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)

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 18/54/05

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This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
26	Niraparib changed to olaparib
61-62	Niraparib changed to olaparib
97	Niraparib changed to olaparib
107	Figure 15 amended to correct legend description.
108	Figure 16 amended to correct erroneous data point.
110-111	TFST, PFS, TFST-PFS and TFST-TTD estimates amended in Table 36.
118	Table 42 amended.
120	Table 43 amended
121-122	Table 45, base case utility values amended
124	Table 47 title amended.
128	Table 49, % utilisation for the 50 mg and 100 mg formulations of cisplatin amended. Text amended to "The number of cycles of olaparib was based on the mean TTD estimated in Study 19 for patients that have had three or more lines of prior platinum-based therapy ([redacted]).
129	Table 51, number of vials amended for cisplatin, doxorubicin, paclitaxel and topotecan.
146-147	Table 69, 50-year scenario and SOLO, HSUV scenario incremental costs changed. Table 70, 50-year scenario incremental cost changed.
150-151	Table 72, TFST Routine surveillance and difference estimates amended. Bullet point ii) amended. Wording of end-of-life criteria amended.

- All study outcomes for the BRCA subgroup analyses were *post hoc*. Similarly, TTD, TFST and TSST were exploratory outcomes added after unblinding of data;

- The sample size calculation for Study 19 was based on a significance level of 0.2 (two-sided alpha of 0.4), which is unusually high even for a phase II trial;

- A large proportion of patients were defined as having "important" deviations from the study protocol, including 18.8% of patients having IVRS miss-stratifications at randomisation, which is one possible reason for imbalances observed in some baseline characteristics; (1) slightly more patients in the placebo group who had had only two prior lines of platinum therapy compared with the olaparib group, which may indicate a more favourable prognosis for patients in the placebo groups, (2) more patients in the placebo group with an ECOG of ≥1 compared with the olaparib group, which is likely to favour olaparib, and (3) a difference in patients' best response to the most recent platinum-based chemotherapy with less patients in the olaparib group with a complete response compared with the placebo group, suggests a more favourable prognosis for patients in the placebo group.

The assumption of PHs has been shown not to hold for several outcomes in Study 19 (PFS [BRCAm subgroups], TFST, and OS) and in SOLO2 (PFS), therefore the HR, CI and associated p-value for these analyses are at best challenging to interpret, potentially misleading and should be interpreted with caution. The ERG considers the Kaplan–Meier curves to give the best illustration of the treatment effect followed by the event rates at certain time points as neither of these are reliant on, or confounded by, non-PHs. If the PHs assumption does not hold for the remaining outcomes, not tested by the company, the HR, CI and p-value for these outcomes are also likely to be misleading.

Crossover from placebo to olaparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for outcomes such as PFS2, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. Though, the ERG notes that, the trial design is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib versus placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

Uncertainty around which clinical trial outcome, PFS, TFST or TTD, best captures symptomatic progression, as assessed in clinical practice. As discussed in section 1.1 and 1.2.2, treatment

Crossover from placebo to olaparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for outcomes such as PFS2, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. Though, the ERG notes that, the trial design is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib versus placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

The ERG has some concerns about the lack of reporting of the methods of independent review of progression and methods for censoring, especially for the sensitivity analysis of BICR of PFS. However, although BICR in general has a lower risk of bias than investigator assessment, as it was done retrospectively in Study 19 and SOLO2, it is likely to be confounded by informative censoring, which may bias the BICR PFS result. The ERG therefore considers investigator assessed progression to be less confounded and more reflective of clinical practice.

The lack of PFS follow-up after the primary analysis, in Study 19, means that although 58% of PFS events had been observed overall, only 44% had progressed in the olaparib group (placebo group 72%). However, the ERG considers OS to be the preferred outcome in oncological studies and data are mature for this outcome. PFS data from the primary analysis of SOLO2 are more mature than PFS data for Study 19, but data are immature for PFS2, TSST and OS.

