Olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy: A Single Technology Appraisal

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Emma Hock summarised and critiqued the clinical effectiveness data reported within the company's submission. John Stevens critiqued the statistical analyses reported within the company's submission. Daniel Pollard and Matt Stevenson critiqued the health economic analysis submitted by the company. Mark Clowes critiqued the company's search strategy. John Tidy provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse Event
AIC	Akaike information criterion
AML	Acute Myeloid Leukaemia
BIC	Bayesian information criterion
BNF	British National Formulary
BRCA	Breast Cancer Susceptibility Gene
CA-125	Cancer Antigen 125
CDF	Cancer drugs fund
CMU	Commercial Medicines Unit
CS	Company Submission
CSR	Clinical Study Report
DCO	Data Cut-Off
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic Market Information Tool
ERG	Evidence Review Group
FACT-O	Functional Assessment of Cancer Therapy—Ovarian Cancer
FDA	US Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
MAICER	Maximum Acceptable Incremental Cost-Effectiveness Ratio
MDS	Myelodysplastic Syndrome
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
OS	Overall Survival
PARP	Poly (ADP-ribose) polymerase
PFS	Progression-Free Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours

STA	Single Technology Appraisal
TOI	Trial Outcome Index
TFST	Time to First Subsequent Treatment
TSST	Time to Second Subsequent Treatment
TTD	Time to Treatment Discontinuation or Death

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company submission (CS) assesses the clinical and cost effectiveness of olaparib (Lynparza®), within its anticipated licensed indication for the maintenance treatment of adult patients with newly diagnosed advanced Breast Cancer Susceptibility Gene (BRCA) mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first line platinum-based chemotherapy. The company's description of advanced ovarian cancer and its management is broadly appropriate. The decision problem addressed by the CS is partly in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). The population considered within the clinical and cost effectiveness sections is the population defined by the SOLO1 randomised trial. In SOLO1, patients with International Federation of Gynaecology and Obstetrics (FIGO) stage II ovarian cancer were excluded; however, advanced ovarian cancer can be interpreted to include these patients. The definition of advanced ovarian cancer provided in the background section of the final NICE scope includes patients with FIGO stage II cancers. As such, this population is missing from the clinical and cost-effectiveness evidence presented in the CS. Furthermore, the anticipated licensed population, and hence the CS, is narrower than the NICE scope, as only patients with high-grade ovarian cancers would be eligible to receive olaparib. There are also issues regarding the alignment of subsequent treatment pathways in the CS and the company's proposed use of subsequent treatments in this appraisal. The CS and clarification response suggest that patients would only receive one poly (ADP-ribose) polymerase (PARP) inhibitor maintenance therapy (either olaparib or niraparib (Zejula®)) within the whole pathway for treating advanced ovarian cancer. As such, the company anticipates that if NICE were to approve olaparib in this setting, then patients would not be eligible to receive subsequent PARP inhibitors. However, the evidence from SOLO1 would appear to contradict this, as [redacted] of patients in the olaparib arm of SOLO1 received a subsequent PARP inhibitor. Furthermore, it is unclear to the evidence review group (ERG) whether or not the use of subsequent PARP inhibitors in the placebo arm of SOLO1 matches current UK clinical practice.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical evidence relating to olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy is based on SOLO1, a Phase III randomised controlled trial (RCT). The ERG is confident that no relevant studies are likely to have been missed.

The ERG is largely satisfied that the relevant population has been included in the CS, with the caveat that there is currently no evidence relating to the efficacy of olaparib in patients with stage II disease, as mentioned in the NICE final scope. The ERG is content that the relevant interventions and

comparators for first-line maintenance have been included in the CS, and that the CS includes evidence relating to all outcomes specified in the NICE final scope.

Patients in SOLO1 received olaparib or placebo in a blinded manner for two years (with no radiological evidence of disease) or until investigator-assessed objective disease progression on imaging, according to the RECIST, version 1.1. Patients with residual evidence of stable disease at the two-year time point were permitted to continue to receive treatment in a blinded manner, at the investigator's discretion. The primary outcome of SOLO1 was investigator-assessed progression-free survival (PFS) at data cut-off (17th May 2018). A smaller proportion of patients in the olaparib arm had progressed or died than in the placebo arm (39.2% versus 73.3%). The median PFS was not reached in the olaparib arm but was estimated by the company to be at least three years longer than that observed with placebo (13.8 months). The results of six pre-planned sensitivity analyses were consistent with the results of the investigator-assessed PFS analysis, including an analysis of PFS assessed by blinded independent central review (BICR).

A key secondary outcome was overall survival (OS). Deaths were reported in 21.2% and 20.6% of patients in the olaparib and placebo arms, respectively, and median OS had not been reached in either arm, however the data were immature. In terms of the time from randomisation to the second disease progression or death (PFS2), there were deaths or second progression events in fewer patients in the olaparib arm (26.5%) than the placebo arm (39.7%) following second-line therapy; the median PFS2 was not reached in the olaparib arm and was 41.9 months in the placebo arm. A greater proportion of patients in the placebo arm required a first subsequent therapy than in the olaparib arm (71.8% and 38.1%, respectively), and the median time to first subsequent therapy (TFST) was considerably longer in the olaparib arm than in the placebo arm (51.8 months and 15.1 months, respectively). Similarly, a greater proportion of patients in the placebo arm required a second subsequent therapy than in the olaparib arm (49.6% and 29.6%, respectively), and the median time to second subsequent therapy (TSST) was not reached in the olaparib arm and was 40.7 months in the placebo arm. Health Related Quality of Life (HRQoL) was maintained over the duration of the trial in both the olaparib and placebo arms, with no worsening reported in either arm.

The safety and tolerability of olaparib in SOLO1 was similar to that of a pooled safety analysis of previous studies of olaparib tablets, with some specific events apparently being experienced by a greater proportion of patients in the olaparib arm of SOLO1 than in the pooled safety data. Most patients in the olaparib (98.5%) and placebo (92.3%) arms experienced at least one adverse event (AE), with 39.2% and 18.5% respectively experiencing at least one Grade 3 AE and 20.8% and 12.3% respectively experiencing at least one serious AE (SAE). The most common AEs reported by patients in the olaparib arm relative to the placebo arm were nausea, fatigue, vomiting, anaemia and diarrhoea, and the most

common SAE was anaemia. There were no treatment-related deaths in either arm during the therapy period or up to 30 days after discontinuation of olaparib/placebo, although three deaths (all cases of acute myeloid leukaemia/myelodysplastic syndrome) were reported in the olaparib arm (and none in the placebo arm) during longer-term follow-up.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The systematic reviews presented in the CS appear to be comprehensive, and the ERG is confident that all relevant studies of olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy were included. The quality assessment tools used to appraise the included studies were considered appropriate by the ERG. All outcomes listed in the NICE scope were presented in the CS.

The ERG has two concerns relating to the reliability of the clinical effectiveness evidence relating to SOLO1. Firstly, a greater proportion of patients in the olaparib arm than the placebo arm was reported as having at least one protocol deviation, with the greatest difference being in the proportion of patients who had RECIST scans outside of a scheduled visit window on more than two occasions. The impact of this protocol deviation is difficult to assess; however the ERG considers this unlikely to impact on the conclusions of SOLO1 and the appraisal. Secondly, patients in SOLO1 were permitted to use a subsequent PARP inhibitor for maintenance therapy later in the clinical treatment pathway, and the potential impact of this on outcomes reported in the CS is difficult to assess. The CS reported an imbalance between the olaparib and placebo arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor, and it is unclear whether all patients who would currently be eligible to receive a subsequent PARP inhibitor in the treatment pathway received one in SOLO1. These factors complicate the interpretation of OS, PFS2 and TSST.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's *de novo* partitioned survival model assesses the cost-effectiveness of olaparib versus routine surveillance in patients with advanced ovarian cancer who have responded (either completely or partially) to first-line platinum-based chemotherapy. Incremental health gains, costs and cost-effectiveness of olaparib are evaluated over a 50-year time horizon from the perspective of the NHS and Personal Social Services (PSS) and were calculated using a discount rate of 1.5% per annum. The company's model comprises three health states (progression free, progressed disease and death) which reflect the PFS and OS clinical outcomes. Survival models for PFS and OS in the olaparib arm, were generated from analyses of time to event data from SOLO1. In the base case, PFS is modelled using the Kaplan-Meier curves for the first two years, and independent log-normal distributions afterwards. OS in the olaparib arm is modelled using the Kaplan-Meier curve for the first two years, and a log-logistic distribution afterwards. OS in the routine surveillance arm is modelled using the Kaplan-Meier curve

for placebo in the first two years, after this point, OS is estimated using a log-logistic distribution fitted to the olaparib arm of SOLO1 and a treatment effect calculated based on time within PFS2. This assumes that the impact of olaparib on PFS 2 is a direct surrogate for the treatment effect of olaparib on OS and ignores the observed OS data. HRQoL is assumed to be principally determined by progression status. Utility estimates were derived from EQ-5D-5L data collected in SOLO1 and, mapped to EQ-5D-3L health state valuations supplemented by literature and assumptions. Resource use estimates and costs were based on data collected in SOLO1, the Yorkshire cancer guidelines network, routine cost sources clinical opinion and other literature.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG critically appraised the company's economic analysis, verified the company's implementation of the curves and checked the formulae in the company's model. The key issue regarding the submission is that the OS curve for the routine surveillance arm in the company's economic model lacks face validity when compared to the observed SOLO1 data, as it diverged from the routine surveillance Kaplan-Meier curve. This leads to a favourable estimate of the life years and quality adjusted life years (QALYs) gained by patients receiving olaparib compared to the scenario where they would have received routine surveillance. Consequently, the ERG believes that the incremental cost-effectiveness ratios (ICERs) presented in the CS are overly favourable to olaparib. Other issues identified by the ERG included: (1) Further concerns regarding the company's curve fitting; (2) Unrealistic treatment pathways; (3) Exclusion of PFS2 from the economic model; (4) Whether olaparib meets the criteria in Section 6.2.19 of the NICE methods guide for discounting costs and QALYs at a rate of 1.5% per annum; (5) Populations in the final scope not included in the model; (6) The implementation of dose reductions within the company's estimates of the cost of olaparib; (7) The inability to remove the effects of niraparib maintenance therapy from the company's model; (8) The use of subsequent PARP inhibitors by patients receiving olaparib; and, (9) The probabilistic sensitivity analysis (PSA) results lack face validity

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company undertook a reasonably comprehensive systematic review of olaparib as a maintenance therapy after response to first-line platinum-based chemotherapy for patients with advanced ovarian cancer. No major limitations were noted in the review. A key strength in the evidence base is that the pivotal trial, SOLO1, was rated as being at low risk of bias by both the company and the ERG.

The company undertook a reasonably comprehensive review of existing economic evaluations for olaparib compared to routine surveillance for patients with advanced ovarian cancer who have

responded to first-line platinum-based chemotherapy. The ERG are satisfied that no other economic evaluations relevant to this appraisal have been missed.

1.6.2 Weaknesses and areas of uncertainty

The key weaknesses in the economic and clinical evidence base relate to:

- The OS curve selected for the routine surveillance arm, which exhibits a lack of face validity when compared to the Kaplan-Meier curve from SOLO1.
- Whether or not the use of subsequent PARP inhibitors in the placebo arm of SOLO1 are reflective of current UK clinical practice.
- The proposed use of olaparib in this appraisal would mean that if olaparib were approved, patients would only be eligible to receive a PARP inhibitors at once in the pathway. This contradicts the use of olaparib in SOLO1, as patients in the olaparib arm were eligible to receive a subsequent PARP inhibitor.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Due to the uncertainties in the extrapolation of overall survival, the ERG does not have a preferred ICER. The ERG believe it is plausible that the ICER of olaparib compared to routine surveillance is in excess of £500,000 per QALY gained. This ICER is different from the ICER in the CS because the ERG explored different assumptions related to OS in exploratory analyses. Other exploratory analyses by the ERG indicated that lowering the utility of patients in the progressed disease health state would moderately decreased the ICER whereas increasing the cost of olaparib, so the model did not include cost reductions due to either dose reductions or interruptions, moderately increased the ICER.

2 BACKGROUND

This report provides a review of the evidence submitted by the company (AstraZeneca) in support of olaparib for maintenance treatment of advanced breast cancer susceptibility gene (BRCA) mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. It considers both parts of the company submission (CS) which consisted of their documents received on the 3rd December 2018 and the executable version of the company's model received on the 17th December 2018, as well as the clarification response received on the 14th January 2019.[1, 2] In response to the clarification questions, the company revised their submitted economic model and this was received by the evidence review group (ERG) on the 31st January 2019.

2.1 Critique of company's description of underlying health problem

The ERG considers that the company's description of the underlying health problem in the CS is appropriate.[1] The company's description of the underlying health problem is briefly described in this section.

