2 trial using the data cut-off date of 19 September 2016 and no further analysis on PFS was pre-planned (see Section 3.1.1 for further details); the only PFS results presented in the CS were from the primary analysis where PFS maturity for the overall SOLO2 population was 63.4%. The EAG notes that the median follow-up for PFS at the

primary analysis for the full SOLO2 population was 22.1 months (IQR: 21.9 to 27.4) for patients treated with olaparib and 22.2 months (IQR: 8.3 to 27.5) for patients who received placebo.[17]

The EAG notes that the primary analysis of PFS comprised investigator-assessed (IA) PFS events and that a sensitivity analysis was conducted using blinded independent central review (BICR). PFS was defined as, "[redacted]".[7] Additionally, the EAG notes that it is reported in the CSR for SOLO2 [redacted].

The terms of engagement for this cancer drugs fund review of olaparib specified that, "*The company should present progression-free survival estimates using radiological disease progression data*". The committee did not specify a preference for IA PFS or BICR PFS. The EAG prefers the use of IA PFS in the model for consistency given that time to treatment discontinuation (TTD) data are also used in the model. Additionally, as discussed in the EAG report for TA620[28] the EAG is concerned that the BICR PFS may be confounded by informative censoring of patients because in the full population of the SOLO2 trial, a [redacted]. Additionally, if patients were assumed to have an event at the next scan (+12 weeks), the BICR PFS for the full trial population showed similar results to the IA PFS, in terms of median PFS. However, results for censoring for the BICR analysis were not presented in the CS or in the CSR for TA620 and they weren't provided for the 2L BRCAm subgroup of SOLO2 in the latest CS. The EAG therefore could not explore the reasons for the difference in IA and BICR PFS further, e.g. if informative censoring was impacting the results for BICR PFS in the 2L BRCAm subgroup of SOLO2 and whether informative censoring was balanced between the treatment groups. The EAG therefore is concerned that the BICR PFS may be subject to bias from informative censoring and thus considers the IA PFS likely to be less confounded and more reflective of clinical practice.

Analysis of IA PFS for the 2L BRCAm subgroup of SOLO2 resulted in a median time to progression benefit of [redacted] months with olaparib compared with placebo (median PFS: [redacted] and [redacted] months, for olaparib and placebo, respectively; Table 12 and Figure 5).[7] PFS assessed by BICR in the SOLO2 2L BRCAm subgroup was [redacted] for olaparib with the BICR assessment. The BICR PFS analysis resulted in a median time to

progression benefit of [redacted] months with olaparib versus placebo (median PFS: [redacted] and [redacted] months, for olaparib and placebo, respectively; Table 12 and Figure 6). The EAG notes that the HR is [redacted] IA PFS and BICR PFS analyses, although the EAG considers the HR should be interpreted with caution. This is because in TA620, the company showed that the PHs assumption is unlikely to hold for the primary analysis of PFS in SOLO2 (full trial population) and hence the resulting HR and associated p-value are likely to be misleading.

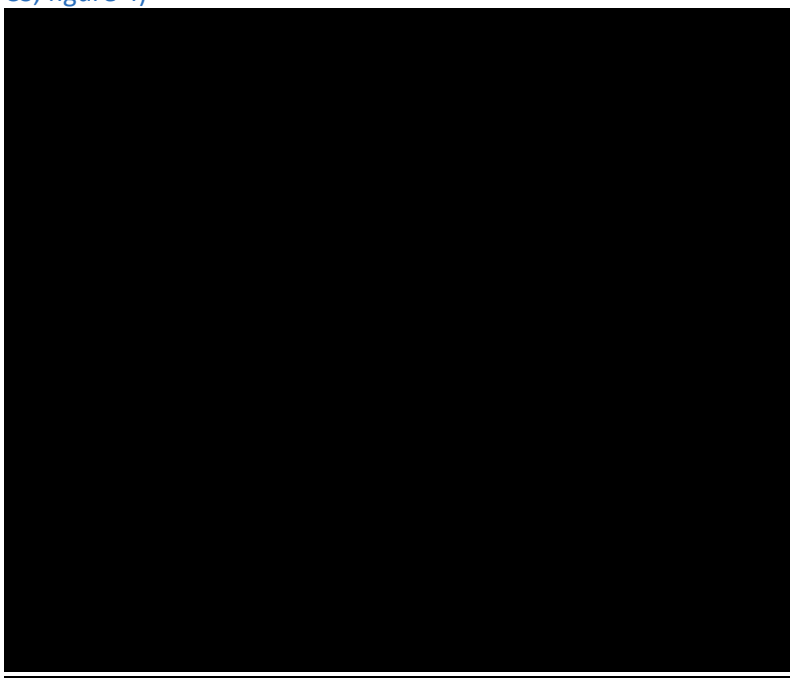
Table 12. Progression-free survival from 2L BRCAm subgroup of SOLO2 (Adapted from CS, Table 8 and Table 9)

PFS assessment	Statistic	Olaparib (N=110)	Placebo (N=62)
Investigator-assessed PFS	Events, n/N (%)	[redacted]	[redacted]
	Median time to event, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p [2-sided]	[redacted]	
Blinded independent central review PFS	Events, n/N (%)	[redacted]	[redacted]
	Median time to event, months (95% CI)	[redacted]	[redacted]
	HR (95% CI); p [2-sided]	[redacted]	

Abbreviations: CI, confidence interval; HR, hazard ratio; N, total number of patients; n, number of patients who experienced progression event; NE, not estimable; PFS, progression-free survival.
Sources: SOLO2 CSR;[7] Data on file[8]

Figure 5. Kaplan–Meier curve for IA PFS from 2L BRCAm subgroup of SOLO2 (Reproduced from CS, figure 3)

Figure 6. Kaplan–Meier curve for PFS by BICR for 2L BRCAm subgroup of SOLO2 (Reproduced from CS, figure 4)



3.2.3 *Time to treatment discontinuation*

The EAG notes that the data for time to treatment discontinuation (TTD) reported in the CS relate to the primary analysis of SOLO2 that took place using the data cut-off of 19 September 2016 when there was only 63.4% maturity of PFS. At the time of the primary analysis there were [redacted] 2L patients ([redacted] in the olaparib arm and [redacted] in the placebo arm) that had discontinued treatment in the 2L BRCAm subgroup of the SOLO2 trial and treatment with olaparib resulted in a median time to event benefit of [redacted] months versus placebo (Table 13 and Figure 7).

In response to clarification question A7d, the company provided the HR for TTD at the final DCO ([redacted]) and the restricted mean survival time for TTD at the final DCO (Table 14). The EAG notes that the HR for the final DCO [redacted], respectively).

Table 13. Time to treatment discontinuation for 2L BRCAm subgroup of SOLO2 (Adapted from CS, Table 10)

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

Abbreviations: CI, confidence interval; HR, hazard ratio; N, total number of patients; n, number of patients experiencing time to treatment discontinuation event.

Source: Data on file[8]

Table 14. Restricted mean survival time for TTD at the final DCO for the 2L BRCAm subgroup (Reproduced from CQ response A4, Table 7)

	Olaparib (N = 110)	Placebo (N = 62)
Restricted mean survival time (SE)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
p value	[redacted]	

Abbreviations: CI, confidence interval; SE, standard error.

Figure 7. Kaplan–Meier curve for TTD in the 2L BRCAm subgroup of SOLO2 (Reproduced from CS, figure 5)

[redacted]

3.2.4 Adverse events

In their response to the clarification questions, the company provided the proportion of patients experiencing treatment emergent adverse events (AEs) of Grade 3 or higher in at least three percent of patients for the full SOLO2 trial population at the final DCO (Table 15). In total, eight adverse events of Grade 3 or higher occurred in at least three percent of patients, of which six were more common in the olaparib arm than placebo arm. The most common AEs of Grade 3 or higher were anaemia (21% of olaparib patients, 2% of placebo patients), neutropenia (7% of olaparib patients, 4% of placebo patients) and fatigue and asthenia (6% of olaparib patients, 2% of placebo patients). The EAG notes that the proportion of patients experiencing each of the Grade 3 or higher AEs reported in Table 15 are generally consistent with the AEs reported at the primary analysis DCO.[7, 18]

Table 15. Treatment emergent AEs of CTCAE >Grade 3 in at least 3% of patients in the full SOLO2 trial population, safety analysis set, final DCO (Reproduced from clarification response A11, Table 13)

	Olaparib (N=195)	Placebo (N=99)
Nausea	6 (3%)	0
Fatigue and asthenia	11 (6%)	2 (2%)
Anaemia	41 (21%)	2 (2%)
Vomiting	5 (3%)	1 (1%)
Abdominal pain	6 (3%)	3 (3%)
Constipation	0	3 (3%)

Leukopenia	7 (4%)	0
Neutropenia	14 (7%)	4 (4%)

Abbreviations: AE, adverse events; CTCAE, common terminology criteria for adverse events

The company also provided data for the Grade 3 or higher treatment-emergent AEs within the 2L BRCAm subgroup of SOLO2 (company response to clarification questions, Table 14). While the 2L BRCAm subgroup AE data corresponds to the survival data used in this submission, the EAG considers the full-trial population to be the most informative source of AEs for the economic analysis. The EAG believes it unlikely that there would be any large differences in safety related to the line of therapy where olaparib is used, and as such the AEs should be informed by the larger sample size of the full population. The EAG notes that the frequency of adverse events was [redacted] the full trial population and 2L BRCAm subgroup, [redacted] in the full trial population.

3.3 Conclusions of the clinical effectiveness section

In general, the EAG considers that the company has adhered to the committee's preferred assumptions from the ToE, although the EAG still considers there to be uncertainty in the estimates of long-term OS for olaparib compared to routine surveillance. The company reported that there were high rates of crossover to subsequent PARP inhibitor therapy following disease progression in the placebo arm ([redacted]%] patients) of the 2L BRCAm subgroup of SOLO2 that they considered limited the interpretation of the OS data from SOLO2. In addition, the EAG notes that [redacted]) of the 2L patients in the olaparib arm of SOLO2 received subsequent PARP inhibitor following disease progression.[17] The EAG is concerned about the use of subsequent PARP inhibitors in both the olaparib and placebo groups of the 2L BRCAm subgroup of SOLO2 and that the post-progression PARP inhibitor use in SOLO2 is not generalisable to current UK practice. The exploratory analyses conducted by the company to investigate the impact of retreatment with a PARP inhibitor in the [redacted] of patients in the olaparib arm of SOLO2 suggest there is little impact on the OS estimates of olaparib and the EAG notes that the company base case analysis only includes adjustment for the [redacted] of placebo-treated patients who received subsequent PARP inhibitor in 2L BRCAm subgroup of SOLO2. The EAG considers that exploratory analysis 1, where the AF for the placebo arm of SOLO2 is also applied to the olaparib arm, is the most appropriate for assessing the impact on OS of the use of subsequent PARP inhibitors by patients in the olaparib arm and considers given the data limitations that it is reasonable to conclude that subsequent PARP inhibitor use in the olaparib arm of the BRCAm 2L subgroup of SOLO2 is likely to have minimal impact on the estimates of OS.

In terms of the results from SOLO2, [redacted]. The placebo adjusted OS for the 2L BRCAm subgroup of SOLO2 demonstrated a median OS benefit of [redacted] months in favour of olaparib versus placebo ([redacted] vs [redacted] months, respectively). Analysis of IA PFS for the 2L BRCAm subgroup of SOLO2 resulted in a median time to progression benefit of [redacted] months with olaparib compared with placebo (median PFS: [redacted] and [redacted] months, for olaparib and placebo, respectively) and PFS assessed by BICR in the 2L BRCAm subgroup of SOLO2 was [redacted] for olaparib with the BICR assessment. Finally, TTD analyses resulted in a median time to event benefit of [redacted] months with olaparib versus placebo. The EAG also notes that the proportion of patients experiencing each of the Grade 3 or higher AEs using the final DCO are generally consistent with the AEs reported at the primary analysis DCO.