SOLO2 was adequately powered to show superiority of olaparib over placebo for both PFS and the secondary endpoint of PFS2 at a two-sided significance level of 5%. However, the assumptions around the expected difference in efficacy or the calculated sample size were not stated for SOLO2. The sample size calculation for Study 19 was based on a significance level of 0.2 (two-sided alpha of 0.4), which is unusually high even for a phase II trial. The ERG is unsure about the rationale behind this decision for the trial as the likelihood of type I error was high (20%).

In Study 19, TTD, TFST and TSST were exploratory outcomes added after unblinding of data. Similarly, all study outcomes for the BRCA subgroup analyses were *post hoc*. In addition, it is unclear if analyses of TTD, TFST and TSST were based on the ITT population, as other efficacy outcomes, or the FAS, however, the difference between the populations was small, and the population used will have limited impact on the results of these outcomes. In addition, a large proportion of patients were defined as having “important” deviations from the study protocol, including 18.8% of patients having IVRS miss-stratifications.

- The assumption of PHs has been shown not to hold for several outcomes in Study 19 (PFS [BRCAm subgroups], TFST, and OS) and in SOLO2 (PFS), therefore the HR, CI and associated p-value for these analyses are at best challenging to interpret, potentially misleading and should be interpreted with caution. The ERG considers the Kaplan–Meier curves to give the best illustration of the treatment effect followed by the event rates at certain time points as neither of these are reliant on, or confounded by, non-PHs. If the PHs assumption does not hold for the remaining outcomes, not tested by the company, the HR, CI and p-value for these outcomes are also likely to be misleading.

- Crossover from placebo to olaparib was not allowed in either trial, but some patients in the placebo groups received post-discontinuation PARP inhibitor treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for outcomes such as PFS2, TSST and OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARP inhibitor therapy. Though, the ERG notes that, the trial design is in line with what would happen in clinical practice as some patients who does not receive olaparib as a maintenance therapy after their second line of platinum-based chemotherapy, are likely to get a PARP inhibitor after a later line. Therefore, the TSST and OS analyses are likely to be conservative estimates of the relative effect of olaparib versus placebo, but potentially a reasonable reflection of the efficacy of olaparib compared with routine surveillance in clinical practice.

- In Study 19 and SOLO2, patients could continue treatment beyond progression based on investigator's discretion. This is not in line with the licence for olaparib or how olaparib is expected to be used in clinical practice, i.e. treatment be continued until progression. However, progression is assessed and defined differently in clinical practice and clinical trials; in Study 19 and SOLO2 progression was assessed according to RECIST criteria, which is usually not used in clinical practice where progression will be assessed based on an increase in symptoms and/or a rise in CA-125 confirmed by a radiological scan. Symptomatic progression, as would be detected in clinical practice, may be more accurately captured in the trials by TTD than by progression according to RECIST; patients who progressed according to RECIST criteria may not have been symptomatic, but were treated until they no longer received a clinical benefit from treatment, that is, until they were likely to have a change in HRQoL. The ERG also notes that it is unclear if the criteria for commencing the next line of chemotherapy were comparable to clinical practice. Any such differences could bias the estimates of outcomes subsequent to PFS.

The company performed the curve selection exercise for TFST, OS and TTD for the full population and selected the 1-knot spline distribution for olaparib and routine surveillance as the best fitting curve for all outcomes (Figure 15 to Figure 17). As the PH assumption was found not to hold for all outcomes, each treatment arm was modelled independently. Log-cumulative hazard plots, AIC/ BIC statistics and plots of all the assessed distributions compared with the KM curve can be found in Section B.3.3 of the company submission.