In brief, ovarian cancers originate in the ovary, fallopian tube or primary peritoneum and are typically diagnosed at an advanced stage. Advanced ovarian cancer is defined in the CS as either Stage III or IV tumour, as defined using the International Federation of Gynaecology and Obstetrics (FIGO) staging system.[1, 3] However, the final scope describes advanced ovarian cancer as falling within stages II to IV.[4] Henceforth, the ERG report will use the definition of advanced ovarian cancer as being a Stage III or IV tumour to be consistent with the CS.[1] In England in 2014, 5% of all ovarian cancer tumours were diagnosed at Stage II, 31% were diagnosed at Stage III and 18% were diagnosed at Stage IV.[5] However, in this dataset 15% of all tumours did not have a recorded stage at diagnosis. Approximately 20 to 25% of patients diagnosed with ovarian cancer will also have a BRCA mutation.[6-10] Similar clinical outcomes are observed in patents with a BRCA mutation regardless of whether the patient has a germline (inherited) or somatic (acquired) mutation.[11-16] The ERG's clinical advisors believe that BRCA mutation testing for germline mutations is likely to be standard practice at diagnosis for patients with ovarian cancer within the next few years. However, testing for somatic mutations is unlikely to become standard practice due to requiring the collection of tumour samples. A subset of patients who are diagnosed with advanced ovarian cancer will receive and respond to first line platinum-based chemotherapy, further details on the treatment pathways for these patients is given in Section 2.2.

No direct evidence exists on the incidence of advanced ovarian cancer for patients with a BRCA mutation who also respond (completely or partially) to first line platinum-based chemotherapy. In the CS, the company estimates that 2241 patients per year present with advanced ovarian cancer.[1] Of these

patients, 476 are estimated be eligible to receive olaparib in this indication, as they will have a BRCA mutation and will have responded to first line platinum-based chemotherapy.

Advanced ovarian cancer is associated with an increased mortality rate compared with the general population. The most recent Cancer Research UK data suggest that the one-year age-standardised net survival for patients diagnosed with ovarian cancer in England in 2014 was 71.0% for patients diagnosed with a Stage III tumour and 51.4% for patients diagnosed with a Stage IV tumour.[5] Outcomes at five years appear to be significantly worse, with the five-year relative survival for patients diagnosed with ovarian cancer, between 2002 and 2006, in the former Anglia cancer network being 18.6% for patients diagnosed with a Stage III tumour and 3.5% for patients diagnosed with a Stage IV tumour. Symptoms of ovarian cancer include: abdominal distention; feeling full and/or loss of appetite; pelvic or abdominal pain; increased urinary urgency and/or frequency; irregular periods; lower abdominal and back pain; constipation; nausea; anorexia; dyspepsia; and extreme fatigue.

2.2 Critique of company's overview of current service provision

In general, the CS provides a reasonable description of service provision for people with BRCA mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.[1] The treatment pathway is briefly described in this section.

After diagnosis, patients with advanced ovarian cancer and a BRCA mutation will typically receive cytoreductive surgery followed by platinum-based chemotherapy regimen, unless the woman cannot tolerate first line platinum-based chemotherapy. The aim of this first line treatment regimen is to cure the patient if possible. In the response evaluation criteria in solid tumours (RECIST) 1.1 definitions, patients can either have a: complete response; partial response; progressive disease; or, stable disease following their first line treatment.[17] The RECIST definitions of these tumour evaluations are given in Box 1.

Box 1: The definition of complete response, partial response, progressive disease and stable disease in the RECIST 1.1 criteria[17]

Complete response: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive disease: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Stable disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

If a patient's ovarian cancer progresses after first-line treatment, then it is typically considered to be incurable. They will usually receive further platinum-based chemotherapy (and be denoted platinum sensitive) if the progression was more than 6 months after they responded (using the RECIST 1.1 definitions) to their last line of treatment, otherwise they will receive non-platinum-based chemotherapy (and be denoted platinum insensitive). Patients can experience further progressions and further lines of chemotherapy. If a patient has a platinum sensitive tumour, then using a poly (ADP-ribose) polymerase (PARP) inhibitor as a maintenance treatment may be considered. PARP inhibitors that have been, or are currently being appraised by the National Institute for Health and Care Excellence (NICE) are niraparib and olaparib. Details on current recommendations and ongoing appraisals for both of these products are provided in the paragraphs below.

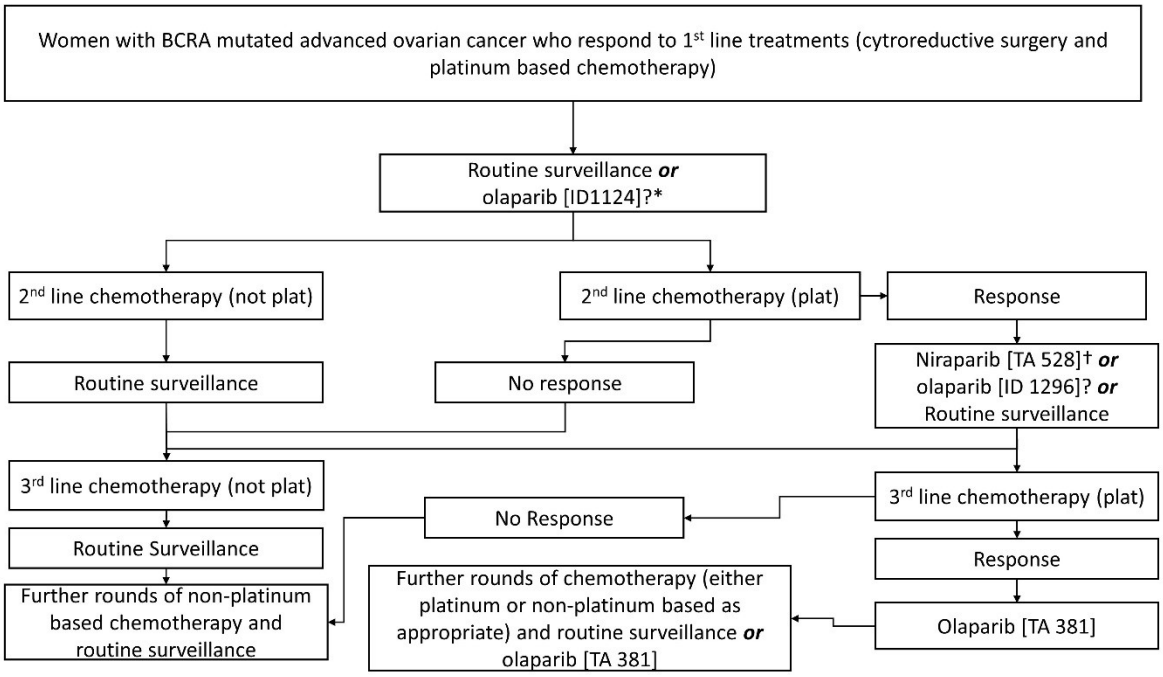
Niraparib is recommended for use within the Cancer Drugs Fund (CDF) as a maintenance treatment option for patients with relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response following platinum-based second-line chemotherapy and who have a germline BRCA mutation where the conditions in the managed access agreement for niraparib are followed.[18] The managed access agreement specifies that patients are not eligible for niraparib if they have previously received any PARP inhibitor.

Olaparib tablets are currently being considered by NICE for use in patients with recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to two treatments with platinum-based chemotherapy [ID1296].[19] Olaparib capsules are recommended by NICE in TA 381 for use as a maintenance treatment for those patients with BRCA mutated, platinum sensitive, ovarian,

fallopian tube or peritoneal cancer who have responded to three or more courses of platinum-based chemotherapy and the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company.[20]

This appraisal considers the use of olaparib after response to first line treatment which includes a platinum-based chemotherapy for patients with a BRCA mutation (either germline or somatic). This represents moving olaparib forward in the treatment pathway from its present position. After responding to first line treatment, current care consists of surveillance up until either: the patient's disease progresses or five years has passed and the patient is discharged. A summary of the current treatment pathways for patients diagnosed with BRCA mutated advanced ovarian cancer is provided in Figure 1. It should be noted that a woman may not progress through the pathway, due to death and/or lack of a subsequent disease progression.

Figure 1: The current pathways for the diagnosis and treatment of BRCA mutated advanced ovarian cancer



BRCA, breast cancer susceptibility gene; plat, platinum-based chemotherapy; non-plat, platinum-based chemotherapy; TA, technology appraisal guidance

Note, death is not included in this figure, but can occur at any time during this pathway.

? – this technology is currently under appraisal by NICE

* - this technology is the indication been considered in this appraisal

† - this treatment is only approved for use within the cancer drugs fund

A subgroup of patients in the population under appraisal would be eligible to receive bevacizumab as an addition to their first-line platinum-based chemotherapy and as a subsequent maintenance treatment, through the CDF. The subgroup would be those patients who have a stage IIIc or IV tumour which is suboptimally debulked either at primary or delayed primary (interval) surgery (including peritoneal and fallopian tube cancer) or is unsuitable for debulking surgery. As bevacizumab is only available through the CDF, it is not within the scope of this appraisal and it is not considered as a direct comparator and will not be discussed further.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This section presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlines in the final NICE scope[4] and addressed in the CS is presented in Table 1.

Table 1: Critique of the company's statement of the decision problem

	Final scope issued by NICE[4]	Decision problem addressed in the CS[1]	Company's rationale if different from the final NICE scope	ERG comment
Population	Patients with newly-diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, who are in response (complete or partial) to first-line platinum-based chemotherapy	As per final scope	NA	The ERG notes that the final scope issued by NICE describes advanced ovarian cancer as FIGO stages II to IV.[4] Patients diagnosed with FIGO stage II ovarian cancer are not included in the population of the CS.[1] Furthermore the population within the CS is limited to patients with high grade serous tumours.
Intervention	Olaparib	As per final scope	NA	
Comparator	Routine surveillance	As per final scope	NA	
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival	As per scope In addition, data are presented for the pre-	NA	The ERG notes that in addition to the best overall response, the CS reports on the additional endpoint of:

	Progression-free survival2 (i.e. progression-free survival on next line of therapy) time to next line of therapy adverse effects of treatment health-related quality of life	specified secondary endpoint of best overall response		time to second subsequent therapy
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	No equality issues related to the use of olaparib have been identified or are foreseen. Consideration of non-standard discount rates should be given, under the criteria in section 6.2.19 of the NICE methods guide.	NA	The ERG does not believe that the criteria in section 6.2.19 of the NICE methods guide are met (see Section 5.3.4).

NICE, national institute for health and care excellence; CS, company submission; ERG, evidence review group; BRCA, breast cancer susceptibility gene; FIGO, International Federation of Gynaecology and Obstetrics

3.1 Population

The population defined in the final NICE scope relates to people with BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer that has responded (completely or partially) to first-line platinum-based chemotherapy.

The ERG notes that there are two potential discrepancies in the population defined in the NICE scope and draft marketing authorisation compared to the evidence presented in the CS.[1, 4]

The first discrepancy relates to the definition of advanced ovarian cancer. The definition in the CS for: advanced ovarian cancer is a tumour that is diagnosed at either Stage III or IV using the FIGO staging system; and response (complete or partial) are based on the RECIST 1.1 criteria.[1, 3, 17] The final scope describes advanced ovarian cancer as being FIGO stages II, III and IV.[4] The ERG notes that there is no clinical or economic evidence provided in the CS for the use of maintenance olaparib for patients diagnosed with FIGO stage II BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.[1]

The second discrepancy relates to the exclusion of patients who do not have a high grade tumour from the population. The grade of cancer that patients are diagnosed with is left unspecified in the NICE scope, implying that the population is all patients with a BRCA mutated advanced ovarian cancer who have responded to one line of platinum-based chemotherapy, regardless of the grade of their cancer.[4] The key study underpinning the CS is the SOLO1 study.[1, 21] The SOLO1 study only included patients with a high grade serous or endometroid ovarian cancer.[21] Consequently, patients without a high grade cancer ovarian cancer were excluded from SOLO1. It should be noted that, this is in line with the proposed marketing authorisation submitted by the company which is "*maintenance treatment of adult patients with newly diagnosed advanced BRCA1/2-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first line platinum-based chemotherapy*".[1]

3.2 Intervention

The intervention under appraisal is olaparib (300mg twice daily). Four 150mg tablets are required per day. Olaparib is a PARP inhibitor. Treatment may be interrupted and dose reduction can be considered, to manage adverse reactions, such as nausea, vomiting, diarrhoea and anaemia. If it is decided to reduce the dose to manage adverse reactions, the dose can be reduced to either 250mg twice daily or 200mg twice daily. Olaparib is available as both a 150mg and as a 100mg tablet for use if the dose is reduced.

As of the time of writing this report, the European Medicines Agency (EMA) is evaluating olaparib in the following indication: "*Monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced BRCA1- or BRCA2-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy*".[1] Consequently, olaparib does not currently hold a European Union (EU) marketing authorisation in this population.

The list price of olaparib stated in the CS is £2317.50 per 56 tablet (14 day) pack.[1] This list price matches that reported in the November 2018 edition of the British National Formulary (BNF).[22] The ERG notes that the cost of an olaparib tablet is the same regardless of whether it is a 100mg tablet or a 150mg tablet.

Contraindications for olaparib tablets include: severe renal impairment (creatinine clearance ≤ 30 ml/min); severe hepatic impairment (Child-Pugh classification C); and, pregnancy.[1] Due to olaparib being contraindicated in pregnant patients, patients of childbearing potential must have a pregnancy test prior to starting treatment and use a hormonal contraceptive during the course of their olaparib treatment and for one month after their treatment has finished. Furthermore, the use of an additional non-hormonal contraceptive should be considered, as it cannot be excluded that olaparib may reduce the effectiveness of hormonal contraceptives. Patients who receive olaparib must not breast feed during treatment and for 1 month after the last dose.