The EAG notes that there is a discrepancy in the DCO used for the PFS data compared with the OS and TTD data presented in the CS. The DCO used for the PFS analyses is from the primary analysis (19 September 2016), whereas the final DCO (3 February 2020) is used for the analyses of TTD and OS. The company reported that because the primary endpoint was met at the primary analysis of the SOLO2 trial, there were no further planned analyses of PFS. [redacted] The EAG therefore considers it a limitation of the available data and notes that there is thus a discrepancy in the DCO used for the analyses of PFS compared with that of the analyses of OS and TTD from SOLO2. The EAG notes that in the primary analysis the PFS maturity for the overall SOLO2 population was 63.4% and OS maturity at the final DCO was [redacted]% in the 2L BRCAm subgroup of SOLO2.

The ToE also required real-world data to be collected within the CDF by Public Health England (PHE) to help support the generalisability of the SOLO2 data. However, the EAG notes that the reporting period for the SACT data collected by PHE during the managed access period was limited and as a result of the short data collection period for the SACT cohort, there were no outcome data available from the SACT dataset. Additionally, the SACT cohort comprises of [redacted] patients and therefore the EAG is unsure of how representative it is of patients in England who would potentially receive olaparib for this indication. The EAG thus considers the 2L BRCAm subgroup from SOLO2 to provide the most robust estimates of efficacy for olaparib use as a maintenance treatment for people who have relapsed, BRCAm, platinum sensitive high-grade epithelial ovarian, fallopian tube or peritoneal

cancer that is in complete or partial response to the second course of platinum-based chemotherapy.

4 Cost effectiveness

This section presents a summary and critique of the changes made to the company's cost-effectiveness analysis of olaparib for the maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy as a result of the cancer drugs fund (CDF) review. For an overview of the company's original base case, Evidence Assessment Group (EAG) critique and committee discussion, please refer to TA620.[5]

Section 4.1 presents a summary and critique of the company's updates to the economic analysis. Section 5 presents the results of the company's updated model and Section 6 presents the results of additional exploratory analyses undertaken by the EAG.

Table 16 presents an overview of the company's CDF base results. As per the National Institute of Health and Care Excellence (NICE) methods guide, the probabilistic incremental cost-effectiveness ratio should be used for decision making.[29] The company have an approved patient access scheme (PAS) discount of [redacted] and all results presented in this report are inclusive of the discount.

Table 16. Company's base case results post clarification ([redacted] PAS discount)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results (10,000 iterations)							
Routine surveillance	[redacted]	-	[redacted]	-	-	-	-
Olaparib	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]

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

4.1 Summary and critique of the company's submitted economic evaluation by the EAG

Table 17 presents an overview of the company's updates to the cost-effectiveness analysis of olaparib and the EAG's comments. Overall, the company's updates are in line with the terms of engagement for the CDF review.

Table 17. Summary of company's updates to the economic model

Model feature	Company's original approach	Updated company approach	EAG comment
Population and source of clinical data	Patients with platinum-sensitive relapsed ovarian cancer, who are in response to platinum-based chemotherapy - **ITT population from Study 19**	Patients with a BRCAm after two courses of platinum-based chemotherapy - **2L BRCAm subgroup of SOLO2**	Aligned with the Terms of Engagement
Baseline characteristics	Informed by Study 19	Informed by SOLO2	Appropriately changed to align with the updated population and source of clinical data
Time horizon	30 years	50 years	Aligned with the Terms of Engagement
Definition and source of PFS	Proxy of time to first-subsequent therapy from Study 19	Investigator assessed PFS from SOLO2 (BICR PFS explored in scenario analysis)	Aligned with the Terms of Engagement
Overall Survival	Informed by Study 19	Informed by SOLO2	Aligned with the Terms of Engagement
Subsequent treatment	Informed by Study 19	Informed by SOLO2	Appropriately changed to align with the source of clinical data

Abbreviations: 2L, second-line; BICR, blinded independent central review; BRCAm, breast cancer susceptibility gene mutation; EAG, Evidence Review Group; ITT, intention-to-treat; PFS, progression-free survival

4.1.1 Population

As per the CDF Terms of Engagement and the NICE final scope[10], the population included in the updated economic model is patients who have relapsed, breast cancer susceptibility gene-mutated (BRCAm), platinum-sensitive high-grade epithelial ovarian, fallopian tube or peritoneal cancer that is in response (complete or partial) to the second course of platinum-based chemotherapy.

To inform the model, the company used baseline characteristics and data from a *post hoc* subgroup of second-line only BRCAm patients from SOLO2 (Appendix 8.1). The mean age and weight in the model are 56.1 years and 71kg, respectively.

The EAG considers the population of the model adheres to the CDF Terms of Engagement[10].

4.1.2 Modelling approach

The company's model structure is the same as that presented in TA620[5]. The key changes to the model as part of this CDF review are the clinical data that inform each health state. In the updated model, the proportion of patients occupying a health state during any given cycle is based on parametric survival curves for the clinical outcomes of progression-free survival (PFS) (used to model the progression-free health state), overall survival (OS) and TTD (used to estimate treatment duration). The proportion of patients occupying the progressed health state for any given cycle is calculated as the difference between OS and PFS per cycle. Survival data in the model are informed by the second-line *post hoc* subgroup from SOLO2, per the committee preferences from TA620[5].

4.1.3 Treatment effectiveness

Treatment effectiveness in the company's updated base case analysis for the CDF review was informed by the second-line *post hoc* subgroup from SOLO2, per the committee preferences from TA620[5]. The key outcomes of PFS and OS inform the economic model. In SOLO2, the primary end-point of PFS was met and the data cut used in the model is from September 2016 and no further data on PFS were collected. The data cut used for OS in the model is from February 2020.

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. See section A.7 of the company submission for AIC and BIC statistics for PFS, OS and TTD.

Progression-free survival

In the company's base case, PFS is based on investigator assessment (IA) as per the EAG preferred approach in TA620[5]. In SOLO2, IA PFS was defined as the time from randomisation until disease progression (according to modified RECIST v1.1 guidelines) or death from any cause. Additionally, the company explored PFS based on blinded independent central review assessment (BICR) in a scenario analysis.

Out of the assessed survival distributions, the company selected the log-logistic distribution (Figure 8) as the most plausible extrapolation of IA PFS, based on statistical and visual fit, as well as clinical expert opinion obtained by the company. At 5 years, PFS is predicted to be approximately [redacted] for routine surveillance and [redacted] for olaparib, which the EAG's clinical experts considered to be reasonable. For the BICR scenario analysis, the log-logistic was also selected and predicted PFS to be to be approximately [redacted] for routine surveillance and [redacted] for olaparib. However, as discussed in Section 3.2.2, the BICR analysis maybe confounded by informative censoring, thus the EAG considers the company's base case using IA PFS is appropriate.

Figure 8. Investigator assessed progression-free survival Kaplan-Meier and log-logistic distribution for olaparib and routine surveillance

Overall survival

As mentioned in Section 3.2.1, the company adjusted OS for placebo to account for crossover to Poly (ADP-ribose) polymerase (PARP) inhibitors upon progression. In the economic model, unadjusted OS for olaparib and adjusted OS for routine surveillance is used for the survival extrapolations. Out of the assessed survival distributions, the company selected the lognormal distribution (Figure 9) as the most plausible extrapolation of OS, based on statistical and visual fit, as well as clinical expert

opinion obtained by the company. Survival at 20 years based on the lognormal distribution was [redacted] for olaparib patients and less than [redacted] for routine surveillance patients, which the company's clinical experts considered plausible.

Figure 9. Overall survival Kaplan-Meier and lognormal distribution for olaparib and adjusted routine surveillance

4.1.3.1 EAG critique

The key issue in TA620[5] was around immature OS data, which for the current CDF review has been resolved by the final data cut-off (DCO) from SOLO2. However, as mentioned in Section 3.2.1, there were high rates of crossover to subsequent PARP inhibitors following disease progression in the placebo arm of the 2L subgroup of SOLO2 but also a limited number of olaparib patients received a subsequent PARP inhibitor. The company highlighted that the post-progression PARP inhibitor use in SOLO2 is not generalisable to current UK practice as the majority of patients who are eligible for maintenance treatment with a PARP inhibitor will receive this after first-line treatment with platinum-based chemotherapy and therefore patients are unlikely to receive PARP inhibitors at third line or beyond. Though the EAG notes, that as patients would receive a PARP inhibitor after first-line treatment with platinum-based chemotherapy, patients are unlikely to receive a PARP inhibitor at second-line or beyond.

Consequently, the company included adjusted OS for routine surveillance to account for treatment switching but did not adjust the olaparib data. However, the EAG considers that it is appropriate for

the olaparib arm to be adjusted for retreatment with PARP inhibitors to better reflect the benefit that would be seen in UK clinical practice. Currently retreatment with a PARP inhibitor is not recommended in the NHS. Thus, the EAG requested the company conduct an analysis of OS where treatment switching in both the olaparib, and placebo arms is adjusted. In their clarification response, the company advised that OS adjustment of the olaparib arm using the Rank preserving structural failure time (RPFST) method was not possible as an appropriate acceleration factor could not be estimated. Instead, the company conducted two analyses to explore the impact of retreatment with a PARP inhibitor on olaparib OS. For further detail on these analyses, please see Section 3.2.1. The company's exploratory analyses concluded there was little impact on survival for olaparib patients as a result of retreatment with a PARP inhibitor and thus they did not explore the results in the economic model.

However, a key consideration for long-term survival of patients on routine surveillance who are PARP inhibitor naïve (which is the modelled population for this CDF review), is that when these patients relapse, they will be eligible for third-line olaparib maintenance treatment after another course of platinum-based chemotherapy (as recommended in TA620). Additionally, relapsed olaparib patients would only receive routine surveillance as maintenance in the NHS as they are no longer PARP inhibitor naïve. However, currently there are second-line PARP inhibitor maintenance treatments recommended for use in the NHS, thus the EAG agrees with the company that it is likely the population eligible for third-line olaparib is diminishing. Nonetheless, the current CDF review needs to consider the treatment pathway as it was at the time of the publication of TA620, when no second-line PARP inhibitor maintenance treatments were recommended for routine use in the NHS.

As accepted in TA620[5], third-line olaparib maintenance treatment is associated with improved survival outcomes for PARP inhibitor naïve patients who would have otherwise received routine surveillance as maintenance. In their clarification response to question A7, the company stated that in SOLO2 subgroup analyses, patients that received second-line olaparib maintenance treatment experienced a similar relative benefit versus placebo to those that received third-line olaparib maintenance treatment. Additionally, the EAG's clinical experts considered that the survival benefit of maintenance olaparib will be similar when given at second- or third-line.

As such, the EAG considers that the survival benefit of third-line maintenance treatment for relapsed routine surveillance patients should be captured in the cost-effectiveness analysis to reflect the treatment pathway in the NHS. One approach to capture the improved survival benefit for routine

surveillance patients would be for the company to explore unadjusted OS for the routine surveillance arm in the model, but there may be limitations to this analysis as it assumes all subsequent PARP inhibitor use would be limited to third-line maintenance only. However, it is not clear to the EAG when subsequent PARP inhibitors were given to placebo patients in SOLO2, for instance if it was just limited to third-line maintenance treatment.

Instead, the EAG considers that over time, the OS curves for second-line olaparib and routine surveillance may eventually converge. The assumption of converging overall survival is a deviation from TA620, but in TA620 the cost-effectiveness of olaparib maintenance treatment was considered by line of therapy and was informed by Study 19, which had minimal crossover in the placebo arm.