Figure 15. Time to first subsequent therapy Kaplan Meier and 1-knot spline distribution for olaparib and routine surveillance

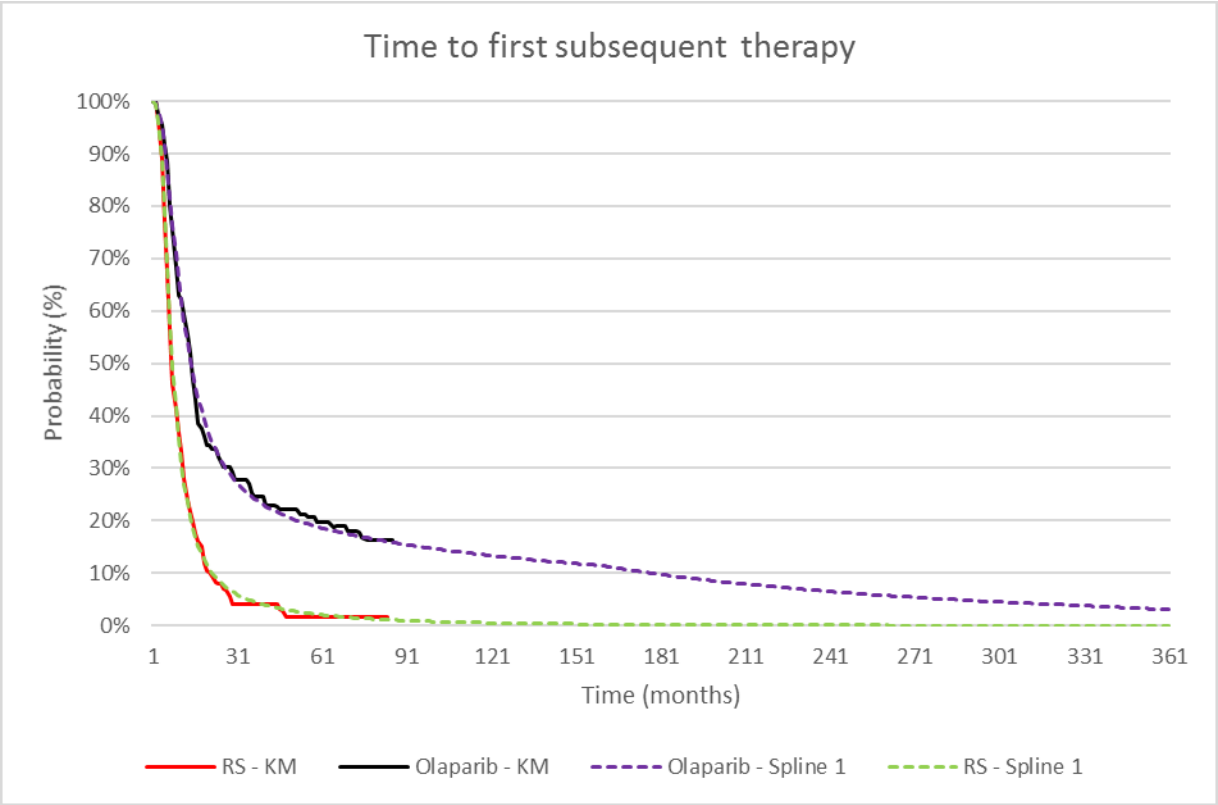

Figure 16. Overall survival Kaplan Meier and 1-knot spline distribution for olaparib and routine surveillance