In response to clarification question B4, the company state "… *it is anticipated that patients will only receive one course of treatment with a PARP inhibitor within the clinical management pathway for advanced ovarian cancer*".[2] The ERG note that [redacted] of patients in the olaparib arm of the SOLO1 study received a subsequent PARP inhibitor, the ERG note that over the same period 39.2% of patients progressed or died in the olaparib arm.[1] Consequently, this proposed use of olaparib is not supported by the key clinical study in this appraisal.

3.3 Comparators

The final NICE scope identified routine surveillance as the only relevant comparator.[4]

The company's review of clinical effectiveness (see Section 4) only identified one study (SOLO1) which included a direct comparison of olaparib versus routine surveillance in the population of interest.[21] The clinical evidence which is used to estimate the differences in costs and quality-adjusted life years (QALYs) between olaparib and routine surveillance in the health economic model is largely based on the data collected in SOLO1.

3.4 Outcomes

The final NICE scope lists the following outcomes[4]:

- Overall survival (OS)
- Progression free survival (PFS)
- Progression free survival 2, progression free survival on the next therapy line (PFS2)
- Time to next line of therapy
- Adverse effects of treatment
- Health related quality of life (HRQoL)

All of these endpoints are reported in the CS.[1] It should be noted that the time to next line of therapy is termed as time to first subsequent treatment (TFST) in the CS.[1] In addition to these outcomes time to second subsequent treatment (TSST), best overall response and time to subsequent PARP inhibitor are also reported.

3.5 Other relevant factors

The CS (page 16) states that there are no equality considerations relevant for the use of olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.[1]

The company claims that olaparib meets the criteria set out in Section 6.2.19 of the NICE methods guide (CS[1], page 64) relating to using discount rates that are 1.5% per annum instead of the standard 3.5%.[1, 23] These criteria require that: olaparib restores people to full health for a long period (normally at least 30 years); people receiving standard care have a severely impaired quality of life or would otherwise die, and; olaparib would not commit the NHS to significant irrecoverable costs. The ERG believes that olaparib does not meet these criteria and, as such, both costs and QALYs should be discounted at 3.5% per annum (see Sections 5.3.4 and 5.4).

4 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS[1] for olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy. Section 4.1 provides a critique of the company's systematic review. Section 4.2 provides a summary of the clinical effectiveness and safety results together with a critique of the included study. Sections 4.3 to 4.5 of the template (relating to indirect comparisons and additional work undertaken by the ERG) are not applicable. Section 4.6 provides the conclusions of the clinical effectiveness section.

4.1 Critique of the methods of review(s)

The company undertook a systematic literature review to identify all relevant published studies reporting the use of health technologies in adult patients with ovarian cancer who have a BRCA mutation and have received first-line platinum-based chemotherapy. The systematic review methods for the clinical evidence are detailed in Section B.2.1 of the CS and CS Appendix C.[1]

4.1.1 Searches

The CS includes an a systematic literature review of clinical effectiveness of health technologies including olaparib in adult patients with ovarian cancer who have a BRCA mutation and have previously received first-line platinum-based chemotherapy.[1]

Literature searches (reproduced in the CS[1] Appendix D, section D1.1) cover the three core databases required by NICE (Medline, EMBASE and CENTRAL – although rather than simply searching CENTRAL, they searched they entire Cochrane Library and applied an unvalidated randomised controlled trial (RCT) filter to the results). Searches were also conducted to identify relevant conference proceedings and NICE health technology assessments.

Unusually, the searches appear to have been conducted in EMBASE (via Ovid) first of all and subsequently run with minimal alteration on Medline and Cochrane. Emtree headings (e.g. "ovary cancer/" have been exploded – increasing sensitivity – but also focused (i.e. only retrieved where they are a major heading). Focusing on major headings only is not advisable when conducting a comprehensive search for the purposes of a systematic review, as articles where 'ovary cancer' is a minor heading may also be relevant. The Emtree headings have not been translated to MeSH for the Medline and Cochrane searches, although the Ovid platform appears to have successfully mapped them between databases. The impact of these errors is expected to be mitigated by the inclusion of a reasonably sensitive title/abstract search string around the same concept.

The ERG notes that the searches on all three databases use a virtually identical RCT filter. While the company state in their clarification response[2] (A17) that this is "*based on accepted filters*", it should be noted that search filters are generally optimized for use on a specific platform and it should not be taken for granted that the same terms will be equally effective when replicated across multiple databases. A wealth of published and validated search filters is available for identifying RCT evidence[24] and using one of these proven strategies with appropriate citation would reassure the ERG that coverage was comprehensive.

The ERG notes that the searches only cover ovarian cancer where the BRCA mutation is mentioned in the title, abstract or indexing fields, and therefore studies reporting mixed populations may potentially have been missed (although in their response to clarification question A18, the company state that they believe this not to be the case and point out that they conducted supplementary reference list searching to avoid missing any studies).[2]

The searches are reasonably thorough and well-reported however without re-running the searches and screening the results (which is not viable within the timelines of this project) it is impossible for the ERG to be certain whether any studies have been missed.

4.1.2 Inclusion criteria

The company provided two sets of inclusion criteria, which differ from one another; one in the CS and another in Appendix D of the CS.[1] The company's inclusion criteria as provided in Document B of the CS are presented in Table 7, page 20, CS.[1] The inclusion criteria are generally consistent with the NICE final scope,[4] with three inconsistencies: (1) in the company's systematic review inclusion criteria, the population has been expanded to include patients who received adjuvant and neoadjuvant treatment; (2) the company's systematic review inclusion criteria list 'any' for the intervention, whereas olaparib is specific as the intervention in the final scope; and (3) no comparators were provided in the company's inclusion criteria despite routine surveillance being listed as a comparator in the final scope.[4] While not consistent with the decision problem, the ERG does not consider these differences to be problematic, as they would make the scope of the review broader, rather than narrower, and should not have resulted in any relevant papers being missed by the review. In response to a request for clarification from the ERG (see clarification response,[2] question A4), the company stated that the scope of the systematic review in CS is broader than the NICE scope in order to meet the requirements of multiple health technology assessments internationally, of which NICE is one.[1] In both sets of criteria, eligibility is restricted to English language publications, which introduces the risk that relevant data not published in the English language may have been missed by the review.

The company also presented a summary of inclusion criteria in Table 4 in Appendix D of the CS.[1] There are some inconsistencies between this description of inclusion criteria and the decision problem, in terms of: (1) under 'intervention', the inclusion criteria in Appendix D state 'any', whereas in the decision problem this is 'olaparib', and in the CS, Table 7, this is reported as 'first-line maintenance therapy in BRCA-mutated ovarian cancer that has responded to platinum-based chemotherapy'; and (2) under 'comparator', the inclusion criteria in Appendix D state, 'another active intervention' and 'placebo', whereas in the CS, Table 7, the comparator is not stated, and in the final scope the comparator is stated to be 'routine surveillance'.[1] The implications of this are unclear, although again the ERG expects that these criteria would make the review more inclusive and thus would not likely result in any relevant studies being missed.

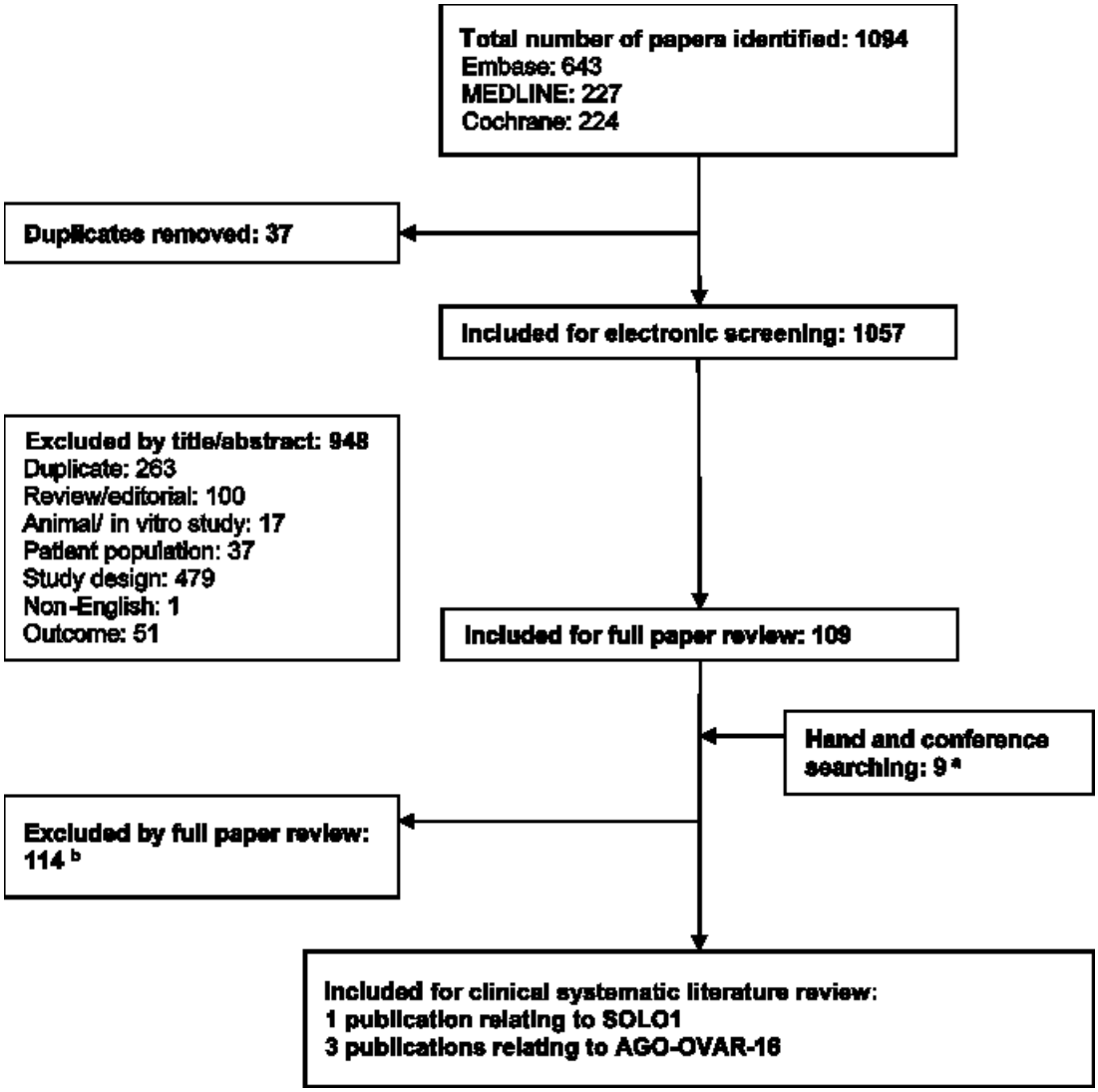
4.1.3 Critique of study selection

The CS states that two independent reviewers screened abstracts of identified records against the eligibility criteria specified in CS, Table 7.[1] Any disputes were discussed and resolved. It was intended that, where there was no resolution, a third reviewer would reconcile disputes, however in response to a request for clarification from the ERG (see clarification response,[2] question A6), the company stated that there were no disputes between independent reviewers that required reconciliation by a third reviewer. The ERG considers this to be an appropriate and high-quality reviewing method. Full texts of all papers meeting the eligibility criteria in the abstract screening were obtained and screened against the eligibility criteria, although no detail is reported in the CS about the number of reviewers who screened full texts for inclusion, or the process of decision-making. Consequently, the ERG cannot comment on this aspect of study selection. No reasons for excluding studies at full text screening have been provided in the CS (Appendix D) nor in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram, and a list of papers excluded at full text screening has not been provided by the company.[1] Therefore, the ERG cannot comment on the reasons for exclusion, nor check for agreement. Nevertheless, neither the ERG nor clinical advisors to the ERG are aware of any additional studies within the scope of this appraisal.

A PRISMA diagram is presented in Appendix D (Figure 1, page 8) of the CS, referring to a total of one study from three publications relating to first-line maintenance and seven studies from 40 publications relating to treatment after second-line or later recurrence.[1] This figure demonstrated inconsistency with the text in terms of the number of included studies, and therefore the ERG sought clarification from the company in terms of the number of publications and studies of first-line maintenance therapy identified (see clarification response,[2] question A5), the number of publications and studies of second-line maintenance therapy identified according to the PRISMA flow diagram (see clarification response,[2] question A10), and text stating that two clinical studies were identified (see clarification response,[2] question A12). In response to these clarification requests, the company provided a revised PRISMA

flow diagram (see Figure 2), which clarifies that one publication relating to the SOLO1 trial of olaparib and three publications relating to the AGO-OVAR-16 study of pazopanib (which were also listed under clarification response,[2] question A5) were included in the company's systematic review. The three publications relating to the AGO-OVAR-16 study of pazopanib were not examined in the CS as pazopanib is outside the scope of the current appraisal, a point on which the ERG agrees.[1, 2] The company also clarified that the SOLO1 trial was identified through hand searching after the date of the electronic literature search (see clarification response,[2] question A12).

Figure 2: PRISMA flow diagram for clinical systematic literature review (updated) (reproduced from company's clarification response, question A10)



Footnotes specifying [a] and [b] were not provided in the clarification response (question A10)[2]

4.1.4 Critique of data extraction

Data were extracted by one reviewer and checked by a second reviewer (CS[1] Appendix D, page 8), with no detail on how any disagreements were resolved, or on which fields were extracted. The ideal

approach to data extraction in systematic reviews is double independent data extraction, however the process of checking by a second reviewer would have rendered errors in data extraction less likely.