In their assessment of extrapolations for OS, the company identified that the 1-knot spline resulted in converging curves but considered this clinically implausible based on the data observed in SOLO2. However, the EAG considers the 1-knot spline to produce clinically plausible estimates of survival given survival for relapsed routine surveillance patients is likely to improve, while for relapsed olaparib patients, survival is likely to decline. Additionally, the 1-knot spline had a better statistical fit and better visual fit to the placebo arm than the lognormal used for the base case (Figure 10).

Figure 10. Overall survival Kaplan Meier and 1-knot spline for olaparib and adjusted routine surveillance

The EAG notes that the 1-knot spline extrapolation utilises placebo KM data from SOLO2 adjusted for crossover to PARP inhibitors, thus the survival benefit of subsequent PARP inhibitors is removed. However, as mentioned previously, it is unknown if PARP inhibitors received by placebo patients in

SOLO2 were restricted to third-line maintenance treatment. As such, the EAG considers the convergence in the survival curves using the 1-knot spline a reasonable approach to account for the benefit of third-line olaparib maintenance treatment and has included it in the EAG base case presented in Section 6.3. However, as OS for routine surveillance exceeds OS for olaparib from approximately year 18 onwards, the EAG capped routine surveillance OS to olaparib.

An alternative approach to account for the survival benefit of third-line olaparib maintenance treatment for routine surveillance patients is to apply the inverse of the unadjusted OS hazard ratio (HR) to the olaparib OS extrapolation as this had not been adjusted for subsequent PARP inhibitor use. Thus, the EAG ran an additional scenario using the unadjusted OS HR of [redacted] to the lognormal olaparib OS extrapolation and curves are presented in Figure 11. The EAG notes that due to a paucity of time, the proportional hazards assumption could not be tested, thus the unadjusted OS HR scenario should be considered illustrative. A comparison of survival predictions for the company's base case, the 1-knot spline and unadjusted HR scenarios are presented in Table 18.

To align benefits with costs, the cost of third-line maintenance olaparib has been included in the scenarios (presented in Section 5.2.2 for the 1-knot spline scenario and Section 6.3 for the unadjusted OS HR scenario). For a discussion of third-line olaparib maintenance treatment costs, please refer to Section 4.1.4.

Figure 11. Overall survival lognormal for olaparib and unadjusted OS HR for routine surveillance

Table 18. Comparison of OS survival predictions based on different approaches

Scenario	Olaparib			Routine surveillance		
	5 years	10 years	20 years	5 years	10 years	20 years
Company base case - lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario - 1-knot spline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted OS HR applied to olaparib lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HR, hazard ratio; OS, overall survival.

*In the EAG base case, routine surveillance OS is capped to olaparib OS.

4.1.4 *Subsequent treatments*

In TA620, subsequent treatments were informed by Study 19. However, to align with the source of clinical data in the updated model, the company included data on subsequent treatments received by each arm from SOLO2. As per TA620[5], the company costed the 10 most common subsequent treatments received in SOLO2 and applied these in the economic model. Number of cycles of treatment, drug acquisition and administration costs of subsequent treatments (presented in Table 19) are as per TA620.[5] Table 20 presents the costs of subsequent treatments based on SOLO2 applied in the company's updated model. Commercial medicines unit (CMU) prices are available for subsequent treatments and analysis including these prices are presented in the confidential appendix to this report.

Table 19. Drug acquisition and administration cost associated with each treatment regimen

Treatment	Cycles per treatment regimen	Vials per admin.	Cost of drug per cycle	Admin. per 30.44-day cycle	Cycle length (days)	Cost of admin.[b]	Total cost
Bevacizumab	10[a]	3	£1,913.34	0.7	21	£110	£20,237
Carboplatin	6	1	£12.92	0.7	21	£110	£740
Cisplatin	4	3	£9.27	0.7	21	£110	£479
Cyclophosphamide	6	2	£35.86	0.7	21	£110	£878
Docetaxel	6	1	£14.23	0.7	21	£110	£748
Doxorubicin	6	2	£6.68	0.9	28	£158	£985
Gemcitabine	6	2	£10.69	0.7	21	£110	£727
Etoposide	4	1	£33.29	3.4	21	£676	£2,839
Paclitaxel	6	2	£23.02	0.7	21	£110	£801
Topotecan	6	1	£395.82	3.4	21	£676	£6,433
Olaparib	[redacted]	-	[redacted]	-	-	£0.00	[redacted]

Abbreviations: admin, administrations

* TTD for olaparib based on SOLO2 data cut from TA620. TTD based on the final data cut from SOLO2 is now [redacted] months.

** Inclusive of [redacted] patient access scheme discount

[a]Maximum number of cycles to be administered as per the Summary of Product Characteristics for bevacizumab. This assumption is considered conservative, as a greater proportion of patients in the olaparib arm of SOLO2 received subsequent treatment with bevacizumab, compared to the placebo arm.

[b]One initial infusion at £173.99 plus subsequent infusions at £205.09.

Table 20. Cost of subsequent treatment based on SOLO2

Treatment	Olaparib		Routine Surveillance		Total cost of regimen	Olaparib	RS
	Number of regimens recorded in SOLO2	%	Number of regimens recorded in SOLO2	%			
Bevacizumab	11	7.53%	7	7.07%	£20,237	£1,525	£1,431
Carboplatin	40	27.40%	23	23.23%	£740	£203	£172
Cisplatin	17	11.64%	8	8.08%	£479	£56	£39
Cyclophosphamide	8	5.48%	9	9.09%	£878	£48	£80
Docetaxel	4	2.74%	1	1.01%	£748	£20	£8
Doxorubicin	15	10.27%	9	9.09%	£985	£101	£90
Gemcitabine	26	17.81%	18	18.18%	£727	£129	£132
Etoposide	1	0.68%	0	0.00%	£2,839	£19	£0
Paclitaxel	21	14.38%	15	15.15%	£801	£115	£121
Topotecan	3	2.05%	9	9.09%	£6,433	£132	£585
Olaparib	0	0.00%	0	0.00%	-	-	-
Total	146	100%	99	100%	-	£2,349	£2,657

Abbreviations: RS, routine surveillance

4.1.4.1 EAG critique

In TA620, the company included the costs of subsequent third-line olaparib maintenance treatment for routine surveillance patients but has opted to omit this in the updated model. The company stated that in current UK practice a small and diminishing number of patients will be PARP inhibitor naïve at third-line and retreatment with a PARP inhibitor is not recommended in the NHS. However, as mentioned in Section 4.1.3.1, at the time of the publication of TA620[5] there were no second-line PARP inhibitor maintenance treatments were recommended by NICE for routine use in the NHS, thus the current CDF review needs to consider the treatment pathway as it was then. Furthermore, the EAG considers that relapsed routine surveillance patients who are PARP inhibitor naïve in the NHS

would receive third-line olaparib maintenance treatment and are likely to have improved survival outcomes, thus costs should be aligned to the benefits.

At the request of the EAG, the company supplied a scenario including the costs of subsequent olaparib maintenance treatment using the third-line SOLO2 TTD from TA620[5] ([redacted] months) and an alternative scenario using the third-line TTD from the final SOLO2 DCO ([redacted] months). Based on data from SOLO2, [redacted] patients in the placebo arm received subsequent olaparib and this has been used in the scenarios. Results of both scenarios are presented in Section 5.2.2 and are inclusive of the PAS discount of [redacted] for third-line olaparib maintenance treatment. The EAG has included the costs of subsequent olaparib maintenance treatment using the third-line TTD from the final SOLO2 DCO in its base case, presented in Section 6.3.

4.1.5 Adverse events

For the base case analysis, the company included grade 3 or higher adverse events (AEs) that were reported by at least 3% of patients in either treatment arm of SOLO2 as per TA620, presented in Table 21. As per TA620, only the costs of AEs are included in the model as the impact of these on quality of life is assumed to be captured in the utility estimate from SOLO2. The unit costs of AEs are consistent with TA620.[5]

Table 21. Grade 3 or higher AEs implemented in the model

Adverse event	Olaparib (N = 195)	Placebo (N = 99)
Anaemia	38 (19.5%)	2 (2.0%)
Neutropenia	5 (2.6%)	4 (4.0%)
Abdominal pain	5 (2.6%)	3 (3.0%)
Fatigue	6 (3.1%)	2 (2.0%)
Vomiting	5 (2.6)	1 (1.0)

Abbreviations: AE, adverse event.

4.1.5.1 EAG critique

The EAG could not verify the AE data used in the model against the data supplied in the company's clarification response to A11 and considers that model maybe based on an older data cut from SOLO2 rather than the final DCO. As such, the EAG has updated the model with the AE data from the final DCO from SOLO2 (Table 22) for the full trial population and presents a corrected company base case in Section 6.1.

Table 22. Grade 3 or higher TEAEs based on the final DCO from SOLO2 - full trial population (Table 13 of the company clarification response)

Adverse event	Olaparib (N = 195)	Placebo (N = 99)
Anaemia	41 (21%)	2 (2%)
Neutropenia	14 (7%)	4 (4%)
Abdominal pain	6 (3%)	3 (3%)
Fatigue and asthenia	11 (6%)	2 (2%)
Vomiting	5 (3%)	1 (1%)
Nausea*	6 (3%)	0
Constipation*	0	3 (3%)
Leukopenia*	7 (4%)	0

Abbreviations: TEAE, treatment emergent adverse event.
* Not included in the model.

The EAG notes that based on the company's response to clarification question A11, nausea, constipation and leukopenia have been omitted from the model. However, due to a paucity of time, the EAG were unable to include these costs in the model but consider that the impact of the omission on the ICER is minimal and unlikely to be a decision modifier.

4.1.6 Costs

Olaparib costs in the model are estimated based on an extrapolation of TTD KM data from the September 2016 data cut from SOLO2. As with the extrapolation of PFS and OS, the company explored 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 AIC and BIC statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the economic model. See section A.7 of the company submission for AIC and BIC statistics for TTD.

Of the assessed survival distributions, the company selected the 1-knot hazard spline (Figure 12) as the most plausible extrapolation of TTD, based on statistical and visual fit, as well as clinical expert opinion obtained by the company. In the company's base case, TTD was not capped by PFS. Consequently, extrapolated TTD exceeds PFS between months 19 and 53 in the company's base case (see Figure 13).

Figure 12. Time to treatment discontinuation Kaplan Meier and 1-knot hazard spline for olaparib

Figure 13. Comparison of modelled TTD and PFS

4.1.6.1 EAG critique

The EAG considers the company's extrapolation of TTD to be appropriate. However, in the company base case, TTD is not capped to PFS and the company's selected extrapolation of TTD results in estimates exceeding PFS between months 19 and 53. According the summary of product characteristics (SmPC)[30] for olaparib, treatment should be continued until progression of the

underlying disease or unacceptable toxicity. As such, the EAG considers TTD should not exceed PFS. Upon request of the EAG, the company supplied a scenario capping TTD to PFS (see Section 5.2.2) but did not implement this in their base case. Nonetheless, the EAG considers it is methodologically appropriate to include a cap on TTD and has included this in the EAG base case, presented in Section 6.3.

5 Cost effectiveness results

5.1 Company's cost effectiveness results

The company's deterministic and probabilistic base case results post clarification are presented in Table 23. As per the National Institute of Health and Care Excellence (NICE) methods guide, the probabilistic incremental cost-effectiveness ratio (ICER) should be used for decision making.[29] The probabilistic sensitivity analysis (PSA) scatterplot and cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) is presented in Figure 14. Based on these analyses, the probability that olaparib is cost effective versus routine surveillance is [redacted] at a willingness to pay (WTP) threshold of £20,000 and £30,000.

Results presented are inclusive of the company's patient access scheme (PAS) discount of [redacted].