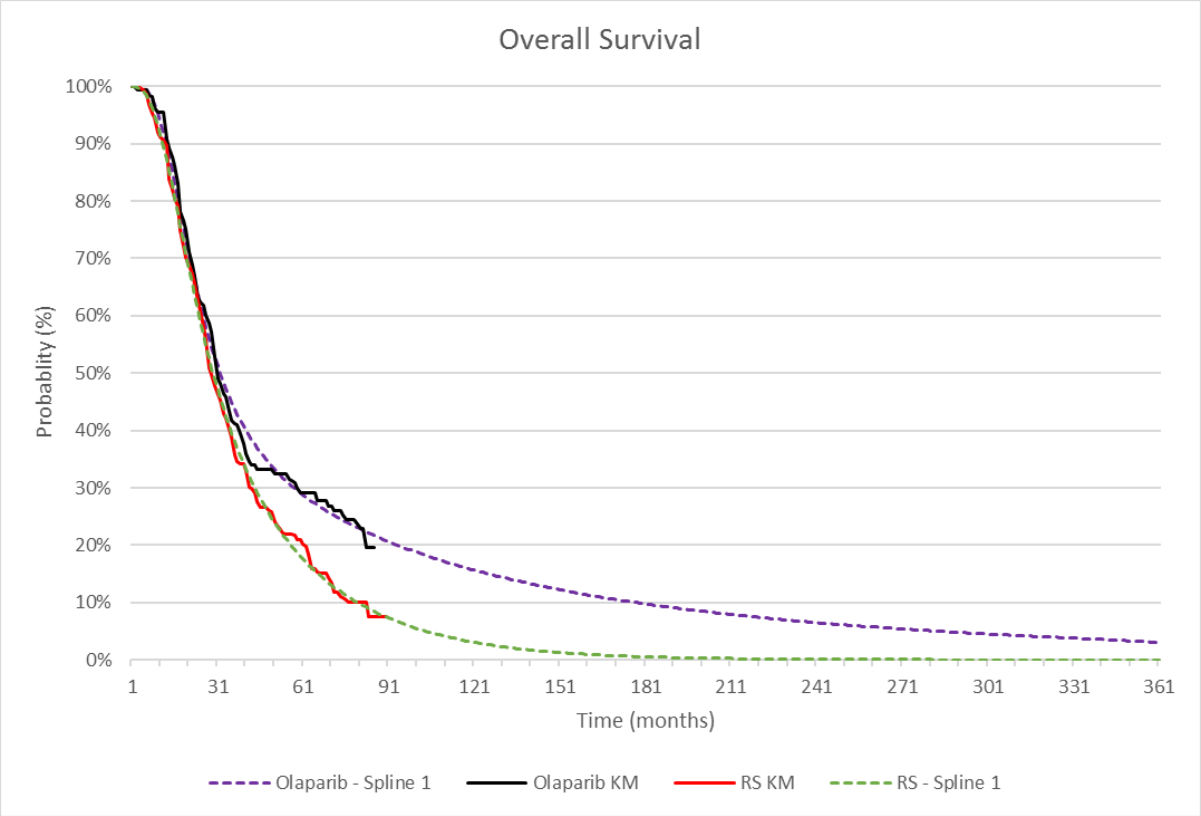

Figure 17. Time to treatment discontinuation Kaplan Meier and 1-knot spline distribution for olaparib and routine surveillance

[redacted]

cessation. Furthermore, a comparison of mean estimates of PFS and TFST from the economic model, based on extrapolated Study 19 data, demonstrates that for olaparib, there is approximately a [redacted] difference between a patient being diagnosed with radiological disease progression and receiving their next anti-cancer therapy (see Table 36). The implications of the difference in the mean estimates of PFS and TFST in the economic model are that patients will accrue the utility benefits of being progression free. Moreover, the difference between the mean estimates of TFST and TTD from the economic model is approximately [redacted], resulting in patients accruing additional pre-progression benefit without the associated treatment costs.

Table 36. Comparison of mean PFS, TFST & TTD estimates the economic model (full population)

Treatment	PFS (investigator)	TFST	TTD	TFST-PFS (difference)	TFST-TTD (difference)
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: PFS, Progression free survival; TFST, Time to first subsequent therapy; TTD, Time to treatment discontinuation					

It is preferable for PFS data from the trial to be used to model the progression free health state, as it is the primary outcome of Study 19 and aligns with the SmPC. However, the ERG considers that cessation of treatment, as measured by TTD, is a better indication of symptomatic disease progression, resulting in changes to HRQoL and costs associated with having progressed disease (such as disease management and monitoring costs) and is aligned with how clinicians would use the drug in clinical practice. Estimates of TTD also have the advantage of being more mature and estimated from the same, later data cut as OS (May 2016). During the clarification stage, the ERG requested the company to perform two scenarios around their base case, the first exploring the use of the TTD extrapolation for olaparib and routine surveillance and a second, more conservative, scenario of implementing PFS in the model. The company performed the requested scenarios and results are presented in Table 37.