In response to a request for clarification from the ERG (clarification response,[2] question A11), the company stated that the following data fields were extracted:

- Reference, year, publication type
- Clinical trial identifier, country(ies) where study was performed
- Study design, treatment (intervention, comparator, duration of follow-up)
- Patient population and baseline characteristics
- Results (OS, PFS, PFS2, time to next line of treatment, adverse events of treatment and health-related quality of life)

The ERG considers this to be comprehensive.

4.1.5 Critique of quality assessment

The process of conducting quality assessment was not described in the CS,[1] and it is thus not clear by whom this was done, if it was checked, and if so, how any disagreements were resolved.

Study quality was assessed using the checklist recommended by NICE for assessing the methodological quality of RCTs, which bears a close resemblance to the Cochrane Risk of Bias tool,[25] which is widely regarded as the most robust tool for the assessment of bias in RCTs.

The overall risk of bias was reported in the CS as being low, however no attempt has been made to integrate the quality assessment into the findings, or to consider the overall impact of the quality of the included trial on the results.[1]

Quality assessment of the included trial, SOLO1, as undertaken by the company and the ERG, is presented in section 4.2.3.

4.1.6 Critique of evidence synthesis

The CS does not include any formal evidence synthesis, which the ERG agrees is appropriate, given only one relevant study is reported.[1]

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Studies included in/excluded from the submission

The CS[1] includes one study that examines the efficacy of olaparib for maintenance treatment in patients with newly diagnosed BRCA-mutated advanced ovarian cancer who had a complete or partial response to first-line platinum-based chemotherapy. SOLO1 is a pivotal international, randomised, double-blind, phase 3 placebo-controlled trial (CS[1] page 66; clinical study report (CSR);[26] Moore et al.2018[21]). The CS and CSR state SOLO1 was conducted across 15 countries: Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, United Kingdom and the United States).[1, 26] Twenty-two patients (5.6%) enrolled in SOLO1 were from six study centres in the UK.[1, 26] The study characteristics of SOLO1 are presented in the CS, Table 8, page 21.[1]

4.2.1.1 Patients

Eligibility criteria for SOLO1 are presented in Table 9 of the CS,[1] pages 23 to 24. There are some differences between the eligibility criteria for the SOLO1 trial and the NICE final scope, which warrant consideration. As mentioned in Section 3.1, advanced ovarian, endometrioid, primary peritoneal and/or fallopian tube cancer was described as FIGO stages II to IV in the NICE final scope,[4] but was defined as FIGO stages III and IV in the SOLO1 inclusion criteria. Therefore, there is currently no evidence relating to patients with stage II disease. It is also worth noting that women with stage II disease were initially within the inclusion criteria in the original version but removed when the protocol was amended.[26]

The SOLO1 inclusion criteria specified that patients must have had one attempt at optimal upfront or interval debulking surgery if stage III, or either a biopsy and/or upfront or interval debulking surgery if stage IV, whereas debulking surgery is not mentioned in the NICE final scope.[4] Other criteria specified for inclusion in SOLO1 but not mentioned in the NICE final scope include: Cancer Antigen 125 (CA-125) measurements below the upper limit of normal, or within 15% of an initial test taken at least seven days previously; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; a life expectancy of at least 16 weeks; and a minimum of six and maximum of nine cycles (with a minimum of four in the case of discontinuation due to toxicity) of first-line chemotherapy. Therefore, there is no evidence for the efficacy of olaparib among patients with an ECOG performance status of 2. Clinical advisors to the ERG agreed that the inclusion criteria were reasonable, with the exception that not all patients in the UK would receive six cycles of chemotherapy in first-line treatment.

Figure 3, page 26 of the CS presents a flow diagram of patient flow through the SOLO1 trial.[1] In response to a request for clarification from the ERG (see clarification response,[2] question C1), the company clarified that the data in Figure 1 was correct at the time of data cut-off, 17th May 2018.

Initially, 391 patients were randomised (olaparib n=260; placebo n=131) and all but one patient in the placebo arm (who withdrew prior to treatment) received at least one dose of the study drug (olaparib or placebo).[1] Of these, 274 patients (olaparib n=183; placebo n=91) were still being followed up at data cut-off (17th May 2018), and 14 patients (olaparib n=13, placebo n=1) were receiving ongoing study treatment. Of the 260 patients randomised to the olaparib arm who received at least one dose of olaparib, 247 (95.0%) discontinued treatment; in the majority of cases this was due to completing two years of treatment as per protocol (see Section 4.2.1.2 for details of the treatment protocol) (47.3%), objective disease progression (19.6%) and adverse events (11.5%). Of the 130 patients randomised to the placebo arm who received at least one dose of placebo, 129 (99.2%) discontinued treatment; in the majority of cases this was due to objective disease progression (60.0%) or completing two years of treatment as per protocol (26.9%).

Demographic and clinical characteristics were comparable between the olaparib and placebo groups at baseline, although the ERG notes that there was a slightly greater proportion of patients in the olaparib arm with stage III disease group than the placebo arm (84.6% versus 80.2%), and, conversely, a slightly smaller proportion of patients in the olaparib arm with stage IV disease than in the placebo arm (15.4% versus 19.8%; see CS[1] Table 10, page 27), which may have been favourable to olaparib. In addition, a slightly smaller proportion of patients in the olaparib than the placebo arm scored "*normal activity*" (76.9% versus 80.2%) and a slightly greater proportion of patients in the olaparib than the placebo arm scored "*restricted activity*" (23.1% versus 19.1%) on the ECOG performance status measure, which may have been favourable to placebo. In terms of mutation type, 73.5% patients in the olaparib arm and 69.5% patients in the placebo arm had a BRCA1 mutation, 25.4% patients in the olaparib arm and 30.5% patients in the placebo arm had a BRCA2 mutation, and 1.2% patients in the olaparib arm and no patients in the placebo arm had both mutations. Clinical advice received by the ERG suggested that the patient characteristics of SOLO1 are broadly reflective of clinical practice in England.

4.2.1.2 Intervention

Patients in the olaparib arm of SOLO1 received 300mg (2 x 150mg tablets) twice daily, for two years (with no radiological evidence of disease) or until investigator-assessed objective disease progression on imaging, according to the RECIST, version 1.1.[21] Patients with residual evidence of stable disease at the two-year time point were permitted to continue to receive treatment in a blinded manner, at the investigator's discretion.[21] In response to a request for clarification from the ERG (see clarification response, question A2[2]), the company stated that the two-year treatment duration was requested and agreed with the US Food and Drug Administration (FDA) at the trial design stage, to avoid overtreatment (and associated risks and potential toxicities) and allow patients a period of time where they could be both progression-free and treatment-free. However, rather than basing the justification on design criteria the company offered further justification on the basis that, in the SOLO1 trial, patients

in the olaparib arm had a median of [redacted] months progression-free and off treatment (based on the difference between a median time to treatment discontinuation or death (TTD) of [redacted] months and a median TFST of 51.8 months), compared with [redacted] months in the placebo arm (based on the difference between a median TTD of [redacted] months and a median TFST of 15.1 months).[2]

Dose reductions were permitted.[1] Other cancer therapies (chemotherapy, immunotherapy, hormonal therapy, radiotherapy, biological therapy or another novel agent) were not permitted while the patient was receiving the study treatment,[26] and crossover between trial arms was not permitted.[21] In response to a request for clarification from the ERG (clarification response, question B4[2]), the company stated that it is anticipated that patients will only receive one treatment with a PARP inhibitor within the clinical management pathway for advanced ovarian cancer. Therefore there is a discrepancy between the clinical management pathway and the SOLO1 trial, as patients were permitted to take a subsequent PARP inhibitor as maintenance therapy following subsequent lines of platinum-based chemotherapy in the SOLO1 trial.[1] The CS reports that [redacted] received a subsequent PARP inhibitor.[1]

Between 0 and 3 months, 80.4% of 260 olaparib patients took a mean daily dose of >500 to ≤600mg olaparib, 13.8% took a mean daily dose of >400 to ≤500mg, and 5.8% took a mean daily dose of ≤400mg.[21, 26] During the 9-12 months period, these figures were 68.6%, 16.2% and 15.2% (of 204 patients), respectively, and during the greater than 12 months period, they were 67.9%, 18.1% and 14.0% (of 193 patients), respectively.[21, 26] The CSR[26] (Table 36, page 136) reports that [redacted] of patients in the olaparib arm had at least one dose modification, compared with [redacted] of patients in the placebo arm. Median total treatment duration was [redacted] weeks (approximately [redacted] months) in the olaparib arm and [redacted] weeks (approximately [redacted] months) in the placebo arm (CSR[26] page 133). Median actual treatment duration (total treatment duration minus treatment interruptions) in both arms was marginally lower ([redacted] and [redacted] weeks in the olaparib and placebo arms, respectively), suggesting that dose interruptions were generally short; [redacted] patients in the olaparib arm had any treatment interruption, compared with [redacted] in the placebo arm.[26]

Patients in both study arms were permitted to take any concomitant medication necessary for the patient's survival at the investigator's discretion, with the exception of medication believed to interfere with the study drug, including other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy, radiotherapy, biological therapy or other novel agent) (CSR,[26] page 44).

In response to a request for clarification from the ERG (see clarification response,[2] question A1), the company stated that 22.3% of patients in the olaparib arm and 38.2% of patients in the placebo arm

received subsequent platinum-based chemotherapy. The company also stated that of subsequent treatments, the most commonly reported were consistent with clinical practice, and included doxorubicin, gemcitabine, bevacizumab, and taxane.[2]

[redacted] ([redacted]) of patients had at least one protocol deviation before or during the SOLO1 trial that was defined as 'important'; this number was disproportionately higher in the olaparib arm ([redacted] [redacted] patients) than in the placebo arm ([redacted] [redacted] patients) (CSR[26] page 81). Please see Section 4.2.3.2 for further details.

4.2.1.3 Comparator

The comparator within the SOLO1 trial was a placebo tablet, matching the characteristics of olaparib. As with olaparib, patients took placebo tablets for two years (with no radiological evidence of disease) or until investigator-assessed objective disease progression on imaging, according to the RECIST, version 1.1.[21] Patients with residual evidence of stable disease at the two-year time point were permitted to continue to receive treatment in a blinded manner, at the investigator's discretion.[21] After the study treatment (olaparib or placebo) had been discontinued, patients could receive further anti-cancer treatment at the investigators' discretion.[1] This may have impacted on OS beyond the two-year treatment duration and/or beyond objective disease progression, and, since a greater proportion of patients in the placebo arm discontinued treatment due to objective disease progression (60.0%) than due to completing two years of treatment (26.9%), relative to the olaparib arm (19.6% and 47.3%, respectively), a greater proportion of patients in the placebo arm may have received subsequent treatment sooner than those in the olaparib arm, which may affect OS and PFS2 over the longer term. The use of concomitant natural/herbal products was permitted but discouraged.[26]

4.2.1.4 Outcomes

Table 2 summarises the outcomes listed in the CS.[1] A small number of outcomes presented in the CS were not included in the final NICE scope and are not directly mentioned in the EMA's guideline on the evaluation of anticancer medicinal products. [1, 4, 27]

All efficacy and HRQoL outcome data were analysed using the Full Analysis Set, consisting of all patients randomised following global recruitment to the study (n=391), on an intention-to-treat basis.[26]

Table 2: Summary of outcomes listed in the CS[1] and their relationship to EMA research recommendations,[27] the final NICE scope,[4] and the company's health economic model

Outcome	Recommended by EMA?	In NICE scope?	Used in economic model?	Defined *a priori*?
Primary outcome				
PFS – time from randomisation to objective disease progression using RECIST 1.1, or death from any cause. Assessed by computed tomography or magnetic resonance imaging every 12 weeks for up to 3 years, and then every 24 weeks. Assessment was also conducted by blinded independent central review, in a sensitivity analysis.	Y	Y	Y	Y
Secondary outcomes				
PFS2 – time from randomisation to second disease progression or death	Y	Y	Indirectly	Y
Time to first subsequent therapy (TFST) – time from randomisation to the first subsequent therapy or death	Could be considered under "alternative endpoints"	Y	N	N, added after the start of patient recruitment [a]
Time to second subsequent therapy (TSST) – time from randomisation to the second subsequent therapy or death	Could be considered under "alternative endpoints"	N	N	N, added after the start of patient recruitment [a]
Overall survival (OS)	Y	Y	Y	Y
HRQoL – assessed using the Trial Outcome Index (TOI) on the Functional Assessment of Cancer Therapy—Ovarian Cancer (FACT-O) questionnaire, change from baseline to 2 years	Y	Y	N	Y
Adverse events	Y	Y	Y	Y
Best overall response	Could be considered under ORR	N	N	Y
Time to treatment discontinuation or death (TTD)	N	N	Y	N, added after the start of patient recruitment [a]

[a] From CSR,[26] Table 6

Primary outcome

The primary outcome was PFS, assessed from the time of randomisation to objective disease progression using RECIST 1.1 criteria, or death from any cause. While OS is arguably the most important outcome of a trial, PFS is considered to be of benefit to patients and can be a feasible primary outcome.[27] Clinical advice to the ERG suggested that PFS is increasingly being used as a primary outcome in ovarian cancer trials.