Table 23. Company's base case results post clarification ([redacted] PAS discount)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results (10,000 iterations)							
Routine surveillance	[redacted]	-	[redacted]	-	-	-	-
Olaparib	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]

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

Figure 14. Probabilistic sensitivity analysis scatterplot and cost-effectiveness plane (Figure 5 of the company's clarification response)

Figure 15. Cost-effectiveness acceptability curve (Figure 6 of the company's clarification response)

5.2 Company's sensitivity analyses

5.2.1 One-way sensitivity analysis

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the values of parameters from their means by ±20%. The results of the OWSA are presented in Figure 16 for the five most influential parameters.

Figure 16. Tornado diagram (Figure 7 of the company's clarification response)

5.2.2 Scenario analysis

Deterministic results of key scenario analyses conducted by the company, inclusive of the [redacted] PAS discount, are presented in Table 24. In their clarification response, the company also provided a number of scenarios upon the request of the Evidence Assessment Group (EAG), also presented in Table 24.

Table 24. Scenario analysis

	Parameter	Base case	Scenario	ICER (£/QALY)
0	**Base case**			[redacted]
1	PFS extrapolation	Log-logistic	Lognormal	[redacted]
2	OS extrapolation	Lognormal	Log-logistic	[redacted]
3	TTD extrapolation	Spline 1-knot	Generalised gamma	[redacted]
4			Weibull	[redacted]
5	PFS estimates	Investigator-assessed	BICR	[redacted]

6	Placebo arm OS estimates	SOLO2	Study 19	[redacted]
7	Olaparib dosing	SOLO2 final DCO - 566.8 mg	TA620 - 568.2 mg	[redacted]
EAG requested scenarios				
8	Costs of 3LM olaparib	Excluded	Included - TA620 TTD from SOLO2 ([redacted] months)	[redacted]
9			Included - SOLO2 final DCO) ([redacted] months)	[redacted]
10	OS extrapolation + costs of 3LM olaparib	Lognormal + costs of 3LM olaparib excluded	1-knot spline (hazard) + costs of 3LM olaparib included (TA620 TTD from SOLO2 - [redacted] months)	[redacted]
11			1-knot spline (hazard) + costs of 3LM olaparib included (TTD from SOLO2 final DCO - [redacted] months)	[redacted]
12	TTD extrapolation	TTD not capped by PFS	TTD capped by PFS	[redacted]

Abbreviations: 3LM, third-line maintenance; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RS, routine surveillance; TTD, time to maintenance treatment discontinuation.

6 Additional economic analysis undertaken by the EAG

6.1 Model corrections

As mentioned in Section 4.1.5.1, the Evidence Assessment Group (EAG) considers that adverse event (AE) data in the model maybe from an older data cut from SOLO2 rather than the final data cut presented in the company's clarification response. As such, the EAG updated the model with AE data supplied by the company in clarification A11. Results of the company's corrected base case are presented in Table 25. Results presented are inclusive of the company's patient access scheme (PAS) discount of [redacted].

Table 25. Corrected company's base case results post clarification ([redacted] PAS discount)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic results (10,000 iterations)							
Routine surveillance	[redacted]	-	[redacted]	-	-	-	-
Olaparib	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]

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

6.2 EAG scenario analysis

During the clarification stage, the EAG requested the company to provide a number of additional scenarios, which were supplied, and results are presented in Section 5.2.2. However, the EAG explored a scenario applying the inverse of the unadjusted overall survival (OS) hazard ratio (HR) of [redacted] to the olaparib lognormal OS extrapolation to generate an unadjusted OS curve for routine surveillance. A combined scenario including third-line olaparib maintenance costs using the final data cut-off (DCO) for time to treatment discontinuation (TTD) ([redacted] months) was also explored. Additionally, the EAG ran a scenario capping routine surveillance OS to olaparib when using the 1-knot spline extrapolation. The results of the scenarios applied to the company's corrected base case is presented in Table 26.

Table 26. Results of the EAG's scenario analyses ([redacted] PAS discount)

	Results per patient	Olaparib	Routine surveillance	Incremental value
0	Corrected company base case			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
1	Inverse of the unadjusted OS HR of [redacted] applied to olaparib OS lognormal extrapolation			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
2	Inverse of the unadjusted OS HR of [redacted] applied to olaparib OS lognormal extrapolation + 3LM olaparib costs using final DCO TTD from SOLO2 ([redacted] months)			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]
3	Routine surveillance OS capped to olaparib when using the 1-knot spline			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)			[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year

6.3 EAG preferred assumptions

In this section, the EAG presents its base case incremental cost-effectiveness ratio (ICER) for olaparib as maintenance treatment for patients who have relapsed, breast cancer susceptibility gene-mutated (BRCAm), platinum-sensitive high-grade epithelial ovarian, fallopian tube or peritoneal cancer that is in response (complete or partial) to the second course of platinum-based chemotherapy. The following assumptions were incorporated into the EAG's base case:

- 1-knot spline for extrapolation of OS with cap on routine surveillance OS - Section 4.1.3.1;
- Third-line olaparib maintenance costs using the final DCO for TTD ([redacted] months) - Section 4.1.4.1; and
- TTD capped to progression-free survival (PFS) - Section 4.1.6.1.

Table 27 presents the cumulative impact of each preferred assumption on the ICER and Table 28 presents the EAG deterministic base case. The EAG were unable to produce a probabilistic base case ICER as, due to a paucity of time, the EAG's scenario capping OS for routine surveillance to olaparib

when using the 1-knot spline could not be appropriately linked to the probabilistic sensitivity analysis (PSA).

Table 27. EAG's preferred model assumptions ([redacted] PAS discount)

Preferred assumption	Section in EAG report	Deterministic ICER (£/QALY)	Cumulative ICER (£/QALY)
Corrected company base case	-	[redacted]	-
1-knot spline for extrapolation of OS + routine surveillance OS cap	4.1.3.1	[redacted]	[redacted]
Third-line olaparib maintenance costs using the final DCO for TTD ([redacted] months)	4.1.4.1	[redacted]	[redacted]
TTD capped to PFS	4.1.6.1	[redacted]	[redacted]

Abbreviations: EAG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 28. EAG's deterministic base case results ([redacted] PAS discount)

Interventions	Total Costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

6.4 Conclusions of the cost effectiveness sections

The EAG's key issue for the cancer drugs fund (CDF) review is the estimation of OS for routine surveillance patients used in the updated model. The EAG considers that when patients on routine surveillance relapse, they will be eligible for third-line olaparib maintenance treatment after another course of platinum-based chemotherapy (as recommend in TA620). Additionally, relapsed olaparib patients would only receive routine surveillance as maintenance in the NHS as they are no longer Poly (ADP-ribose) polymerase (PARP) inhibitor naïve. However, currently there are second-line PARP inhibitor maintenance treatments recommended for use in the NHS, thus the EAG agrees with the company that it is likely the population eligible for third-line olaparib is diminishing. Nonetheless, the current CDF review needs to consider the treatment pathway as it was at the time of the publication of TA620, when no second-line PARP inhibitor maintenance treatments were recommended for routine use in the NHS.

As such, the EAG considers that it is clinically plausible that survival for relapsed routine surveillance patients who are PARP inhibitor naïve is likely to be improved as they will have access to third-line

olaparib maintenance treatment. In TA620, olaparib was recommended as maintenance treatment for BRCAm patients who have had three or more courses of platinum-based chemotherapy. Additionally, the company stated that in SOLO2 subgroup analyses, patients that received second-line olaparib maintenance treatment experienced a similar relative benefit versus placebo to those that received third-line olaparib maintenance treatment.

The company's analysis to adjust OS for crossover to PARP inhibitors for the placebo arm of SOLO2 may underestimate survival for the routine surveillance arm, thus an unadjusted placebo OS scenario may be worthwhile for the company to explore. However, it is not clear to the EAG how subsequent PARP inhibitors were given to placebo patients in SOLO2. As such, a scenario exploring unadjusted placebo OS may be subject to limitations if subsequent PARP inhibitor was not limited to third-line maintenance treatment only.

Instead, the EAG considers that over time, the OS curves for second-line olaparib and routine surveillance may eventually converge and that this should be included as part of the assessment of the cost-effectiveness of second-line olaparib maintenance treatment. As such, the EAG considers the convergence in the survival curves using the 1-knot spline a reasonable approach to account for the benefit of third-line olaparib maintenance treatment.

Nonetheless, the EAG considers that no one approach to account for improved survival for routine surveillance patients is more robust than others, but it is important for the committee to consider which approach best accounts for improved survival for routine surveillance.

Additionally, when considering improved survival benefit for routine surveillance patients as a result of access to third-line olaparib maintenance treatment, the costs of treatment should be included in the cost-effectiveness analysis.

Finally, all results in this report are inclusive of the company's [redacted] PAS discount.

7 References

1. Office for National Statistics. Cancer registration statistics, England, 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland. Date accessed: 26 Jul 2022.
2. Office for National Statistics. Death registrations summary tables - England and Wales, 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables. Date accessed: 26 Jul 2022.
3. Rose M, Burgess JT, O'Byrne K, Richard DJ, Bolderson E. PARP Inhibitors: Clinical Relevance, Mechanisms of Action and Tumor Resistance. *Front Cell Dev Biol* 2020; **8**: 564601.
4. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005; **434**: 917-21.
5. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer - Final Appraisal Document, 2019. Available from: https://www.nice.org.uk/guidance/ta620/documents/final-appraisal-determination-document-3. Date accessed: 26 Jul 2022.
6. National Institute for Health and Care Excellence. Managed access agreement. Olaparib tablets for maintenance treatment of BRCAmutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer, after response to platinum-based chemotherapy [TA620], 2020. Available from: https://www.nice.org.uk/guidance/ta620/resources/managed-access-agreement-pdf-7025932189. Date accessed: 26 Jul 2022.
7. AstraZeneca. A Phase III randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy - Clinical Study Report DCO1. 2017.
8. AstraZeneca. Data on File. 2022.
9. NAtional Institue for Health and Care Excellence. Final scope for olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (CDF review of technology appraisal 620), 2022. Available from: https://www.nice.org.uk/guidance/gid-ta10712/documents/final-scope-3. Date accessed: 26 Jul 2022.
10. National Institute for Health and Care Excellence. Terms of engagement for CDF review (TA620). 2020.
11. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy - Technology appraisal guidance, 2019. Available from: https://www.nice.org.uk/guidance/ta598/resources/olaparib-for-maintenance-treatment-of-brca-mutationpositive-advanced-ovarian-fallopian-tube-or-peritoneal-cancer-after-response-to-firstline-platinumbased-chemotherapy-pdf-82607270456005. Date accessed: 26 Jul 2022.
12. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy - Final Appraisal Document, 2021. Available from: https://www.nice.org.uk/guidance/ta673/documents/final-appraisal-determination-document. Date accessed: 26 Jul 2022.
13. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to