Table 37. TTD and PFS scenario analyses - list price (company's clarification response)

Scenario	ICER
Company base case	[redacted]
TTD for the progression free health state	[redacted]
PFS for the progression free health state	[redacted]
Abbreviations: ICER, incremental cost effectiveness ratio; PFS, progression free survival; TTD, time to treatment discontinuation	

As mentioned in Section 5.4.2, the NICE final scope outlined that consideration should be given to subgroups according the BRCAm status, which the company addressed only for the clinical analyses of Study 19, but did not include in the economic analyses. Furthermore, the company have stated that patients who meet the NICE eligibility criteria for olaparib will initiate treatment on the tablet formulation and eventually the capsule formulation will be phased out within the NHS. Currently, patients are only eligible for olaparib in the NHS if they have had three or more prior lines of platinum-

Table 41. AIC/BIC statistics for TTD – 3rd line non-BRCAm population (Appendix 3, company clarification response)

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Weibull	145.03	147.12	85.38	87.16	230.41	234.28
Gompertz	133.48	135.57	86.56	88.34	220.03	223.90
Lognormal	136.21	138.29	86.74	88.52	222.94	226.81
Loglogistic	134.97	137.05	87.44	89.22	222.40	226.27
Exponential	147.56	148.61	96.64	97.53	244.20	246.13
Generalised gamma*	-	-	-	-	-	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.
*Note: The generalised gamma model is not included due to convergence issues (non-finite finite-difference value)

Table 42. AIC/BIC statistics for OS – 3rd line non-BRCAm population (Appendix 3, company clarification response)

Model	Olaparib		Placebo		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Lognormal	152.22	154.31	154.84	156.62	307.06	310.93
Loglogistic	152.61	154.70	155.96	157.74	308.58	312.45
Weibull	157.21	159.30	157.13	158.91	314.34	318.21
Gompertz	159.02	161.10	159.51	161.29	318.53	322.40
Exponential	157.02	158.07	160.39	161.28	317.42	319.35
Generalised gamma*	-	-	-	-	-	-

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.
*Note: The generalised gamma model is not included due to convergence issues (non-finite finite-difference value)

5.4.6 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 Study 19, presented in Table 43. In the company submission, it was not clear if AEs included in the model were treatment related or treatment emergent. In response to clarification questions, the company explained that grade 3 or higher AEs reported in Study 19 and SOLO2 are for all events and no distinction is made for those that are treatment-related.

Table 43. Grade 3 or higher AEs implemented in the model (Table 46, page 135 of the CS)

Adverse event	Olaparib (N = 136)	Placebo (N = 128)
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]

The impact of adverse events on patients' quality of life is considered in the model and is described further in Section 5.4.7, while the costs of managing adverse events are discussed in Section 5.4.8.

5.4.6.1 ERG critique

The ERG considers the company's approach to selecting AEs to be included in the model is reasonable. The ERG's clinical experts confirmed that all AEs expected to be encountered in patients receiving olaparib that have an impact on patients' quality of life, or are associated with substantial costs, have been included in the model. However, the ERG's primary concern with the AE data implemented in the model is that it is based on Study 19, which assessed the capsule formulation of olaparib. Safety data for SOLO2, which assessed the tablet formulation of olaparib, is available and the ERG considers that it would be more appropriate to implement these data in the economic model.

Compared with Study 19, AEs that were grade 3 or higher were lower in the SOLO 2 trial (43.4% vs 37% for patients on olaparib), though it should be noted that SOLO2 was focused solely on BRCAm population. The ERG's clinical experts considered that there is no evidence to suggest that AEs would differ by BRCAm status. During the clarification stage, the company supplied a scenario exploring the use of SOLO2 AE data, but this had a negligible impact on the ICER. Other scenarios requested by the ERG during the clarification stage that focused on AEs were also found to have a negligible impact on the ICER and, as such, AEs are not considered to be a key driver of the cost-effectiveness analyses.