PFS was assessed every 12 weeks for up to three years, and then every 24 weeks, using computed tomography or magnetic resonance imaging.[1, 21] The use of RECIST 1.1 criteria to determine disease status in the SOLO1 trial is partially consistent with clinical practice in England. Clinical advice to the ERG suggested that assessment is rarely this frequent in clinical practice, with RECIST assessments usually being made when patients presented with symptoms that may indicate a suspected relapse.

The primary outcome was originally specified as PFS assessed by blinded independent central review (BICR), however this was amended to investigator-assessed PFS, because emerging data suggested that it may not have been possible to obtain the events required for PFS assessed by BICR without changing the protocol design, due to a possible underestimate of the assumed median PFS for patients with BRCA mutated ovarian cancer (CSR[26] Table 6, page 72). The ERG suggests that the power of the test could have been maintained by increasing the sample size, although recognises that this would have meant an increase in the cost and duration of the study. A sensitivity analysis was undertaken using PFS assessed by BICR, and the hazard ratio (HR) for olaparib vs. placebo was very similar (see Section 4.2.4.1 of this report), so there seems to be little impact of this change in outcome on the trial findings. The CSR [26] (page 98) reported a 15% discordance between investigator and central reviews in declaring progression, but suggested this was not likely to introduce bias favouring the olaparib arm due to a positive difference between treatment arms in the early discrepancy rate and a negative difference between treatment arms in late discrepancy rate. The ERG suggests that unless the discrepancy between the outcome of the methods used to assess PFS is random then the impact on the logrank test and the difference in PFS survival functions is unknown.

Secondary outcomes

Outcomes listed in the final NICE scope[4] and reported in the CS[1] as secondary outcomes included:

- Overall survival (OS)
- Time to second progression or death (PFS2)
- Time to first subsequent therapy (TFST)
- HRQoL
- Adverse events

EMA research recommendations advise that OS be considered a secondary outcome in phase III trials where PFS is the primary outcome, and should demonstrate or show a trend towards superiority.[27]

PFS2 (defined as time from randomisation to second progression or death[28]) can provide an indication of the duration of treatment effects following initial disease progression (and subsequent treatment), and therefore can be a useful indicator of longer-term treatment effect where OS data are not mature.[27]

TFST/TSST might be considered among the "*alternative endpoints*" suggested by the EMA research recommendations[27] as acceptable. However, TFST, TSST and TTD were not pre-planned, but were introduced to the trial in amendments made after the start of patient recruitment; the reason given in the CSR[26] (Table 6) was to further assess efficacy. As such, these outcomes could be considered *post hoc* assessments, as they were not planned prior to the start of the trial. Clinical advice received by the ERG suggests that TFST may differ from PFS in that not all patients who progress will go on to receive subsequent treatment, either through patient choice or due to co-morbidities. Data from the CSR[26] suggest that 90.1% and 92.5% of the patients who progressed received subsequent chemotherapy in the olaparib and placebo arms, respectively.

HRQoL was assessed in SOLO1 using the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) questionnaire, the main outcome of which was the Trial Outcome Index (TOI) subscale.[1] The TOI assesses physical and functional wellbeing, and symptoms specific to ovarian cancer, and scores range from 0 to 100, with higher scores indicating better function.[29, 30] A change of ≥10 points was considered in the CS to be a clinically relevant or minimally important difference.[1] The EMA research recommendations[27] and EMA guidance on measuring HRQoL in oncology[31] recommend a validated cancer-specific HRQoL measure where possible (although they do not specify which instrument should be used), and as such, the FACT-O fulfils this criterion. Clinical advice received by the ERG suggested that these measures would not be used in clinical practice routinely, and HRQoL would normally be subjectively evaluated using clinical judgement. HRQoL was assessed from randomisation to 97 weeks, and therefore there are no data on the longer-term impact of olaparib on HRQoL beyond the end of the SOLO1 trial.

The method of measuring adverse events (AEs) was not given in the CS,[1] although the SOLO1 trial journal article (Moore *et al.,* 2018[21]) reported that the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 was used to grade AEs. The CSR[26] specified that the safety analysis set consisted of all patients who received at least one dose of randomised study drug as part of the global enrolment, including patients who had a dose reduction. All those who received olaparib were analysed in the olaparib arm for the safety analysis set; likewise for placebo (CSR[26] page 54). AEs

and serious adverse events (SAEs) were recorded from informed consent until 30 days after the last dose of olaparib/placebo, with the exception of myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) or any new primary malignancy occurring after the 30-day follow-up period, which were to be reported as an SAE (CSR[26] page 65). Treatment-related adverse events (or deaths) were those assessed by the investigator to have been reasonably caused by olaparib or placebo.[26] No definition of what constituted an SAE is present in the CS or CSR.[1, 26] It is also unclear whether AE data was actively elicited from patients as part of the assessment procedure, or recorded upon patient presentation with an AE.

4.2.1.5 Study design

SOLO1 was a double-blind, placebo-controlled, international, multi-centre, phase III RCT, where eligible patients (n=391) were randomised to olaparib or placebo. Patients were randomised at a 2:1 ratio olaparib:placebo stratified based on complete or partial response to first-line platinum chemotherapy. The ERG considers this an acceptable trial design to evaluate the efficacy of olaparib against routine surveillance, and the EMA evaluation guidelines[27] recommend the use of double-blind phase III RCTs for establishing the benefit-risk profile of a medicinal product.

4.2.1.6 Ongoing studies

The SOLO1 trial is currently ongoing, with data from the 17th May 2018 data cut-off used in the CS.[1] Further data are therefore expected from the SOLO1 trial on the efficacy and safety of olaparib. Study data collection was expected to last approximately 10 years from randomisation for all outcomes[28] (except for the primary outcome PFS, which was planned to be analysed when approximately 196 events had occurred [50% data maturity] or at 36 months after the last patient was randomised, whichever came first[1]), and final OS analyses are planned at approximately 60% maturity ([redacted]).[1] The planned follow-up duration was initially planned to be approximately seven years from randomisation.[28] No reason has been given for this protocol amendment.[26]

Seven additional trials of olaparib for various clinical indications are also listed in the CS,[1] however they are not relevant to the NICE final scope and will not be discussed further.

4.2.2 Details of relevant studies not included in the submission

The ERG is confident that SOLO1 is the only relevant study in this patient population, and that no relevant studies have been omitted from the CS.[1]

4.2.3 Summary and critique of the company's quality assessment

4.2.3.1 Critical appraisal of study quality of SOLO1

The company provided a critical appraisal of the validity of SOLO1 using the checklist recommended by NICE, which bears a close resemblance to the Cochrane Risk of Bias tool,[25] as noted in Section 4.1.5. A summary of the risk of bias in the SOLO1 trial undertaken by the company alongside the ERG's independent quality assessment is presented in Table 3. The ERG has also specified the level of risk of bias for each criterion.

Table 3: Company and ERG quality assessment of SOLO1 (adapted from CS[1], Table 11)

Quality assessment criterion question	Company quality assessment (yes/no/not clear/NA)		ERG quality assessment (yes/no/not clear/NA)	
	Grade	**Explanation**	**Grade**	**Explanation**
Was randomisation carried out appropriately?	Yes	In SOLO1, eligible patients were randomly assigned to the olaparib and placebo treatment groups in a set 2:1 ratio using an Interactive Voice Response System (IVRS). The investigators/sites determined the appropriate stratification variables for each patient at the time of randomization. A blocked randomisation was generated, and all centres used the same list to minimise imbalance in numbers of patients assigned to each group	Yes (Low risk)	Patients were randomised using an Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS) in a 2:1 ratio to olaparib tablets and placebo, stratified for response to first-line platinum chemotherapy (CR or PR).
Was the concealment of treatment allocation adequate?	Yes	In SOLO1, the actual treatment given to individual patients was determined by a concealed randomisation scheme that was loaded into the IVRS database. The randomisation scheme was produced by a computer software program called GRand (AZ Global Randomisation system) that incorporates a standard procedure for generating random numbers	Yes (Low risk)	IVRS/IWRS computer software was used for allocation.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline demographic and disease characteristics were well-balanced across the olaparib and placebo treatment groups in SOLO1	Yes (Low risk)	The olaparib and placebo arms were roughly equivalent on baseline disease characteristics, although there were some small differences on FIGO stage and BRCA mutation status.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely	Yes	Blinding was maintained throughout SOLO1. Un-blinding did not occur until after all planned analyses had been completed, unless in the case of medical emergency. Treatment identity was concealed using appearance-matched placebo and identical	Yes (Low risk)	Patients and care providers, and those who performed clinical assessments were blinded to the study treatment. Patients were not to be unblinded prior to the PFS analysis, except in medical emergencies. 38 (14.6%) patients in the olaparib arm and 52 (39.7%) patients in the placebo arm were

impact on the risk of bias (for each outcome)?		packaging, labelling and schedule of administration.		unblinded in total, 4 and 1 patients, respectively, were unblinded prior to investigator-assessed modified RECIST 1.1 progression. Unblinding prior to investigator-assessed RECIST 1.1 progression may have biased assessment of PFS, although the numbers concerned are small and therefore impact would be minimal. Unblinding following RECIST 1.1 assessment is unlikely to have impacted on OS as this is an objective outcome, and is also unlikely to have affected PFS2, TFST and TSST, as these are dependent on disease progression.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Few patients were lost to follow-up in SOLO1	No (Low risk)	29.6% and 30.5% patients in the olaparib and placebo arms, respectively, had terminated their involvement in the study at DCO, and reasons were broadly similar between arms.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All primary and secondary endpoint analyses are reported in the SOLO1 primary manuscript and Clinical Study Report	No (Low risk)	All outcomes specified in the protocol were reported on in the CS,[1] CSR[26] and/or Moore *et al.* (2018)[21] publication.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	SOLO1 efficacy data were analysed in the ITT population, which included all patients who underwent randomisation. Subgroup analyses are presented in Section B.2.7 and discussed in full detail within the Clinical Study Report	Yes (Low risk)	The full analysis set for the efficacy data used the ITT population, which included all patients randomised, which the ERG considers appropriate.

CR - complete response; DCO - data cut-off; IVRS - interactive voice response system; ITT - intent-to-treat; NA - not applicable; PR - partial response; RECIST - Response Evaluation Criteria in Solid Tumours, version 1.1.

The company's critical appraisal and the ERG's critical appraisal of the SOLO1 trial were similar. The ERG concludes that there is a low risk of bias for SOLO1. A disproportionately higher proportion of patients in the placebo arm compared with the olaparib arm (39.7% versus 14.6%) were unblinded during the trial, however the majority of these cases (34/38 [89%] in the olaparib arm and 51/52 [98%] in the placebo arm) were unblinded after investigator-assessed modified RECIST 1.1 progression. Thus, the ERG considers that the impact on PFS would have been minimal. The ERG considers it unlikely that unblinding following progression would have impacted on OS, which is a binary state, or PFS2, TFST or TSST, as these outcomes were dependent on disease progression in the trial.

4.2.3.2 Protocol deviations

The CSR[26] reports that [redacted] ([redacted]) patients were defined as having at least one important protocol deviation, with a disproportionately greater number in the olaparib arm ([redacted] patients [redacted]) than in the placebo arm ([redacted] patients [redacted]). In the olaparib arm, there was a greater proportion of patients who had RECIST scans outside of a scheduled visit window on >2 occasions, compared with the placebo arm ([redacted] and [redacted], respectively). In response to a request for clarification from the ERG (see clarification response,[2] question A8), the company stated that this difference may likely reflect the longer time to progression among patients in the olaparib arm, and, consequently the greater number of scans. The company also expressed a judgement that these protocol deviations were unlikely to have influenced the overall study conclusions, on the basis that the conclusions are considered robust and representative of the overall study data, and that the primary analysis of investigator-assessed PFS was consistent with the pre-planned sensitivity analysis presented in CS Table 13,[2] although no further details on this judgement were provided, or on which sensitivity analysis the company were referring to in the clarification response. The impact of this protocol deviation is difficult to assess; however, the ERG considers this unlikely to impact on the conclusions of the SOLO1 trial and the appraisal, in particular in relation to OS.

4.2.4 Summary and critique of results

The data cut-off for the primary analysis was 17th May 2018, and at this point the median duration of follow-up across both olaparib and placebo arms was 41 months.[1, 21] In response to a request for clarification from the ERG (see clarification response,[2] question A7), the company stated that the median follow-up time from randomisation to the date of censoring was 40.7 months ([redacted]) in the olaparib arm, and 41.2 months ([redacted]) in the placebo arm, and the data cut-off occurred 38 months after the last patient entered the trial.

4.2.4.1 PFS (primary endpoint)

Investigator-assessed PFS was analysed after 198 (of the 391 patients enrolled) had progressed or died, which the CS stated was at 50.6% data maturity, and the primary analysis is outlined in Table 12, page 31 of the CS.[1] A smaller proportion of patients in the olaparib arm had progressed or died than in the placebo arm (39.2% versus 73.3%).[1] The median PFS was not reached in the olaparib arm (but was estimated by the company to be at least three years longer than that observed with placebo based on PFS sensitivity analyses and analyses of mean TFST), and was 13.8 months in the placebo arm, and the hazard ratio (HR) was reported as being 0.30 (0.23, 0.41), $P<0.0001$, suggesting significantly greater efficacy of olaparib over placebo on investigator-assessed PFS. The CSR[26] (Table 18, page 95) reports the proportion of patients with PFS in the olaparib and placebo arms at 6 months as 93.9% and 80.6%, respectively; at 12 months as 87.7% and 51.4%, respectively; at 24 months as 73.6% and 34.6%, respectively; at 36 months as 60.4% and 26.9%, respectively; and at 48 months as 52.6% and 11.4%, respectively.