platinum-based chemotherapy ID1296 - single technology appraisal, 2018. Available from: https://www.nice.org.uk/guidance/ta620/documents/committee-papers. Date accessed: 26 Jul 2022.
14. Stone A, Gebski V, Davidson R, Bloomfield R, Bartlett JW, Sabin A. Exaggeration of PFS by blinded, independent, central review (BICR). *Ann Oncol* 2019; **30**: 332-8.
15. Dodd LE, Korn EL, Freidlin B, Jaffe CC, Rubinstein LV, Dancey J, et al. Blinded independent central review of progression-free survival in phase III clinical trials: important design element or unnecessary expense? *J Clin Oncol* 2008; **26**: 3791-6.
16. Campigotto F, Weller E. Impact of informative censoring on the Kaplan-Meier estimate of progression-free survival in phase II clinical trials. *J Clin Oncol* 2014; **32**: 3068-74.
17. Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2021; **22**: 620-31.
18. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2017; **18**: 1274-84.
19. Public Health England. Olaparib for maintenance treatment of BRCA mutated platinum sensitive relapsed ovarian, fallopian tube and peritoneal cancer – data review. 2020.
20. National Institute for Health and Care Excellence. Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer, 2021. Available from: https://www.nice.org.uk/guidance/ta693/resources/olaparib-plus-bevacizumab-for-maintenance-treatment-of-advanced-ovarian-fallopian-tube-or-primary-peritoneal-cancer-pdf-82609438840261. Date accessed: 26 Jul 2022.
21. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy - final appraisal document, 2019. Available from: https://www.nice.org.uk/guidance/ta598/documents/final-appraisal-determination-document. Date accessed: 26 Jul 2022.
22. Pujade-Lauraine E. SF, Scambia G., et al. . Maintenance olaparib rechallenge in patients (pts) with ovarian carcinoma (OC) previously treated with a PARP inhibitor (PARPi): Phase IIIb OReO/ENGOT Ov-38 trial. *Annals of oncology* 2021; **32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741**.
23. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Communications in Statistics-Theory and Methods* 1991; **20**: 2609-31.
24. National Institute for Health and Care Excellence. NICE DSU technical support document 16: adjusting survival time estimates in the presence of treatment switching, 2014. Available from: https://eclass.uoa.gr/modules/document/file.php/MED1174/Lectures/Unit%207%20%28Missing%20data%20and%20non-compliance%29/TSD16_Treatment_Switching.pdf. Date accessed: 26 Jul 2022.
25. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *New England Journal of Medicine* 2016; **375**: 2154-64.
26. Penson R, Kaminsky-Forrett MC, Ledermann J, Brown C, Plante M, Korach J, et al. Efficacy of olaparib maintenance therapy in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) by lines of prior chemotherapy: Phase III SOLO2 trial (ENGOT Ov-21). *Annals of Oncology* 2017; **28**: v331.
27. Latimer NR, White IR, Abrams KR, Siebert U. Causal inference for long-term survival in randomised trials with treatment switching: Should re-censoring be applied when estimating counterfactual survival times? *Stat Methods Med Res* 2019; **28**: 2475-93.

28. Edwards SJ, Karner C, Jhita T, Kew K, Marceniuk G. Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (including a review of technology appraisal no. 381): A Single Technology Appraisal. *BMJ Technology Assessment Group* 2018.
29. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual, 2022. Available from: www.nice.org.uk/process/pmg36. Date accessed: 26 Jul 2022.
30. European Medicines Agency. Lynparza (tablet formulation): summary of product characteristics, 2018. Available from: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf. Date accessed: 26 Jul 2022.

8 Appendices

8.1 Baseline characteristics

Table 29. Baseline characteristics of the 2L BRCAm subgroup of SOLO2 (Reproduced from CQ response A1, Table 1)

	Olaparib (N=110)	Placebo (N=62)
Age, years		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
ECOG performance status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Primary tumour location, n (%)		
Ovary	[redacted]	[redacted]
Fallopian tubes or primary peritoneal	[redacted]	[redacted]
Histology type, n (%)		
Serous	[redacted]	[redacted]
Endometroid	[redacted]	[redacted]
Mixed, Epithelial	[redacted]	[redacted]
Other	[redacted]	[redacted]
Patients with >2 cm target lesions at baseline, n (%)	[redacted]	[redacted]
Response to previous platinum therapy, n (%)		
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Platinum-free interval, n (%)		
>6 - 12 months	[redacted]	[redacted]
>12 months	[redacted]	[redacted]
Prior use of bevacizumab, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table 30. SACT cohort patient characteristics (Adapted from PHE report[19], Tables 3-7)

Patient characteristics		N	%
Sex	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Performance status	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
BRCA test	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
BRCA mutation	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Response status at start of olaparib	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Previous PARP inhibitor use	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Abbreviations: BRCA, breast cancer susceptibility gene; CDF, cancer drugs fund; CT, computerised tomography; PARP, poly (ADP-ribose) polymerase.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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) [ID3788]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 19 August 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Notes:

1. Minor typos and misspellings in the ERG report have not been corrected in this checklist.
2. We have categorised our response into four different tables, covering:
    - Factual errors (e.g., in reproduction of trial data, or errors identified in the ERG rebuild model and relevant results produced in the report).
    - Misleading statements, that have material impact on the interpretation and conclusions drawn from the evidence provided.
    - Further clarifications based on comments in the ERG report (in case useful to the ERG/NICE in preparation for technical consultation).

Factual Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3, Page 20 "The Terms of Engagement (ToE) requested further follow-up from SOLO2 to provide longer-term progression-free survival (PFS) and overall survival (OS) data"	"The Terms of Engagement (ToE) requested further follow-up from SOLO2 to provide longer-term overall survival (OS) data"	Regarding PFS, the ToE stipulates that *"the company should present progression-free survival estimates using radiological disease progression data as well as time to treatment discontinuation data from the SOLO-2 trial"*. At the time of the original TA620 submission, PFS had met its primary endpoint and therefore further data collection for PFS was not necessary. Data, including PFS from Study 19 was used in TA620 as the key evidence base for the submission; the ToE therefore did not request further data collection of PFS but simply states that PFS must be updated with data from the SOLO2 trial which aligns with the company approach.	Not a factual error; no change required. The ToE (September 2020) states: "[redacted]".
Section 3.2.1.2.2, Page 34 "The EAG therefore considers this analysis may over-estimate the OS for olaparib as the patients wouldn't be PARP inhibitor naïve and the AF is derived from the placebo arm in which patients would be expected to be PARP inhibitor naïve."	This statement should either be removed or further justification for why this analysis may overestimate the OS for olaparib should be provided by the EAG.	The application of the acceleration factor (AF) from the placebo group, to the olaparib group retreated with subsequent PARP inhibitor shrinks the survival time in the olaparib arm to account for any potential inflation in survival time due to treatment switching. This methodology in effect reduces the survival time in the olaparib arm by the same amount as the reduction in survival time applied in the placebo arm. This is despite the greater use of subsequent PARP inhibitor in the placebo arm ([redacted]) as compared to the olaparib arm ([redacted]), and the known limited benefit retreatment with a PARP inhibitor. The	The EAG thanks the company for highlighting this error and has removed the text highlighted by the company from the EAG report.

		incremental OS benefit of olaparib vs. placebo in the context following adjustment would therefore be expected to be an underestimation rather than an overestimation in favour of olaparib.	
Section 3.2.4, Page 40 "In total, eight adverse events of Grade 3 or higher occurred in at least three percent of patients, of which seven were more common in the olaparib arm than placebo arm."	In total, eight adverse events of Grade 3 or higher occurred in at least three percent of patients, of which six were more common in the olaparib arm than placebo arm."	Abdominal pain was reported by [redacted] of patients in both the olaparib and placebo arms.	The EAG thanks the company for highlighting this error and has amended the EAG report.
Section 3.2.4, Page 41 "…fatigue and asthenia (11% of olaparib patients, 2% of placebo patients)."	"…fatigue and asthenia (**6%** of olaparib patients, 2% of placebo patients)."	Incorrect proportion quoted in the olaparib arm.	The EAG thanks the company for highlighting this error and has amended the EAG report.

Misleading Statements

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1, Page 13 The EAG critique of the company's adherence to the Committee's preferred assumptions from the ToE highlight some "issues with the company's implementation of OS and the implication of long-term survival….".	Reference to the company's update of overall survival should be removed from Section 1.1.	Section 1.1 by definition, is only relevant where the company has deviated from the Committee-preferred assumptions outlined in the ToE. The company believe the context of this EAG critique is misplaced; it suggests the company's update of OS – the main uncertainty warranting inclusion of olaparib in the CDF – is inconsistent with the ToE. This is inaccurate and misleading; in relation to OS, the ToE states *"The company should update the overall survival estimate using*	Not a factual error, no change required.

		SOLO-2 trial data" which is fully in line with the company's approach. To be specific, the company has updated the OS data (previously derived from Study 19) in both their clinical and economic modelling with the final data cut off from the SOLO2 clinical trial. To address the generalisability of the OS data, the company also adjusted for treatment switching to olaparib using the latest OS data from SOLO2. These updates do not constitute a deviation from the ToE as suggested by the EAG.	
Section 1.6, Page 17 *(also applicable to Section 4 (Page 44), Section 5 (Page 59), Section 6.1 (Page 63), Section 6.3 (Page 65)* "The company have an approved patient access scheme (PAS) discount of [redacted]% and all results presented in this report are inclusive of the discount. Additionally, the company has proposed commercial discount of [redacted]% but this has yet to be approved and so is presented as a scenario only."	The company have an approved patient access scheme (PAS) discount of [redacted]% and all results presented in this report are inclusive of the discount. Additionally, the company has submitted analyses at the current commercial agreement discount of [redacted]%, presented here as a scenario.	While accurate to the manner in which this has been described in the company submission, we would propose this wording is updated to reflect that the [redacted]% discount is currently applied for the indication relevant to this appraisal (i.e., TA620) and, as such, these analyses remain relevant for decision-making.	Not a factual error, no change required.
Section 1.4, Page 16 "However, at the time of the publication of TA620 there were no second-line PARP inhibitor maintenance treatments were	In the EAG report it is not clear why the treatment pathway considered in the CDF Exit appraisal should reflect an historical precedent to adhere to the	The company recognises that the scope of the CDF Exit should be consistent with the original decision problem and aligned with the ToE; this is to enable the data collection agreement, as part of the managed access agreement, to sufficiently resolve uncertainties that	Not a factual error, no change required.

recommended by NICE for routine use in the NHS, thus the current CDF review needs to consider the treatment pathway as it was then.”	decision problem and Terms of Engagement.	necessitated entry to the CDF. However, this does not preclude the need to ensure that outcomes, such as overall survival are generalisable to the current UK pathway and consequently clinical practice. Indeed, one recent example includes the CDF Exit appraisal of niraparib in TA784 where the company data was not considered generalisable to UK clinical practice given the high extent of crossover and missing data. In this instance the Committee preferred using Study 19 data as the key evidence base to ensure generalisability. In addition, when externally validating outcomes derived from modelling (long-term OS for example) based on the updated SOLO2 data, clinicians do so with consideration of both the current UK treatment pathway and their practice. The EAG’s suggestion that the current CDF review should consider the historical treatment pathway limits the relevance of the outcomes observed in the latest dataset to the current UK clinical practice. The limited utilisation of PARP inhibitors in the third-line setting can be considered established clinical practice. Although baseline funding has been available since 2016, the treatment landscape has evolved substantially, with PARP inhibitors mostly used in the first line and, to a lesser extent, in the second line setting since the recommendation of olaparib in 2018. As a result, using the SOLO2 unadjusted data, or scenarios where OS curves converge do not reflect established practice in the third line setting.	

		The company presented a scenario analysis based on the placebo arm of Study 19 (equivalent to routine surveillance) - where post-progression subsequent PARP inhibitor utilisation in the placebo arm was fewer. The company would like to highlight that this could be considered a more reliable alternative interpretation (versus the company base case) of the likely survival benefit of olaparib in the 2L setting with consideration to the current UK clinical practice.	