5.4.7 Health-related quality of life

As described in Section 5.2, the company identified published HSUVs through a SLR. A summary of the 10 included studies reporting HSUVs from four unique randomised controlled trials (RCTs) (OVA-301, ICON7, NOVA, SOLO2) is provided in Table 49 of the CS. One of the four identified RCTs

(NOVA) collected HRQoL data in the same population as the license for olaparib (maintenance treatment for patients with platinum-sensitive relapsed ovarian cancer, regardless of BRCAm status) and was used to inform the recent appraisal of niraparib, TA528.[34] The remaining three trials OVA-301, ICON7 and SOLO2 reported HSUV data in a subset of patients with platinum-sensitive relapsed ovarian cancer, or in patients at an earlier part of the treatment pathway. Therefore, the company concluded that HRQoL data from NOVA best represented the HRQoL of patients in the full licensed population for olaparib.

During the NOVA study, patients completed the EQ-5D-5L questionnaire after every two treatment cycles through to cycle 14, and thereafter every three cycles. Using these data, EQ-5D-3L utilities were derived by mapping the 5L descriptive system data onto the 3L valuation set using the algorithm published by van Hout *et al.* 2012.[35]

Mapped EQ-5D-3L utilities were generated for the PFS and PD health states for each treatment arm (niraparib and routine surveillance) presented in Table 1.

Table 1. Utility values employed within TA528[34]

Health state	Utility value
PFS	0.801
PD	0.719
Abbreviations used in the table: PD, progressed disease; PFS, progression-free survival	

The company also explored the mapped EQ-5D-3L utilities derived from SOLO2 and a combination of the mapped FACT-O (from Study 19) to EQ-5D-3L and literature-based utilities used in TA381 in sensitivity analyses, presented in Section **Error! Reference source not found.**.[36]

In the model, progression was defined by TFST, based on the assumption that the initiation of subsequent treatment was more likely to trigger a reduction in a patient's quality of life than a RECIST defined progression. As a result, patients with progressed disease who are yet to receive subsequent treatment, have the same quality of life as patients who are progression free. The HSUVs for the progression-free health state (pre-FST) and PD (post-FST) used in the company's analyses are given in Table 2.

Table 2. Utiltiy values used in the model (adapted from Tables 50 and 51 of the CS)

Health state	Base case (TA528)[34]	SOLO2 study summary statistics	Study 19 FACT-O mapped to EQ-5D-3L (PF) and ERG-derived mean of two values from TA222 (PD)* [31, 36]
PF (pre-FST)	0.801	0.802	0.77
PD (post-FST)	0.719	0.739	0.68
*Taken from the ERG report for TA381. Abbreviations: ERG, Evidence Review Group; FACT-O, Functional Assessment of Cancer Therapy–Ovarian; PD, progressed disease; PF, progression-free			

quality of life compared with patients who received two prior lines of platinum-based chemotherapy. Although the subgroup analysis is caveated by a reduced sample size, the results reiterate the need to explore cost-effectiveness analyses by line of therapy.

As mentioned previously, at the time of writing this report, the company informed NICE and the ERG that the BRCAm subgroup analysis informed by SOLO2, using HSUVs by treatment line, is ongoing. As discussed in Section 5.4.5.1, the company provided subgroup analyses by BRCAm status and line of therapy based on Study 19, but failed to amend any of the assumptions around relevant utility values for the subgroups. As such, the ERG ran several scenarios implementing the HSUVs by line of therapy presented in Table 3, for the subgroup analyses and results are presented in Section 6.2.

Table 3. SOLO2 HSUVs, by line of therapy (EQ-5D-3L crosswalk) (adapted from Table 26 of the company's clarification responses)

Statistic	Overall	PFS	PD
Full analysis set			
Number of completed questionnaires	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
2 prior lines of platinum therapy			
Number of completed questionnaires	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
≥ 3 prior lines of platinum therapy			
Number of completed questionnaires	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-3L, 3-level EuroQol 5-dimension Questionnaire; IQR, interquartile range; PD, progressed disease; PFS, progression free survival SD, standard deviation.