The results of six pre-planned sensitivity analyses were also reported in the CS (Table 13, page 33),[1] including assessment of PFS made using BICR, as was originally intended to be the primary outcome (CSR,[26] Table 6, page 72) (outcomes are critiqued in Section 4.2.1.4 of this report). HRs ranged from 0.25 to [redacted], and all were consistent with the results of the investigator-assessed PFS analysis.

4.2.4.2 OS

At data cut-off OS data had reached 21% maturity; final OS analyses are planned at approximately 60% maturity ([redacted]).[1] In the olaparib and placebo arms, respectively, 21.2% and 20.6% of patients had died, and median OS had not been reached in either arm (HR 0.95; 95% CI 0.60, 1.53; $P=0.8903$).[1] Thus, data from the current analysis show a small observed OS benefit of olaparib compared with placebo, however the majority of patients were still alive at data cut-off (17th May 2018) and the data were immature. The effect of olaparib on OS may have been impacted by the subsequent use of PARP inhibitors not reflecting current pathways or the proposed use of olaparib in this appraisal ([redacted],[1] see Section 3.2 for details). Subsequent use of olaparib will potentially be inconsistent with the current UK clinical management pathway for advanced ovarian cancer if olaparib is approved for use in first-line maintenance therapy (clarification response,[2] question B4). Furthermore, it is unclear whether the use of subsequent PARP inhibitors in the placebo arm reflects the current UK pathway (see Section 3.2).

4.2.4.3 PFS2

There were deaths or second progression events in 26.5% of patients in the olaparib arm and 39.7% of patients in the placebo arm following second-line therapy, and the median PFS2 was not reached in the olaparib arm and was 41.9 months in the placebo arm (HR 0.50; 95% CI 0.35, 0.72; $P=0.0002$).[1] The

CS reported an imbalance between the olaparib and placebo arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor ([redacted]) (see Section 2.2 for more detailed consideration of subsequent treatment).

4.2.4.4 TFST and TSST

A greater proportion of patients in the placebo arm required retreatment than in the olaparib arm (71.8% and 38.1%, respectively), and the median TFST was considerably longer in the olaparib arm than in the placebo arm (51.8 months and 15.1 months, respectively; HR 0.30; 95% CI 0.22, 0.40; $P<0.0001$).[1] Similarly, a greater proportion of patients in the placebo arm required a second subsequent therapy than in the olaparib arm (49.6% and 29.6%, respectively), and the median TSST was not reached in the olaparib arm, and 40.7 months in the placebo arm (HR 0.45; 95% CI 0.32, 0.63; $P<0.0001$).[1] As with PFS2, the analysis of TSST may have been confounded by subsequent PARP inhibitor use, which was disproportionate between trial arms ([redacted]), which complicates interpretation of this outcome.

4.2.4.5 HRQoL

The CS[1] reported that relatively high baseline TOI scores (73.6 and 75.0 for the olaparib and placebo arms, respectively) were maintained over 97 weeks, with no clinically meaningful changes in HRQoL over this duration, and no clinically meaningful difference between arms. Thus, the CS[1] suggested that there was no detriment to HRQoL as a result of olaparib maintenance therapy. An exploratory analysis of HRQoL in terms of health state utility assessed by the EQ-5D-5L index was also undertaken to 204 weeks post-treatment, which also found no worsening of mean EQ-5D-5L over time for patients in the olaparib arm compared with placebo (CS,[1] Figure 9). The value set used to generate the utilities from the EQ-5D-5L for this analysis is not stated in the CS.[1] Given that the company used the van Hout *et al.* crosswalk algorithm for the economic analysis (see Section 5.2.5.2), it is likely that the same algorithm has also been used in this analysis.[32]

4.2.4.6 Best overall response

The CS reported a comparison of objective response rate between the olaparib and placebo arms in a subset of patients who had evaluable disease (target or non-target lesions) at study entry, and gave the size of this subset as 90 patients; [redacted] in the olaparib arm and [redacted] in the placebo arm (page 36).[1] These numbers of patients do not match with any of the data reported in the CS (Table 10, pages 27-28) nor the text relating to sample characteristics.[1] In response to a request for clarification from the ERG (clarification response,[2] question A9), the company stated that the subset size of 90 patients was taken

from the analysis of best overall response presented in the SOLO1 CSR (Section 7.1.2.8, Table 30), however the CSR does not specify where this number came from either, and so this is still unclear.[26]

The CS[1] reported that within the subset of patients with evaluable disease at study entry, [redacted] and [redacted] of patients in in the olaparib and placebo arms, respectively, had a complete or partial response. Of these, the median duration of response was [redacted] and [redacted] among patients in the olaparib and placebo arms, respectively. Therefore, there appears to be some efficacy benefit for olaparib in terms of response to evaluable disease following first-line platinum-based chemotherapy.

4.2.4.7 Time to treatment discontinuation or death

Median time to TTD was [redacted] and [redacted] for olaparib and placebo, respectively ([redacted]).

4.2.4.8 Safety and tolerability

Adverse events and treatment-related adverse events

The CS stated that "*The safety and tolerability observed in SOLO1 is consistent with that observed in previous studies*" (page 42), but did not provide any further details on these previous studies.[1] In response to a request for clarification from the ERG (clarification response,[2] question A3), the company stated that these previous studies were 11 AstraZeneca sponsored trials of 1060 patients with solid tumours (including 635 patients with ovarian cancer) who received olaparib monotherapy at the recommended tablet dose (300mg BD), which contributed data to a pooled safety analysis (see Table 4 and

Table 5). These 11 studies were specified as being:

- SOLO1 (NCT01844986): Phase III randomised, double-blind, placebo-controlled trial of olaparib in patients with newly diagnosed advanced BRCA mutated ovarian cancer patients who were in complete or partial response to first-line platinum-based chemotherapy
- SOLO2 (NCT01874353): Phase III randomised, double-blind, placebo-controlled trial of olaparib in patients with platinum-sensitive relapsed (PSR) BRCA mutated ovarian cancer who were in complete or partial response following platinum-based chemotherapy
- OlympiAD (NCT02000622): Phase III randomised, open-label trial of olaparib versus physician's choice of chemotherapy (capecitabine, eribulin or vinorelbine) in patients with histologically or cytologically confirmed BRCA mutated HER2-negative metastatic breast cancer
- D0816C00004 (NCT01921140): Phase I study in patients with advanced solid tumours to determine the effect of food on the pharmacokinetics (PK) and to provide data on the effect on QT interval of olaparib
- D0816C00005 (NCT01894243): Phase I multicentre study of the PK, safety and tolerability of olaparib in patients with advanced solid tumours and normal hepatic function or hepatic impairment
- D0816C00006 (NCT01894256): Phase I multicentre study of the PK, safety and tolerability of olaparib in patients with advanced solid tumours and normal renal function or renal impairment
- D0816C00007 (NCT01900028): Cytochrome P450 [CYP] inhibitor study: two-part, Phase I, multicentre study in patients with advanced solid tumours to characterise the PK of olaparib in the presence and absence of itraconazole
- D0816C00008 (NCT01929603) Phase I, multicentre study in patients with advanced solid tumours to characterise the PK of olaparib in the presence and absence of rifampicin
- D0810C00024 (NCT00777582): Phase I study to determine bioavailability, maximum tolerated dose and appropriate Phase III tablet dose in advanced solid tumours
- D081BC00001 (NCT01813474): Phase I, dose escalation (multiple dosing) of olaparib in Japanese patients with advanced solid tumours
- D081BC00002 (NCT02430311): Phase I, dose escalation (multiple dosing) of olaparib tablets in Chinese patients with advanced solid tumours
- D081CC00001 (NCT02093351): Phase I multicentre study to assess the safety and effect of olaparib at steady-state on the PK of the anti-hormonal agents anastrozole, letrozole, and tamoxifen at steady-state, and the effect of the anti-hormonal agents on olaparib in patients with advanced solid cancer

It was not clear in the clarification response[2] whether safety data from the olaparib arm of SOLO1 was included in the pooled safety data, as the clarification response (question A3) listed 12 studies, but specified 11 were used for the pooled safety analysis. If the pooled safety analysis of 1060 patients did include 260 patients from the SOLO1 trial, this may potentially confound any comparison of SOLO1 data with pooled olaparib safety data.

Table 4: Number (%) of patients who had at least one adverse event in SOLO1 and the olaparib 300 mg BD tablet pool (reproduced from company's clarification response, Table 1, question A3)

Adverse event (AE)	SOLO1		Tablet pool
	Olaparib N=260	Placebo (N = 130)	Olaparib (N = 1060)
Any AE	256 (98.5)	120 (92.3)	[redacted]
Any AE of CTCAE Grade 3 or higher	102 (39.2)	24 (18.5)	[redacted]
Any AE with outcome of death	0	0	[redacted]
Any SAE (incl. events with outcome of death)	54 (20.8)	16 (12.3)	[redacted]

Source: SOLO1 EMA Clinical Overview, Table 17

AE – adverse event; CTCAE – Common Terminology Criteria for Adverse Events; SAE – serious adverse event

Table 5: Number (%) of patients who had at least one adverse event in SOLO1 and the olaparib 300 mg BD tablet pool (reproduced from company's clarification response, Table 2, question A3)

Adverse event (AE)	SOLO1		Tablet pool
	Olaparib N=260	Placebo (N = 130)	Olaparib (N = 1060)
Any AE	256 (98.5)	120 (92.3)	[redacted]
Nausea	201 (77.3)	49 (37.7)	[redacted]
Fatigue	106 (40.8)	39 (30.0)	[redacted]
Vomiting	104 (40.0)	19 (14.6)	[redacted]
Anaemia	99 (38.1)	12 (9.2)	[redacted]
Diarrhoea	89 (34.2)	32 (24.6)	[redacted]
Constipation	72 (27.7)	25 (19.2)	[redacted]
Dysgeusia	68 (26.2)	5 (3.8)	[redacted]
Arthralgia	66 (25.4)	35 (26.9)	[redacted]
Abdominal pain	64 (24.6)	25 (19.2)	[redacted]
Asthenia	63 (24.2)	16 (12.3)	[redacted]
Headache	59 (22.7)	31 (23.8)	[redacted]
Dizziness	51 (19.6)	20 (15.4)	[redacted]
Decreased appetite	51 (19.6)	13 (10.0)	[redacted]
Abdominal pain upper	46 (17.7)	17 (13.1)	[redacted]
Dyspepsia	43 (16.5)	16 (12.3)	[redacted]
Cough	42 (16.2)	28 (21.5)	[redacted]
Neutropenia	41 (15.8)	9 (6.9)	[redacted]
Back pain	40 (15.4)	16 (12.3)	[redacted]
Dyspnoea	39 (15.0)	7 (5.4)	[redacted]
Pyrexia	31 (11.9)	12 (9.2)	[redacted]
Urinary tract infection	31 (11.9)	8 (6.2)	[redacted]
Myalgia	28 (10.8)	13 (10.0)	[redacted]
Pain in extremity	28 (10.8)	11 (8.5)	[redacted]
Upper respiratory tract infection	28 (10.8)	12 (9.2)	[redacted]
Nasopharyngitis	27 (10.4)	17 (13.1)	[redacted]
Insomnia	27 (10.4)	16 (12.3)	[redacted]
Depression	13 (5.0)	13 (10.0)	[redacted]

Source: SOLO1 EMA Clinical Overview, Table 18

AE – adverse event

The profile of any adverse event (AE), any AE of CTCAE Grade 3 or higher, any AE with the outcome of death and any SAE appear to be comparable between SOLO1 and the olaparib pooled safety data (Table 4).

Many of the specific AEs appear to have a similar incidence rate in SOLO1 as in the pooled safety data (

Table 5), however there are a few specific AEs that appear to have been experienced by a greater proportion of olaparib patients in the SOLO1 trial than among the pooled safety data. These are: nausea, diarrhoea, constipation, dysgeusia, arthralgia, abdominal pain, asthenia, headache, dizziness, abdominal pain upper, dyspepsia, myalgia and pain in extremity. There do not appear to be any specific AEs that were experienced by fewer patients in the olaparib arm of SOLO1 than among the pooled safety data.

The most common AEs reported by patients in the olaparib arm relative to the placebo arm were nausea, fatigue, vomiting, anaemia and diarrhoea, and the majority of specific AEs were reported by a greater proportion of patients in the olaparib arm than the placebo arm, although some events were experienced by a similar or higher proportion in the placebo arm (arthralgia, headache and cough) (see CS,[1] Table 17).

Treatment-related AEs (AEs considered by the investigator to be causally related to study treatment[26]) were not presented in the CS, but have been summarised in the CSR[26] (page 149, and Table 11.3.12.8). As might be expected, the proportion of patients reporting treatment-related AEs was higher in the olaparib arm than in the placebo arm (94.2% versus 70.8%, respectively), the majority of which were in the gastrointestinal system organ class (reported by 80.0% and 40.8% of patients in the olaparib and placebo arms, respectively).[26] The most frequently reported treatment-related AEs were nausea (70.4% of patients), anaemia (36.2% of patients), fatigue (33.1% of patients) and vomiting (30.4% of patients) in the olaparib arm, and nausea (31.5% of patients), fatigue (16.9% of patients), diarrhoea (7.7% of patients) and asthenia (6.9% of patients) in the placebo arm.