Further clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2 , Page 20 "Due to this earlier availability of olaparib in the treatment pathway…."	"Due to this earlier availability of olaparib and niraparib in the treatment pathway…."	More accurate description of the UK treatment pathway	Not a factual error; no change required.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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) [ID3788]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Technical engagement response form

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Thursday 15 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

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) [ID3788]

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Extrapolation of overall survival in the model: Is it plausible that people who have olaparib as 2nd line maintenance and routine surveillance as 3rd line maintenance would have similar overall survival to people who had routine surveillance as 2nd line maintenance and olaparib as 3rd line maintenance? Does the treatment sequencing impact survival?	No	As previously discussed in the company's response to the EAG clarification questions, it is reasonable to assume that the ***treatment effect*** with olaparib in PARP inhibitor naïve patients is likely maintained across second- and third-line settings. It is however important to highlight that variation in overall survival outcomes are likely to be observed across treatment lines due to differences in ***prognostic factors*** such as age, volume of residual disease, and performance status. In addition, the likelihood and duration of response to platinum-based chemotherapy sharply declines with each subsequent line attributed to cumulative toxicities and the onset of platinum resistance. Those who relapse within 6 months of receiving platinum chemotherapy are considered to have platinum-resistant disease. Patients in whom the use of PARP inhibitor is delayed to later lines are therefore more likely to be ineligible for targeted maintenance therapy due to platinum resistance, which can have significant negative impact on prognosis. Furthermore, the randomised study of olaparib in the first-line maintenance setting for women with newly diagnosed advanced ovarian cancer demonstrated a clinically meaningful benefit with the potential for cure (SOLO1). In contrast,

		relapsed ovarian cancer is usually considered incurable and the treatment strategy in the relapsed setting mainly aims to provide disease control, delay subsequent initiation of chemotherapy, minimise the toxicity burden and maintain quality of life. Clinical studies on olaparib therefore supports the implementation of PARP inhibitors in the earliest line of relapse possible to maximise the chances of experiencing prolonged progression-free survival or cure. This is reflected in the shift observed in clinical practice following the availability of PARP inhibitor in the earlier settings; clinicians now offer majority of eligible patients' maintenance with a PARP inhibitor after first-line chemotherapy. The advantages of PARP inhibitors use - olaparib included - in as early in the treatment line as possible is consistent with clinical expert feedback which strongly indicated that the greatest possible benefit from maintenance treatment with olaparib is derived from the earlier settings. Based on the above factors, it is unlikely that survival outcomes would be similar in the second- vs. third-line setting.
Costs of subsequent olaparib for routine surveillance patients: Would people from the routine surveillance arm who have relapsed and are PARP inhibitor naïve receive third-line olaparib maintenance treatment? Should the costs of 3rd line olaparib be included in the model?	No	It is possible for a PARP-naïve patient to receive olaparib in the third-line setting. However, given that multiple PARP inhibitors have been reimbursed for several years across first and second-line maintenance settings (TA598, TA673, TA398 & TA784) it would be highly unlikely that a clinician (or patient) would delay maintenance therapy for an eligible patient in earlier lines for a reason that didn't then preclude them for a PARP inhibitor in the third-line setting. Clinical validation sought by AstraZeneca suggested that a diminishing proportion of patients would receive olaparib in subsequent lines given the optimised clinical benefit of PARP therapy in the first-line setting. As outlined in the company submission, interpretation of the OS data from SOLO2 is limited by the high rate of post-progression PARP inhibitor use which is not generalisable to current UK practice.

		A notable proportion of patients ([redacted]) in the placebo group received subsequent PARP inhibitor following disease progression. The impact of switching particularly in the control group underestimates the survival benefit and the generalisability of the OS results, which necessitates adjusting for treatment switching. In the company base case, 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 improve the generalisability of the outcomes from the SOLO2 trial. With this is mind, it would be technically inconsistent and invalid to include the costs of third line olaparib within the base case which is informed by the OS results adjusted to account for treatment switching. This is in line with NICE methods and TSD 16 DSU guidance which states *"it would be preferable to accurately adjust survival estimates for switching and to exclude the costs of switching treatments".* The company however believe it is internally valid and appropriate to include third line olaparib costs in the scenarios where the treatment effect is also considered, this include: 1) Scenario analysis in the company submission based on placebo arm from Study 19 This scenario utilises the final OS estimates for olaparib derived from SOLO2 but, for the routine surveillance arm, this is sourced from Study 19; the method taken is consistent with the recently accepted approach for decision making in the NICE appraisal of TA784.The rationale for this approach is because relatively fewer proportion of patients received subsequent post-progression PARP inhibitor in the Study 19 trial which is likely more reflective of the current UK clinical practice. This scenario therefore offers a realistic estimation of survival and the impact on the cost-effectiveness. Given the inclusion of subsequent PARP inhibitor benefits in

		this scenario, it would be internally consistent for the costs of subsequent olaparib to be included. 2) 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. Although it is appropriate and consistent to include the costs of third line olaparib in the unadjusted analysis provided by the EAG, the interpretation of the OS is limited by the high rate of post-progression PARP inhibitor use as outlined above. To conclude, the company maintains that it would be inappropriate and internally inconsistent to include the costs of subsequent olaparib in base case given the exclusion of subsequent treatment benefit through treatment switching adjustment.
Time-to-treatment discontinuation (TTD) not capped to progression free survival. Do you agree that treatment with olaparib would be stopped once a person's ovarian cancer has progressed?	No	The summary of product characteristics for olaparib in platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer recommended that treatment with olaparib be continued until progression of the underlying disease or unacceptable toxicity. Following the EAG clarification question stage, the company included an update in the economic modelling capping TTD to PFS which has a minimal impact on the cost-effectiveness results (£[redacted]/QALY vs. £[redacted]/QALY without and with the cap applied, respectively).

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4: Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 3: TTD not capped to PFS	Exclusion of TTD capped to PFS in the model	Inclusion of TTD capped to PFS in the model	£[redacted]/QALY (-£1,189)
Adverse events	Adverse events rates derived from primary data cut-off	Adverse event rates updated with final data cut-off results	£[redacted] /QALY (-£1,169)
Company's base case following technical engagement (or revised base case)	**Incremental QALYs:** [redacted]	**Incremental costs: £**[redacted]	**£**[redacted] **/QALY (-£1,169)**

Table 1: Average results based on PSA (10,000 iterations)

Technologies	Total costs (£)	Total QALYs	Incremental		ICER (£/QALY)
			Costs (£)	QALYs	
Routine surveillance	[redacted]	[redacted]			
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1: Cost-effectiveness plane

Figure 2: Cost-effectiveness acceptability curve

Table 2: Results of deterministic 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 3: Tornado diagram

Table 3: Results of scenario analyses (based on [redacted] PAS for olaparib)

Outcome	Scenario	Technology	Inc. costs	Inc. QALYs	ICER	Impact on base case (£)
Company base case ([redacted] *PAS*)					£[redacted]	
PFS extrapolation	Lognormal	RS				–
		Olaparib	£[redacted]	[redacted]	£[redacted]	-£[redacted]
OS extrapolation	Log logistic	RS				
		Olaparib	£[redacted]	[redacted]	£[redacted]	£[redacted]
TTD extrapolation	Generalised gamma	RS				
		Olaparib	£[redacted]	[redacted]	£[redacted]	£[redacted]
	Weibull	RS				
		Olaparib	£[redacted]	[redacted]	£[redacted]	-£[redacted]
PFS estimates	BICR-assessed PFS	RS				
		Olaparib	£[redacted]	[redacted]	£[redacted]	-£[redacted]
Placebo arm OS estimates	Placebo arm from Study 19	RS				
		Olaparib	£[redacted]	[redacted]	£[redacted]	£[redacted]

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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) [ID3788]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with ovarian cancer or caring for a patient with ovarian cancer. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.2).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments: **see email text for deadline**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with ovarian cancer

Table 1 About you, ovarian cancer, current treatments and equality

1. Your name	Florence Wilks
2. Are you (please tick all that apply)	☒ A patient with ovarian cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with ovarian cancer? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Ovarian Cancer Action
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with ovarian cancer? **If you are a carer (for someone with ovarian cancer) please share your experience of caring for them**	I was diagnosed in 2010 with Stage 3C Ovarian Cancer. I have had chemotherapy on 4 separate occasions…2010/2011, 2012, 2013, 2016/2017. This is gruelling, emotionally and physically, has enormous impact on your family and relationships. In 2013 due to a tumour in my bowel I now have a permanent stoma. After that I had Avastin for 2 and a ¼ years. In 2017 I started on the wonder drug that is Olaparib. It has transformed my life. It has provided me with the largest extension of life that I could have ever have imagined. It is so much easier to take than chemotherapy, being tablet form. There are side effects, mine being insomnia and fatigue. But these do not compare with those I experienced in chemotherapy. My family and I are forever grateful for this life changing drug.
7a. What do you think of the current treatments and care available for recurrent, platinum-sensitive ovarian cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**There are not enough treatment options available to women in this situation.** **For me it seemed chemotherapy/Avastin/Olaparib. Of which I am very grateful.** **I know there are other parp inhibitors. Various trials. Immunotherapy and targeted therapies. But there needs to be improved outcomes for women with this horrible disease. I know this means more funding/more research/therefore better outcomes. It also means there should be a screening tool, and earlier diagnosis.** **I am aware of a few women who have had parp inhibitors, but not responded and died. Others who have been on trials. In my circle I know about half a dozen women who have died of OC. I seem to be an outlier in response to Olaparib, and I am very grateful. Being BRCA and being able to have Olaparib has transformed my life and the life of my family.**

8. If there are disadvantages for patients of current NHS treatments for recurrent, platinum-sensitive ovarian cancer (for example, how the treatment is given or taken, side effects of treatment, and any others) please describe these	Olaparib:Side effects include insomnia and fatigue. I would not say these are disadvantages in this drug just side effects. In my view it is easy to take, 4 tablets a day. Chemotherapy…is very hard, the side effects very challenging, brutal. But when there are no other options you take it. It is basically a matter of life or death. If you don't take the chemotherapy offered your life will be shorter.
9a. If there are advantages of olaparib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does olaparib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**So many advantages of Olaparib over other current treatments.** **Easy to take (4 tablets a day)** **Prescribed every 2 months/based on blood test/minimal interaction with hosp/saving medical time/resources** **Minimal side effects (insomnia/fatigue…so many more side effects in chemotherapy)** **Quality of life very good in comparison with chemotherapy.** **It WORKS! It has extended my life by 5 wonderful years. It seems if used after first line chemo for some women it is curative. This is such a game changer in treatment for this horrible disease.**
10. If there are disadvantages of olaparib over current treatments on the NHS please describe these. For example, are there any risks with olaparib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I do not see any disadvantages
11. Are there any groups of patients who might benefit more from olaparib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	I understand you have to be BRCA to benefit from Olaparib, there need to be more options for non-Brca patients.

dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering ovarian cancer and olaparib? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	no

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Extrapolation of overall survival in the model: Is it plausible that people who have olaparib as 2nd line maintenance and routine surveillance as 3rd line maintenance, would have similar overall survival to people who had routine surveillance as 2nd line maintenance and olaparib as 3rd line	I would think the earlier you are offered or take Olaparib the better, but if you are not able to take as 2nd line treatment then you should ne able to as 3 rd line. I would not know if the order impacts survival. All I know is that patients are not statistics. I had chemo 4 times before I accessed Olaparib, and have been on it over 5 years.

Patient expert statement

maintenance? Does the treatment sequencing impact survival?	
Costs of subsequent olaparib for routine surveillance patients: Would people from the routine surveillance arm who have relapsed and are PARP inhibitor naïve receive 3rd line olaparib maintenance treatment? Should the costs of 3rd line olaparib be included in the model?	Yes, I believe it should.
Time-to-treatment discontinuation (TTD) not capped to progression free survival. In your experience, is treatment with olaparib stopped once the ovarian cancer has progressed?	We consider patient perspectives may particularly help to address this issue. I always thought once my disease progressed my ability to have olaparib would end. But I guess it depends at what specific point it ends……after ca125 has doubled? After ct scan shows progression? I am not sure what medics do. But I suppose once you have clear and specific progression this very expensive treatment must stop.
Are there any important issues that have been missed in ERG report?	