The ERG is concerned that HRQoL benefits accrued in the progression-free health state have been extended by the company's definition of progression in the model. As described in Section **Error! Reference source not found.**, the proportion of patients residing in the progression-free health state at each time point was determined by extrapolation of the TFST endpoint, rather than PFS, which was the primary endpoint of the trial. The HSUV from NOVA for the progression-free health state is based on patients who have progressed, according to RECIST, and stopped treatment.[46] As a result, the company's approach potentially overestimates the progression-free benefits, as during the time between TFST and PFS, patients' quality of life would decline as they come off treatment, which they could continue receive beyond diagnosis

	1000	1	7.75	0.01	100	
	2000	1	26.12	0.01	0	
Doxorubicin	10	1	1.34	0.13	0	3.63
	50	1	3.63	0.07	100	
	200	1	16.82	0.08	0	
Topotecan	1	1	7.13	7.13	0	114.74*
	4	5	114.74	5.74	100	
Paclitaxel	30	1	3.44	0.11	0	16.68
	100	1	9.85	0.10	0	
	150	1	10.52	0.07	0	
	300	1	16.68	0.06	100	
Cyclophosphamide	500	1	8.62	0.02	0	25.99
	1000	1	15.89	0.02	0	
	2000	1	25.99	0.01	100	
Docetaxel	20	1	3.85	0.19	0	20.62
	80	1	14.74	0.18	0	
	140	1	20.62	0.15	100	
	160	1	46.75	0.29	0	
Cisplatin	10	1	1.84	0.18	0	4.48
	50	1	4.48	0.09	100	
	100	1	10.13	0.10	0	
Etoposide	100	1	2.30	0.02	0	9.65
	500	1	9.65	0.02	100	
*Corrected by the ERG in the revised model from £114.74 to £22.95 (described further in Section 5.4.8.7)						

Table 4. Drug administration costs (adapted from Table 54 of the CS)

Resource	Unit cost	NHS Reference Costs, year 2016-17 currency description[49]
Initial infusion chemotherapy administration	£173.99	Deliver Simple Parenteral Chemotherapy at First Attendance, Outpatient (SB12Z)
Subsequent chemotherapy administration	£205.09	Deliver Subsequent Elements of a Chemotherapy Cycle, Outpatient (SB15Z)

The company obtained the number of cycles for each subsequent treatment, apart from olaparib, from the recommended dosing by the York cancer network reported in TA381. The number of cycles of olaparib was based on the mean TTD estimated in Study 19 for patients that have had three or more lines of prior platinum-based therapy ([redacted]).

The total cost of the 10 most common subsequent treatments received in Study 19 based on the recommended dosing by the York cancer network is given in Table 5. A mean body surface area (BSA) of 1.77 m^2 and glomerular filtration rate (GFR) of 84.4 was obtained from Study 19 to calculate doses dependent on surface area and creatine clearance.

Table 5. Drug acqusition and administration cost associated with each treatment regimen (taken from the revised economic model provided at clarification)

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.[c]	Total cost
Bevacizumab	10[a]	3	£4,019	1.4	21	£266	£42,857
Carboplatin	6	1	£27	1.4	21	£266	£1,760
Cisplatin	4	3	£19	1.4	21	£266	£1,143
Cyclophosphamide	6	2	£75	1.4	21	£266	£2,049
Docetaxel	6	1	£30	1.4	21	£266	£1,776
Doxorubicin	6	2	£8	1.1	28	£192	£1,198
Gemcitabine	6	2	£22	1.4	21	£266	£1,732
Etoposide	4	1	£70	7.2	21	£1,455	£6,101
Paclitaxel	6	2	£48	1.4	21	£266	£1,887
Topotecan	6	1	£832	7.2	21	£1,455	£13,720
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

admin. administrations

[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 Study 19 received subsequent treatment with bevacizumab, compared to the placebo arm.

[b]Calculated values are based on the 15-month PAS currently in use.