Adverse events ≥grade 3

As mentioned earlier, the proportion of olaparib patients with any AE of CTCAE Grade 3 or higher, appear to be comparable between SOLO1 and the olaparib pooled safety data (Table 4). Specific AEs of grade 3 or higher reported in more than 3% of patients were anaemia, neutropenia and diarrhoea. All AEs of grade 3 or higher were experienced by a greater proportion of patients in the olaparib arm compared with the placebo arm, with the exception of headache, dizziness and vomiting (see CS,[1] Table 17).

Serious adverse events and AEs leading to discontinuation

A greater proportion of patients in the olaparib arm than the placebo arm reported serious AEs (20.8% versus 12.3%, respectively), and anaemia was the most commonly reported serious AE in the olaparib arm.[1]

AEs leading to discontinuation of the intervention were reported among 11.5% and 2.3% of patients in the olaparib and placebo arms, respectively (see CS,[1] Table 17). Similarly, a greater proportion of

patients in the olaparib than the placebo arm reported AEs that led to dose reduction (28.5% versus 3.1%, respectfully) and dose interruption (51.9% versus 16.9%, respectively) (see CS,[1] Table 17).

Adverse events of special interest

Three cases of acute myeloid leukaemia (1.2%) (and no cases of myelodysplastic syndrome) were identified in patients in the olaparib arm during long-term safety data collection (beyond treatment discontinuation and 30-day follow-up).[1, 26] All three cases resulted in death. These deaths were not considered to be treatment-related AEs as they occurred more than 30 days after treatment discontinuation. No cases of acute myeloid leukaemia or myelodysplastic syndrome were identified among patients in the placebo arm.

Death

There were no AEs resulting in death in either arm during the trial intervention or up to 30 days after discontinuation of the intervention,[1] although three adverse event related deaths were reported in the olaparib arm (and none in the placebo arm) during longer-term follow-up.

4.2.4.9 Subgroups

In response to a request for information about potential prognostic factors and treatment effect modifiers from the ERG (see clarification response,[2] question A15), the company referred to Hoppenot *et al.* (2018[33]) and stated that known clinical predictors of prognosis and long-term survival in ovarian cancer include:

- Younger age at diagnosis
- Earlier clinicopathologic stage
- Lower grade
- Non-serous histology
- Absence of ascites
- Optimal surgical debulking
- Response to chemotherapy (complete or partial)

In addition, the company stated that BRCA mutations are associated with short-term chemosensitivity, but do not appear to improve long-term survival.

Figure 10 (CS,[1] page 40) presented a forest plot of the analyses of PFS by predefined subgroups from a single Cox proportional hazards model. In response to request from the ERG, the company stated that a global interaction test was statistically significant at the 10% level (*P*=0.0469) and that "*the only interaction seen was quantitative and not clinically meaningful and was based on complete or partial*

response at study entry" (see clarification response,[2] question A16). The CS stated that all subgroups demonstrated the superiority of olaparib over placebo, and that patients with a partial response had better PFS relative to those who entered the study with a complete response to first-line platinum-based chemotherapy at trial entry (CS,[1] Figure 10). Nevertheless, the forest plot shows that the effect of olaparib on PFS was greater for those with a BRCA2 mutation compared with those with a BRCA1 mutation, patients aged <65 compared with those aged ≥65, patients with Stage III disease at initial diagnosis compared with those with Stage IV disease, patients with no residual macroscopic disease compared with those with residual macroscopic disease, patients from the rest of the world compared with patients from Brazil, Poland, Russia, Japan and Korea, and patients who are White compared with patients who are Asian (CS,[1] Figure 10). Region and race do not appear in the CS,[1] Figure 10, however they are presented in the CSR,[26] Figure 8.

The ERG has a preference for modelling age as a continuous variable rather than dichotomising age according to some cut-off; dichotomising age implies that the hazard of PFS is discontinuous at the cut-off rather than allowing it to change continuously with increasing age according to an appropriate function of age.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Not applicable.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

4.6.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence relating to olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy is based on SOLO1, [21, 26] a Phase III RCT. The ERG is confident that no relevant studies (published or unpublished) of olaparib for maintenance treatment of newly diagnosed BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer, after response to first-line platinum-based chemotherapy are likely to have been missed.

4.6.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The ERG is largely satisfied that the relevant population have been included in the CS, with the caveat that there is currently no evidence relating to the efficacy of olaparib in patients with stage II disease, as mentioned in the NICE final scope.[1, 4] The ERG also notes that the patient sample of SOLO1 contains a greater number of patients with stage III disease and a smaller number of patients with stage IV disease than have been reported in UK incidence figures.[34] The ERG is content that the relevant intervention and comparator have been included in the CS.[1]

The primary outcome of the SOLO1 trial was investigator-assessed PFS at data cut-off (17th May 2018), where the median follow-up duration was 41 months, which is a recommended outcome according to the EMA.[27] The primary outcome was changed from PFS assessed by BICR to investigator-assessed PFS during the study, due to emerging data suggesting it may not have been possible to obtain the events required using BICR. Since the results of a sensitivity analysis using BICR were very similar to investigator-assessed PFS results, the ERG does not consider this to be a major source of bias in the trial. With this in mind, the SOLO1 trial found that a smaller proportion of patients in the olaparib arm had progressed or died than in the placebo arm (39.2% versus 73.3%). The median PFS was not reached in the olaparib arm but was estimated by the company to be at least three years longer than that observed with placebo. The results of six pre-planned sensitivity analyses were consistent with the results of the investigator-assessed PFS analysis.

Secondary outcomes of the SOLO1 trial included OS, PFS2, TFST, TSST, HRQoL, AEs, best overall response and TTD. OS and PFS2 are recommended outcomes according to the EMA,[27] which suggests that OS should demonstrate or show a trend towards superiority. Mortality events were reported in 21.2% and 20.6% of patients in the olaparib and placebo arms, respectively, and median OS had not been reached in either arm. Thus, data from the current analysis show a small observed OS benefit of olaparib compared with placebo, however the majority of patients were still alive at data cut-off (17th May 2018) and the data were immature. The effect of olaparib on OS may have been impacted by an imbalance between the trial arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor.

In terms of PFS2, there were deaths or second progression events in 26.5% of patients in the olaparib arm and 39.7% of patients in the placebo arm following second-line therapy, and the median PFS2 was not reached in the olaparib arm and was 41.9 months in the placebo arm, which suggests that olaparib demonstrates efficacy relative to placebo in PFS following subsequent therapy. The CS reported an imbalance between the olaparib and placebo arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor.[1]

TFST, TSST and TTD were not pre-planned, but were introduced to the trial in amendments made after the start of patient recruitment. With this in mind, the findings of SOLO1 indicate that a greater proportion of patients in the placebo arm required retreatment than in the olaparib arm (71.8% and 38.1%, respectively), and the median TFST was considerably longer in the olaparib arm than in the placebo arm (51.8 months and 15.1 months, respectively). Similarly, a greater proportion of patients in the placebo arm required a second subsequent therapy than in the olaparib arm (49.6% and 29.6%, respectively), and the median TSST was not reached in the olaparib arm, and 40.7 months in the placebo arm. As with PFS2, the analysis of TSST may have been confounded by subsequent PARP inhibitor use, which was disproportionate between trial arms.

HRQoL was assessed for 97 weeks over the duration of the SOLO1 trial using the FACT-O questionnaire. A validated measure of HRQoL is recommended by the EMA.[27] The relatively high baseline FACT-O TOI scores (73.6 and 75.0 for the olaparib and placebo arms, respectively) were maintained over 97 weeks, with no clinically meaningful changes in HRQoL over this duration, and no clinically meaningful difference between arms. Similarly, an exploratory analysis of HRQoL in terms of health state utility assessed by the EQ-5D-5L found no worsening of mean EQ-5D-5L over time for patients in the olaparib arm compared with placebo. Therefore, there does not appear to be a HRQoL detriment as a result of olaparib maintenance therapy during the treatment duration. It is difficult for the ERG to assess the longer-term impact of olaparib on HRQoL.

Little detail on the measurement of AEs in SOLO1 was reported. The safety and tolerability of olaparib was similar to that of previous studies (in a pooled safety analysis, which is unclear on whether or not data from SOLO1 were included), with some specific events apparently being experienced by a greater proportion of patients in the olaparib arm than in the pooled safety data. Most patients in the olaparib (98.5%) and placebo (92.3%) arms experienced at least one AE, with 39.2% and 18.5% respectively experiencing at least one Grade 3 AE and 20.8% and 12.3% respectively experiencing at least one SAE. There were no deaths in either arm during the trial intervention or up to 30 days after discontinuation of the intervention, although three deaths (all cases of AML/MDS) were reported in the olaparib arm (and none in the placebo arm) during longer-term follow-up. The most common AEs reported by patients in the olaparib arm relative to the placebo arm were nausea, fatigue, vomiting, anaemia and diarrhoea, and the most common SAE was anaemia.

4.6.3 Uncertainties surrounding the reliability of the clinical effectiveness

The ERG has two concerns relating to the reliability of the clinical effectiveness evidence relating to SOLO1. First, a greater proportion of patients in the olaparib arm (14.2%) than the placebo arm (7.6%) were reported as having at least one protocol deviation, with the greatest difference being in the

proportion of patients who had RECIST scans outside of a scheduled visit window on >2 occasions (7.3% and 1.5%, respectively). The impact of this protocol deviation is difficult to assess, however the ERG considers this unlikely to impact on the conclusions of the SOLO1 trial and the appraisal, in particular in relation to OS.

Second, patients in the SOLO1 trial were permitted to use a subsequent PARP inhibitor later in the clinical treatment pathway, as maintenance therapy following second-line and/or or third-line platinum-based chemotherapy. It is unclear whether the use of subsequent PARP inhibitors reflect the current UK pathways. As such, it is difficult for the ERG to assess the potential impact of this on outcomes reported in the CS.[1] The CS reported an imbalance between the olaparib and placebo arms in the proportion of patients who received subsequent maintenance therapy with a PARP inhibitor, which complicates interpretation of OS, PFS2, and TSST.[1]

5 COST EFFECTIVENESS

5.1 ERG's comment on company's review of cost-effectiveness evidence

5.1.1 Objective of cost effectiveness review

Appendix G of the CS reports the company searches for cost-effectiveness evidence which were conducted on 25th May 2018.[1] Searches for cost-of-illness and health state utility values cover the period from 1974 to 2018; the economic searches cover from 2008-2018 only.

The searches for all three types of evidence were run simultaneously using the same disease terms, with additional strings added to filter results by study type. No citation is provided to indicate that published and validated filters have been used, though it is noted that in the clinical review filters were based on acknowledged sources and a similar approach is assumed to have been employed here (the terms used include most of those the ERG would expect to see, though without a citation to a published validation study their sensitivity or specificity cannot be guaranteed).

As with the clinical review, the EMBASE search strategy appears to have been designed first and the subsequently run on Medline and Cochrane with minimal alteration. Emtree subject headings are used on all three databases (instead of translating them to MeSH for Medline and Cochrane) however Ovid appears to have successfully mapped 'ovary cancer' to the MeSH heading 'ovarian neoplasms'. Again, it is surprising to see this term has only been searched for as a major heading (using the Focus feature) but the addition of sensitive title/abstract strings around the same concept mean that it is unlikely studies will have been missed.

In addition to the database searches, the company also examined recent proceedings of relevant conference series (2016-2017 or 2018 if available) and data from the previous five NICE HTA submissions for olaparib. Reference lists of included studies were also checked for missed studies.

5.1.2 The inclusion and exclusion criteria used in the study selection

The inclusion and exclusion criteria are provided in Appendix G, Table 10 of the CS.[1] The ERG has concerns that the only included comparators were "*Another active included intervention*" or "*Placebo*". If strictly applied, these inclusion criteria could exclude routine surveillance as neither an active intervention or placebo are given during routine surveillance in the UK. However, given that the SOLO1 trial reported (October 2018) after the date that the searches were conducted (May 2018), it is unlikely that any studies which would be more relevant to the decision problem than SOLO1 have been missed.[21]

5.1.3 Findings of the cost effectiveness review

Following de-duplication, the company's searches found 1057 studies. Nine hundred and forty-eight studies were excluded based on either the title or abstract and a further 74 studies were excluded after reading the full paper. No publications were found which considered the cost-effectiveness of a maintenance treatment for patients with advanced ovarian cancer who had responded to first-line platinum-based chemotherapy and 26 publications were found for maintenance treatments for patients with advanced ovarian cancer who had received more than one prior line of chemotherapy.

5.1.4 Conclusions of the cost effectiveness review

The company does not explicitly conclude anything from the review of cost-effectiveness studies. Due to the fact that the company developed a *de novo* cost-effectiveness model, it is implicitly concluded that there was no evidence on the cost-effectiveness of olaparib for maintenance treatment of BRCA-mutated advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. As such, it was necessary to develop a *de novo* cost-effectiveness model. The ERG agrees with this conclusion.