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Olaparib is a game changer in treatment for Ovarian Cancer in terms of extension of life
- Side effects are minimal in comparison to other treatments
- Quality of life so good in comparison with other treatments
- Olaparib should be offered to as many patients as possible
- Easy to take/minimal interaction with the hospital/saving medical time

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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) [ID3788]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with ovarian cancer or caring for a patient with ovarian cancer. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.2).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments: **see email text for deadline**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with ovarian cancer

Table 1 About you, ovarian cancer, current treatments and equality

1. Your name	Rachel Downing
2. Are you (please tick all that apply)	☐ A patient with ovarian cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with ovarian cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Target Ovarian Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with ovarian cancer? **If you are a carer (for someone with ovarian cancer) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for recurrent, platinum-sensitive ovarian cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for recurrent, platinum-sensitive ovarian cancer (for example, how the treatment is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of olaparib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?**	

9c. Does olaparib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of olaparib over current treatments on the NHS please describe these. For example, are there any risks with olaparib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from olaparib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering ovarian cancer and olaparib? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Extrapolation of overall survival in the model: Is it plausible that people who have olaparib as 2nd line maintenance and routine surveillance as 3rd line maintenance, would have similar overall survival to people who had routine surveillance as 2nd line maintenance and olaparib as 3rd line	

Patient expert statement

maintenance? Does the treatment sequencing impact survival?	
Costs of subsequent olaparib for routine surveillance patients: Would people from the routine surveillance arm who have relapsed and are PARP inhibitor naïve receive 3rd line olaparib maintenance treatment? Should the costs of 3rd line olaparib be included in the model?	
Time-to-treatment discontinuation (TTD) not capped to progression free survival. In your experience, is treatment with olaparib stopped once the ovarian cancer has progressed?	We consider patient perspectives may particularly help to address this issue From experiences of patients who contact Target Ovarian Cancer's support line or use our online communities olaparib is stopped once they experience a progression
Are there any important issues that have been missed in ERG report?	The availability of timely BRCA testing is key in ensuring patients can start olaparib. The majority of newly diagnosed patients will have had both BRCA and HRD testing but for those who have not it is vital that

Patient expert statement

	there enough capacity in the genomic testing system to ensure results are available in time for treatment to start

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

Patient expert statement

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

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) [ID3788]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.2). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments: **see email text for deadline**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating recurrent, platinum-sensitive ovarian cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Rebecca Bowen
2. Name of organisation	Royal United Hospital Bath NHS Trust and University of Bath British Gynaecological Cancer Society
3. Job title or position	Medical Oncologist and visiting professor
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with ovarian cancer? ☐ A specialist in the clinical evidence base for ovarian cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	This oral maintenance treatment is given following response to platinum-base chemotherapy aiming to slow progression and delay the time to need further intravenous systemic anti-cancer treatment and to improve overall survival. This is not a curative intervention.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Significant progression-free and overall survival advantage without reduction in quality of life
10. In your view, is there an unmet need for patients and healthcare professionals in recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy?	Yes. There are a number of unmet needs in advanced ovarian cancer but the delivery of oral maintenance PARPi in the platinum-sensitive (PARP-naïve) population as per this indication is a significant advance in the treatment of relapsed disease
11. How is recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently maintenance PARP inhibitor therapy is standard of care for women who have benefitted from platinum-based chemotherapy for relapsed disease and who have not received prior PARP inhibitor therapy • NICE: relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults, only if they have a germline BRCA mutation and have had 3 or more courses of platinum-based chemotherapy (NICE pathways – Managing Advanced Ovarian Cancer). Also TA784 for maintenance niraparib and TA611 for maintenance Rucaparib. • Well established treatment pathway defined and in England it is limited by funding but choice of individual PARPi may vary from centre to centre with individual preference where funding may allow the option of more than one PARPi

	• It has had a big impact on the pathway of care since introduced and as an oral therapy, during the COVID-19 pandemic and in recovery, maintaining women on outpatient treatment with remote consultations and delaying the need for intravenous chemotherapy has been invaluable
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes • n/a • Secondary care within specialist outpatient clinics • Already running as standard so no extra investment to introduce anticipated
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Maintenance olaparib in this setting provides clinically meaningful benefits compared with no maintenance treatment (PFS and OS) • Yes compared with no maintenance treatment • Yes

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Greater benefit is seen with PARPi maintenance for those with a BRCA1 or BRCA2 mutation (germline or somatic) and for those with non-BRCA HRD (homologous recombination defects) tumours but all patients who have responded to platinum-based therapy can benefit even those who have homologous recombination proficient disease (approx. 50%) albeit to a lesser extent.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This is already running as standard of care. When administering oral PARPi maintenance therapy as standard of care there is a requirement for monthly blood tests and clinical review which might otherwise have been approximately 3 monthly if receiving no maintenance therapy. However blood tests can be performed in the community and medications sent to patients alongside virtual clinic appointments to minimise hospital attendances for patients
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment is only commenced where there is evidence of response to the current line of platinum-based chemotherapy and olaparib is continued until unacceptable toxicity or disease progression
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	yes
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	• Yes • Improves outcomes in terms of PFS and OS for patients with relapsed disease responding to platinum-based chemotherapy
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Olaparib is well-tolerated and side effects are usually predictable, rarely severe, occurring predominantly in the first few cycles of treatment and can be readily managed with dose adjustments and supportive medications and clinical trials have repeatedly confirm that it does not impact negatively on quality of life
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes • Real world studies suggest benefit in the real populations mirror that in clinical trials • Progression-free and overall survival with maintenance of quality of life – these all support the use of maintenance olaparib in this setting • N/a • None
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	As above – real world studies support the benefit and the safety/ tolerability seen in the trial data
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into	No I am not aware of any potential equality issues

account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Extrapolation of overall survival in the model: Is it plausible that people who have olaparib as 2nd line maintenance and routine surveillance as 3rd line maintenance would have similar overall survival to people who had routine surveillance as 2nd line maintenance and olaparib as 3rd line maintenance? Does the treatment sequencing impact survival?	It is possible but unlikely. It is preferable to use PARPi maintenance sooner rather than later. Despite significant cross-over in SOLO2 for PARPi maintenance following subsequent lines of platinum based chemotherapy in the placebo arm overall survival was significantly improved and clinically relevant in the Olaparib arm
Costs of subsequent olaparib for routine surveillance patients: Would people from the routine surveillance arm who have relapsed and are	Yes if they respond to platinum-based chemotherapy once again but this is not guaranteed. Platinum sensitivity, in the absence of maintenance therapy, tends to reduce with each line

Clinical expert statement

PARP inhibitor naïve receive 3rd line olaparib maintenance treatment? Should the costs of 3rd line olaparib be included in the model?	of platinum-based chemotherapy. Patients may miss the window of opportunity for benefit from olaparib maintenance
Time-to-treatment discontinuation (TTD) not capped to progression free survival. Do you agree that treatment with olaparib would be stopped once a person's ovarian cancer has progressed?	Olaparib would be stopped when there is symptomatic or clinically significant disease progression warranting further systemic chemotherapy
Are there any important issues that have been missed in ERG report?	None

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

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) [ID3788]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (section 1.2). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments: **see email text for deadline**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating recurrent, platinum-sensitive ovarian cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Jonathan A Ledermann
2. Name of organisation	UCL Cancer Institute
3. Job title or position	Professor of Medical Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with ovarian cancer? ☐ A specialist in the clinical evidence base for ovarian cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for recurrent, platinum-sensitive ovarian, fallopian tube and	Most patients with BRCA mutated ovarian cancer will receive a PARP inhibitor as frontline treatment but there are a small number of patients with BRCA

peritoneal cancer that has responded to platinum-based chemotherapy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	mutated ovarian cancer who are not able to access a PARP inhibitor after firs-line chemotherapy. These are the patients who are diagnosed with early ovarian cancer – FIGO stage I or stage II who are not able to access a PARP inhibitor in the front-line treatment setting as it is not included in the licence. These patients represent around 30% of all patients with high grade ovarian cancers, and this percentage could increase as more women have a BRCA mutation identified through screening, and a proportion of these women will have undiagnosed ovarian cancer at the time of surgery. Whilst most women with early-stage ovarian cancer do well with surgery and chemotherapy, a proportion will relapse. This particularly applies to patients with stage II disease, who in the generally population comprised around 12% of patients with ovarian cancer. The absolute number of patients who relapse is hard to ascertain, but it should be noted that in a few women with an incidental finding of ovarian cancer at risk-reducing salpingo-ophorectomy, chemotherapy is given, without a second 'staging' operation; a few of these patients may have missed stage III disease. If one assumes there are 6000 new patients with high grade ovarian cancer are diagnosed each year, there will be approximately 900 patients with a germ line BRCA mutation each year in the UK. About 30% will have stage I/II disease and about 15% will relapse - approximately 40 patients in this group, most of whom will respond to platinum-based therapy and will be eligible for olaparib maintenance. The aim of treatment in this group of women with recurrent ovarian cancer who have responded to platinum-based chemotherapy in the second line is to extend the period of disease control, delaying the need for further chemotherapy as long as possible. By so doing, this increases the survival time, and possibly in some patients it leads to a cure.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	See above. Most of these patients will start maintenance olaparib in remission from surgery/chemotherapy. However, it should be noted that olaparib maintenance treatment is also therapeutic- with a proportion of patients having a deepening of the response to chemotherapy. In SOLO2 for patients with measurable disease at entry to the trial, there was a 41% further reduction in tumour (RECIST partial response) compared with 17% on placebo (due to a carryover effect of chemotherapy)
10. In your view, is there an unmet need for patients and healthcare professionals in recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy?	Whilst most patients with BRCA mutated recurrent ovarian cancer will respond to platinum-based therapy, without maintenance treatment the progression free survival is approximately 5.5 months. This means that half the patients who are treated with chemotherapy will need to be considered for further chemotherapy within 5.5 months of completing second line chemotherapy. There is a great need for better treatment of patients with recurrent BRCA mutated ovarian cancer
11. How is recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Current guidelines for treatment, based on national international guidelines from professional societies (eg BGCS and ESMO) recommend olaparib maintenance treatment, if it has not been previously used, for patients with BRCA mutated ovarian cancer who have responded to platinum-based chemotherapy after relapse. This recommendation is supported by the Cancer Drugs Fund and olaparib is available for such patients.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It is not proposed that there will be any change in the current use, as approved by the CDF. However, the number of patients accessing olaparib for recurrent ovarian cancer is reducing as more of these patients are able to access the drug in the front-line setting Olaparib is used in centres experienced in the management of ovarian cancer. These are hospitals that are either designated gynaecological cancer treatment centres, or those working in collaboration with the centres. Current all patients with newly diagnosed ovarian cancer are offered testing for germ line BRCA mutations
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The overall survival data from SOLO2 show an improvement in survival with a favourable hazard ratio- interpretation of overall survival data is confounded by cross over and long post-progression survival of these patients. Furthermore, the overall survival data for SOLO2 included patients entered after second line (~60%) or later line chemotherapy (~40%). Sensitivity analyses have been performed controlling for PARP cross over and number lines of treatment. The difference in survival is greatest in those receiving olaparib after 2 lines of therapy. Health-related Quality of Life (HRQoL) is difficult to assess during maintenance treatment. Given that patients are in remission when the start a PARP inhibitor, it is difficult to expect HRQoL to improve. None of the trials measuring HRQoL have continued measurements sufficiently long to pick up the adverse effects of an earlier progression in the patients not receiving active treatment. Exploratory analyses measuring QTWIST- Quality adjusted time without symptoms and toxicity have shown a benefit for maintenance therapy with PARP inhibitors

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	No No implication problems as the technology is currently being used
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	These are currently in place. There is widespread use of PARP inhibitors in clinical practice with well-established methods for monitoring treatment and dispensing medication.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	This is difficult as there may be a small proportion of patients who are cured and will therefore have a normal life expectancy. This will not occur in a population who cannot access a PARP inhibitor at this point
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	It has been shown to be clinically effective in patients already. Meaningful improvements in the progression-free survival and a strong trend to an overall