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

Using the number of subsequent treatments recorded in Study 19, the company calculated the proportion of patients receiving each treatment, based on the assumption that 100% of patients receive some form of subsequent treatment (Table 6). The proportions from Study 19 were multiplied by the total cost of each regimen (Table 5) to provide the mean total cost of one line of subsequent treatment for each treatment arm (Table 6). Following this, the mean total cost for one line of subsequent treatment in the model was [redacted] for olaparib and [redacted] for routine surveillance.

Table 6. Cost of subsequent treatment use in Study 19 (taken from the updated economic model provided at clarification)

Treatment	Olaparib		RS		Total cost of regimen	Olaparib	RS
	Number of regimens recorded in Study 19	%	Number of regimens recorded in Study 19	%			
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (1-knot spline) for modelling the progression-free health state			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Use of SOLO2 HSUVs by line of therapy			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
ERG's preferred base case ICER			[redacted]

Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.

Table 7. ERG base case ICER – 3rd line+ BRCAm population (list price)

Results per patient	Olaparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (1-knot spline) for modelling the progression-free health state			

Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Use of SOLO2 HSUVs by line of therapy			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
ERG's preferred base case ICER			[redacted]
Abbreviations: BRCAm, breast cancer susceptibility gene mutation; ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years; TTD, time to treatment discontinuation.			

Table 8. ERG base case ICER – 2nd line non-BRCAm population (list price)

Results per patient	Olaparib	Routine Surveillance	Incremental value
Company's revised base case			
Total Costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
50-year time horizon			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
TTD (2-knot spline) for modelling the progression-free health state			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Inclusion of drug wastage			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
ICER with all changes incorporated			[redacted]
Distribution of subsequent therapy costs over 30.44 days			

7 END OF LIFE

NICE end-of-life status should be applied when the following criteria are satisfied:

(i) the treatment provides an extension to life of more than an average of three months compared to current NHS treatment, and;

(ii) the treatment is indicated for patients with a short life expectancy, normally less than 24 months.

The company proposes that patients with platinum-sensitive, relapsed ovarian cancer, irrespective of BRCAm status or line of therapy, qualifies for NICE end-of-life criteria. The ERG agrees with the company that the median estimates of OS for patients in the olaparib and placebo groups in Study 19[16] may not provide a representative measure of the treatment effect or the average life expectancy. The company has demonstrated that olaparib maintenance treatment leads to [redacted] months ([redacted]) extension of OS compared to placebo in Study 19, based on a restricted means analysis. The company's survival modelling over the full time horizon (30 years) estimates a mean survival benefit for patients on olaparib of [redacted] months compared with patients in the placebo group, which satisfies the first criterion of an extension to life of more than an average of three months (Table 9).

Table 9. Means for clinical outcomes estimated in the economic model

Outcome	Mean (months)		
	Olaparib	Routine surveillance	Difference
Progression-free survival	11.4	5.8	5.6
Time to first subsequent therapy	49.5	11.4	38.1
Overall survival	65.8	38.4	27.4

However, according to the company's health economic model, the mean life expectancy in the placebo group is [redacted] months, substantially longer than the 24-month threshold to satisfy the second NICE end-of-life criterion (Table 9). The company highlights that the observed survival time in the placebo group of Study 19 is expected to be longer than the life expectancy for patients with platinum-sensitive, relapsed, ovarian cancer in clinical practice for several reasons: (i) UK survival outcomes for ovarian cancer are worse than in many other countries in Europe, (ii) patients in clinical trials, like Study 19, are typically healthier than those seen in the real-world setting, and (iii) the OS estimate in the placebo group of Study 19 is inflated because some patients in the placebo group received subsequent PARP inhibitor therapy. The ERG notes that some patients in clinical practice are expected to receive PARP inhibitor therapy as olaparib capsules are recommended for patients after three or more lines of platinum-based chemotherapy. In that respect the trial data maybe representative of current UK clinical

practice, although it is unclear if the proportion of patients who received subsequent PARP inhibitor therapy in the trial is similar to clinical practice.