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	survival benefit. A small proportional of patients experience exceptional benefit, remaining on olaparib > 5 years without further progression (around 20 %)
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Olaparib is a well-tolerated drug in most patients. There is considerable knowledge about managing side effects in treatment centres. Discontinuation for toxicity in the SOLO2 trial was 11%
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes- olaparib is used in patients with a recurrent BRCA mutated ovarian cancer following a response to platinum-based chemotherapy The SOLO2 trial showed significant improvement in progression-free survival, delay in restarting chemotherapy and a clinically meaningful improvement in overall survival. A small proportion of patients are 'exceptional responders' and continue to take the drug with benefit for more than 5 years The main long-term side effect that needs to be considered is the development of myelodysplastic syndrome or Acute Myeloid Leukaemia. The incidence is low, but it did increase with prolonged follow up in SOLO2. It should be noted that this side effect was seen in the control arm too, but the incidence was lower. This risk needs to be balanced against death from ovarian cancer and the long term benefit of olaparib outweighs the risk of these haematological toxicities
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	

23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	None

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Extrapolation of overall survival in the model: Is it plausible that people who have olaparib as 2nd line maintenance and routine surveillance as 3rd line maintenance would have similar overall survival to people who had routine surveillance as 2nd line maintenance and olaparib as 3rd line maintenance? Does the treatment sequencing impact survival?	Current data from the recently published SOLO1 first line data with olaparib show greatly improved survival in the olaparib arm and strongly suggest that the greatest clinical benefit from a PARP inhibitor occurs when it is used early in the treatment pathway of ovarian cancer. Thus, it is likely that second line use will have a more prolonged effect on survival than 3rd line use of the drug. Also, the percentage of patient eligible for third line use is lower than in second line as not all patients receive third line therapy, and some of those do not respond to re-challenge with platinum-based treatment
Costs of subsequent olaparib for routine surveillance patients: Would people from the routine surveillance arm who have relapsed and are	See above

Clinical expert statement

PARP inhibitor naïve receive 3rd line olaparib maintenance treatment? Should the costs of 3rd line olaparib be included in the model?	
Time-to-treatment discontinuation (TTD) not capped to progression free survival. Do you agree that treatment with olaparib would be stopped once a person's ovarian cancer has progressed?	From clinical experience, there are situations where there is evidence of tumour progression and clinical benefit persists from continuing the drug. A small proportion of patients in SOLO2 and study 19 are in this category and the data are currently being collected for publication. Some patients have single site relapse of tumour and the beneficial effects of olaparib can continue after removal of the tumour or ablation of the recurrence. The key reason to stop olaparib is disease progression requiring 3rd line therapy. Chemotherapy is not always started immediately after radiological progression
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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) [ID3788]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Technical engagement response form

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Thursday 15 September 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

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) [ID3788]

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Mariama Jarjue
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG response
Extrapolation of overall survival in the model: Is it plausible that people who have olaparib as 2nd line maintenance and routine surveillance as 3rd line maintenance would have similar overall survival to people who had routine surveillance as 2nd line maintenance and olaparib as 3rd line	No	As previously discussed in the company's response to the EAG clarification questions, it is reasonable to assume that the ***treatment effect*** with olaparib in PARP inhibitor naïve patients is likely maintained across second- and third-line settings. It is however important to highlight that variation in overall survival outcomes are likely to be observed across treatment lines due to differences in ***prognostic factors*** such as age, volume of residual disease, and performance status. In addition, the likelihood and duration of response to platinum-based chemotherapy sharply declines with each subsequent line attributed to cumulative toxicities and the onset of platinum resistance. Those who relapse within 6 months of receiving platinum chemotherapy are considered	As stated in the EAG report, at the time of the publication of TA620 there were no second-line PARP inhibitor maintenance treatments recommended by NICE for routine use in the NHS, thus the current CDF review needs to consider the treatment pathway as it was then. While the EAG agrees that currently, in the NHS, patients are unlikely to be PARP inhibitor naïve, the appropriate comparator in the model for the CDF review is routine surveillance. By definition, routine surveillance patients are PARP inhibitor naïve and would be eligible for third-line maintenance treatment with olaparib when they relapse (as recommend in TA620). Additionally, relapsed olaparib BRCAm patients would only

maintenance? Does the treatment sequencing impact survival?		to have platinum-resistant disease. Patients in whom the use of PARP inhibitor is delayed to later lines are therefore more likely to be ineligible for targeted maintenance therapy due to platinum resistance, which can have significant negative impact on prognosis. Furthermore, the randomised study of olaparib in the first-line maintenance setting for women with newly diagnosed advanced ovarian cancer demonstrated a clinically meaningful benefit with the potential for cure (SOLO1). In contrast, relapsed ovarian cancer is usually considered incurable and the treatment strategy in the relapsed setting mainly aims to provide disease control, delay subsequent initiation of chemotherapy, minimise the toxicity burden and maintain quality of life. Clinical studies on olaparib therefore supports the implementation of PARP inhibitors in the earliest line of relapse possible to maximise the chances of experiencing prolonged progression-free survival or cure. This is reflected in the shift observed in clinical practice following the availability of PARP inhibitor in the earlier settings; clinicians now offer majority of eligible patients' maintenance with a PARP inhibitor after first-line chemotherapy. The advantages of PARP inhibitors use - olaparib included - in as early in the treatment line as	receive routine surveillance as maintenance in the NHS as they are no longer PARP inhibitor naïve. As accepted in TA620, third-line olaparib maintenance treatment is associated with improved survival outcomes for BRCAm patients who would have otherwise received routine surveillance as maintenance. As such, the EAG considers that over time, the overall survival for second-line olaparib and routine surveillance patients may eventually converge due to the options available at third-line and this should be considered in the CDF review.

		possible is consistent with clinical expert feedback which strongly indicated that the greatest possible benefit from maintenance treatment with olaparib is derived from the earlier settings. Based on the above factors, it is unlikely that survival outcomes would be similar in the second- vs. third-line setting.	
Costs of subsequent olaparib for routine surveillance patients: Would people from the routine surveillance arm who have relapsed and are PARP inhibitor naïve receive third-line olaparib maintenance treatment? Should the costs of 3rd line olaparib be included in the model?	No	It is possible for a PARP-naïve patient to receive olaparib in the third-line setting. However, given that multiple PARP inhibitors have been reimbursed for several years across first and second-line maintenance settings (TA598, TA673, TA398 & TA784) it would be highly unlikely that a clinician (or patient) would delay maintenance therapy for an eligible patient in earlier lines for a reason that didn't then preclude them for a PARP inhibitor in the third-line setting. Clinical validation sought by AstraZeneca suggested that a diminishing proportion of patients would receive olaparib in subsequent lines given the optimised clinical benefit of PARP therapy in the first-line setting. As outlined in the company submission, interpretation of the OS data from SOLO2 is limited by the high rate of post-progression PARP inhibitor use which is not generalisable to current UK practice. A notable proportion of patients ([redacted]) in the placebo group received subsequent PARP	While the EAG agrees that a diminishing proportion of patients will be eligible for third-line olaparib, as stated above and in the EAG report, the current CDF review needs to consider the treatment pathway as it was then, where only third-line olaparib was recommended as a maintenance treatment option for these patients. The EAG considers that relapsed routine surveillance patients who are PARP inhibitor naïve in the NHS would receive third-line olaparib maintenance treatment and are likely to have improved survival. Thus, costs of subsequent olaparib maintenance treatment in addition to adjusted survival for routine surveillance patients should be included in the cost-effectiveness analysis.

		inhibitor following disease progression. The impact of switching particularly in the control group underestimates the survival benefit and the generalisability of the OS results, which necessitates adjusting for treatment switching. In the company base case, 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 improve the generalisability of the outcomes from the SOLO2 trial. With this is mind, it would be technically inconsistent and invalid to include the costs of third line olaparib within the base case which is informed by the OS results adjusted to account for treatment switching. This is in line with NICE methods and TSD 16 DSU guidance which states *"it would be preferable to accurately adjust survival estimates for switching and to exclude the costs of switching treatments".* The company however believe it is internally valid and appropriate to include third line olaparib costs in the scenarios where the treatment effect is also considered, this include: 1) Scenario analysis in the company submission based on placebo arm from Study 19	

		This scenario utilises the final OS estimates for olaparib derived from SOLO2 but, for the routine surveillance arm, this is sourced from Study 19; the method taken is consistent with the recently accepted approach for decision making in the NICE appraisal of TA784.The rationale for this approach is because relatively fewer proportion of patients received subsequent post-progression PARP inhibitor in the Study 19 trial which is likely more reflective of the current UK clinical practice. This scenario therefore offers a realistic estimation of survival and the impact on the cost-effectiveness. Given the inclusion of subsequent PARP inhibitor benefits in this scenario, it would be internally consistent for the costs of subsequent olaparib to be included. 2) 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. Although it is appropriate and consistent to include the costs of third line olaparib in the unadjusted analysis provided by the EAG, the interpretation of the OS is limited by the high rate of post-progression PARP inhibitor use as outlined above. To conclude, the company maintains that it would be inappropriate and internally inconsistent to	

		include the costs of subsequent olaparib in base case given the exclusion of subsequent treatment benefit through treatment switching adjustment.	
Time-to-treatment discontinuation (TTD) not capped to progression free survival. Do you agree that treatment with olaparib would be stopped once a person's ovarian cancer has progressed?	No	The summary of product characteristics for olaparib in platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer recommended that treatment with olaparib be continued until progression of the underlying disease or unacceptable toxicity. Following the EAG clarification question stage, the company included an update in the economic modelling capping TTD to PFS which has a minimal impact on the cost-effectiveness results [redacted]/QALY vs. [redacted]/QALY without and with the cap applied, respectively).	No further comments from the EAG. The company provided a scenario capping TTD to PFS and this is included in the EAG base case.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base

case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4: Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG response
Issue 3: TTD not capped to PFS	Exclusion of TTD capped to PFS in the model	Inclusion of TTD capped to PFS in the model	£[redacted]/QALY (-£1,189)	The EAG has verified the ICER and it is correct.
Adverse events	Adverse events rates derived from primary data cut-off	Adverse event rates updated with final data cut-off results	£[redacted]/QALY (-£1,169)	The EAG has verified the ICER and it is correct.
Company's base case following technical engagement (or revised base case)	**Incremental QALYs:** [redacted]	**Incremental costs:** [redacted]	**£[redacted]/QALY (-£1,169)**	The EAG has verified the ICER and it is correct.

Table 1: Average results based on PSA (10,000 iterations)

Technologies	Total costs (£)	Total QALYs	Incremental		ICER (£/QALY)
			Costs (£)	QALYs	
Routine surveillance	[redacted]	[redacted]			
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1: Cost-effectiveness plane

Figure 2: Cost-effectiveness acceptability curve

Table 2: Results of deterministic sensitivity analysis

Technical engagement response form

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 3: Tornado diagram

[redacted]

Table 3: Results of scenario analyses (based on [redacted] PAS for olaparib)

Outcome	Scenario	Technology	Inc. costs	Inc. QALYs	ICER	Impact on base case (£)	EAG response
Company base case ([redacted] *PAS*)					[redacted]		ICER has been verified
PFS extrapolation	Lognormal	RS				–	
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	ICER has been verified
OS extrapolation	Log logistic	RS					
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	ICER has been verified
TTD extrapolation	Generalised gamma	RS					
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	ICER has been verified
	Weibull	RS					
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	ICER has been verified
PFS estimates	BICR-assessed PFS	RS					
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	ICER has been verified
Placebo arm OS estimates	Placebo arm from Study 19	RS					
		Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	ICER has been verified