5.2 Summary of company's submitted economic evaluation by the ERG

5.2.1 Population

The population included in the company's health economic analysis reflects patients with newly diagnosed advanced BRCA-mutated advanced ovarian, fallopian tube or peritoneal cancer that has responded (completely or partially) to first-line platinum-based chemotherapy. Advanced cancers were defined as FIGO stage III or IV tumours.[3] Response was defined according to the RECIST 1.1 criteria.[17]

5.2.2 Interventions and comparators

In the SOLO1 study, the intention was to administer 300mg of olaparib tablets twice daily. Dose reductions to 250mg twice daily or 200mg twice daily could be considered to manage adverse reactions (e.g. nausea, vomiting, diarrhoea and anaemia). No active maintenance treatments after response to first-line platinum-based chemotherapy were provided to patients in the comparator arm which was routine surveillance.

It the disease of patients in either arm progressed then they would be available to receive treatment in accordance with best practice.

5.2.3 Perspective, time horizon and discounting

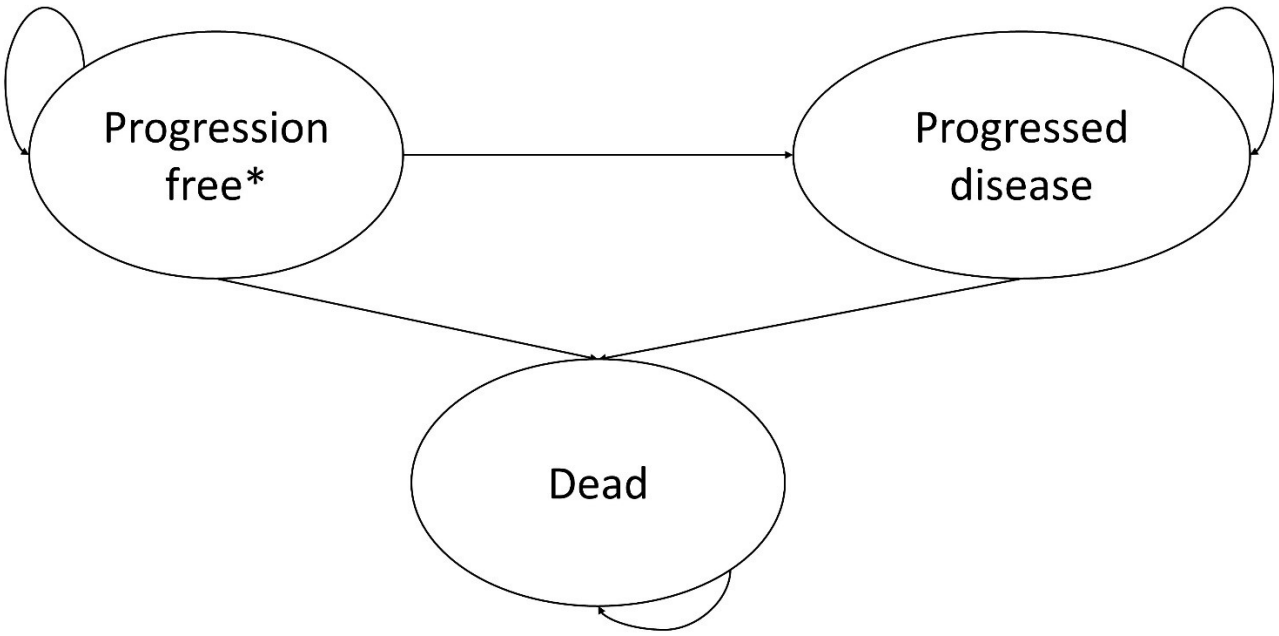
The base case model adopts and NHS and Personal Social Services (PSS) perspective. The time horizon of the model is 50 years from initiation of olaparib maintenance therapy or routine surveillance. Both

costs and QALYs were discounted at 1.5%, as the company claims that the criteria provided in section 6.2.19 of the NICE methods guide are met.[23] These criteria are detailed in Section 3.5.

5.2.4 Model structure

As part of its submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®. The submitted model adopts a partitioned survival approach which consists of three health states: (1) progression free; (2) progressed disease; and (3) dead. A diagram of the company's model is provided in Figure 3. Patients enter the model in the progression free health state at an age of 53.2 years which represents the mean age of patients in SOLO1. Health state transitions are estimated over a 50-year time horizon using 600 monthly time cycles. After 50 years, more than 99.9% of people in both arms of the company's model have died. In both arms, the OS curve was constrained so that cumulative OS could not be less than cumulative PFS. The probability of being alive and relapse free is calculated using the cumulative PFS curve. The probability of being dead is calculated from the cumulative OS curve. The probability of having progressed disease is calculated as the difference between cumulative OS and cumulative PFS.

Figure 3: Company's model structure



* - Progression free is split into time on treatment and time off treatment in the olaparib arm using the time to treatment discontinuation or death data from SOLO1.

PFS is modelled in both arms using a piecewise model, which consists of three parts: (1) the Kaplan-Meier function for the first two years; (2) a log normal parametric function after year two until year seven; and (3) a general population probability of death which was adjusted, using a hazard ratio, to reflect the risk of death in a population of patients with a BRCA mutation after year seven.

The probability of being alive at any time is modelled differently for the olaparib and the comparator arms although both approaches use the Kaplan-Meier data for the first 24 months. Beyond 24 months, in the olaparib arm OS is modelled using a log logistic parametric function. In the routine surveillance arm, the company chose not to directly fit models to the OS data in the routine surveillance arm of SOLO1 instead, using a treatment effect applied to the parameters of the olaparib OS log-logistic curve. This treatment effect was estimated using a log-logistic function (consequently, the treatment effect was a constant acceleration factor) fitted to the PFS2 data in both arms of SOLO1. This produces values for OS in the comparator arm that are markedly different from the data observed in SOLO1; this is discussed in more detail in Section 5.2.5.1.

Modelling HRQoL impacts

The model assumes that HRQoL is principally determined by time spent alive, whether or not a patient has progressed and the incidence of adverse events in each arm. Within both arms of the model, health state utilities are applied in the progression-free and progressed disease health states. No explicit effect of subsequent progressions (i.e. second and later progressions) on HRQoL is included within the estimation of QALYs within the company's model. These health state utilities are adjusted over time for age, using data on age- and gender-adjusted population norms for utility.[35] QALY losses are applied in each arm of the model to adjust for the incidence of adverse events observed in the SOLO1 trial.

Modelled treatment pathway

The company's model includes the following cost components: (i) drug acquisition; (ii) drug administration; (iii) health state resource use; (iv) cost of subsequent chemotherapy and PARP inhibitor use; and (v) a cost associated with death.

Within the olaparib group the model assumes the following treatment pathway:

- Patients receive first line olaparib at a total daily dose of [redacted]. Patients discontinue olaparib treatment according to the time to treatment discontinuation (TTD) Kaplan-Meier curve up until 51 months post-randomisation. At the end of month 51, it is assumed that any patients still receiving olaparib will discontinue their treatment.
- Patients were followed up in monthly clinics with their consultants. Blood tests and CT scans were conducted every three months.

Within the routine surveillance group, the model assumes the following treatment pathway:

- All patients who relapse receive three lines of subsequent chemotherapy regimens, further details of which are given in Section 5.2.5.3.

- Patients were followed up in clinics with their consultants, every three months. Blood tests and CT scans were conducted every three months.

Following relapse, the logic of the treatment pathway is the same in both arms of the model. All patients who relapse receive three lines of subsequent chemotherapy regimens which consisted of platinum-based regimens (carboplatin or cisplatin in combination with either docetaxel or doxorubicin, or paclitaxel) or non-platinum-based regiments (docetaxel or doxorubicin, or paclitaxel). This pathway implicitly assumes that: (1) all patients who relapse will relapse three times prior to death; and, (2) that no patient who relapses has a cancer which becomes platinum-insensitive. A proportion of relapsed patients will receive a subsequent PARP inhibitor, which is assumed to be niraparib. The subsequent use of a PARP inhibitor was not directly incorporated within the model structure. Instead, the use, and timing, of subsequent PARP inhibitors was assumed to be informed by the observed data in SOLO1.

5.2.4.1 Key structural assumptions employed within the company's model

The company's model employs the following structural assumptions:

- All patients enter the model in the progression free health state
- PFS2, not OS, should be used to estimate the effect of olaparib on the OS hazard after two years
- The OS hazard is assumed to follow the modelled hazard for PFS after the point at which the cumulative PFS and OS curves cross.
- For costing of the chemotherapy regimens, every patient who relapses experiences three relapses prior to death.

5.2.5 Evidence use to inform the company's model parameters

The evidence sources used to inform the model parameters are summarised in

Table 6. It is implicitly assumed that the evidence sources used in the company's model are generalisable to UK clinical practice.

Table 6: Evidence sources used to inform the company's parameters

Parameter type	Parameter	Source(s)
Time to event data	Progression - olaparib	SOLO1[21], assumption, ONS[36], Mai *et al*.[37]
	Progression – routine surveillance	
	Death -olaparib	SOLO1[21]
	Death – Treatment effect for routine surveillance versus olaparib	SOLO1[21], estimated using an analysis of the time of PFS2 data.
	Treatment discontinuation or death - olaparib	SOLO1[21]
	Subsequent use of PARP inhibitors	SOLO1[21]
Adverse events	Incidence of Grade ≥ 3 adverse events	SOLO1[21]
HRQoL	Health utility	SOLO1[21]
	QALY decrements associated with adverse events	Swinburn *et al*[38], Nafees *et al.*[39], NICE TA411,[40] assumption
Resource use and costs	Olaparib acquisition cost	AstraZeneca
	Subsequent chemotherapies	BNF,[22] CMU[41], Yorkshire Cancer guidelines network[42]
	Subsequent PARP inhibitor use	AstraZeneca, SOLO1,[21] Study19[43]

SOLO1, ; ONS, office for national statistics; PFS2, second progression free survival; NA, not applicable; NICE, National Institute for Health and Care Excellence; BNF, British National Formulary; CMU, commercial medicines unit; PARP, poly(ADP-ribose) polymerase

5.2.5.1 Time to event

Progression free survival

Kaplan-Meier curves for PFS for patients receiving olaparib and routine surveillance were obtained from the SOLO1 study.[21] The Kaplan-Meier plot is provided in Figure 16 of the CS.[1] PFS was defined as the interval from the data of randomisation to the first of the date of death or the date of first progression, as defined using the RECIST 1.1 criteria. Standard parametric distributions, including the exponential, Weibull, Gompertz, log logistic, log normal and generalised gamma distributions were fitted separately to the routine surveillance and olaparib data. Two approaches to fitting the distributions were taken. In the first approach the distributions were fitted to the entire dataset. In the second approach, the distributions were fitted to the post-2-year period of study follow-up, with the Kaplan-

Meier curves used to estimate PFS between randomisation and the two years after randomisation. The company justified the use of piecewise functions for PFS and OS as: (1) a single curve may not be plausible, as it is expected that a subset of patients will be "exceptional" responders to first line treatment; and, (2) most patients in the olaparib arm discontinued treatment at two years.[1] Approximately [redacted] of patients had discontinued olaparib treatment by month 25, this is broadly in line with expectations, as 81.8% patients had a complete response at baseline and as such would be ineligible to receive olaparib for more than two years (CS[1], Figure 11 and page 72). In response to a request for clarification from the ERG (see clarification response,[2] question B11), curves for spline models were included in Figures 19 of the CS as standard output from the statistical program used to analyse the data but were not considered when choosing the best fitting model. Other potentially plausible distributions (e.g. gamma and generalised F distributions) and more flexible models, such as fractional polynomials, were not considered.

To assess the relative goodness-of-fit of different models fitted to the PFS data the company: (1) generated arm-based Akaike information criterion (AIC) and Bayesian information criterion (BIC); (2) visually assessed the parametric curves against the Kaplan-Meier curve; (3) compared the routine surveillance extrapolation to the BRCA mutated subgroup of the Edinburgh Ovarian Cancer Database; and (4) sourced clinical opinion.

The AIC and BIC statistics are provided in Table 21 of the CS.[1] On the basis of the AIC and BIC statistics for models fitted to the entire data, the company preferred the log-logistic distribution for olaparib and the generalised gamma distribution for routine surveillance. For models fitted to the 24 months' post randomisation data, the company preferred the lognormal distribution for olaparib and the exponential distribution for routine surveillance.

The ERG notes that: 1) the AIC and BIC assess which is the best fitting model from a finite set of models and that none of the models assessed may provide both a reasonable representation of the observed data and clinically plausible extrapolation; 2) the best fitting model to the sample data may not provide the most plausible model overall; and 3) a difference in BIC of up to two is barely worth a mention.[44]

The predictions of cumulative PFS from the various PFS curves were compared to the available Kaplan-Meier data from SOLO1 in Table 23 of the CS.[1] Predictions within 1% of the Kaplan-Meier were coloured green, within 1% to 3% of the Kaplan-Meier predictions were coloured amber and greater than 3% difference from the predictions were coloured red.

The company then compared the progression-free survival estimates for the routine surveillance arm to the data from the BRCA mutated subgroup of the Edinburgh Ovarian Cancer Database. [redacted] On the basis of these comparisons, survival estimates from a piecewise model using a Kaplan-Meier curve up to two years and a lognormal distribution post-24 month provided the closest estimates to the BRCA mutated subgroup of the Edinburgh Ovarian Cancer Database.

Overall, the company's preferred model for PFS was to use Kaplan-Meier curves up to two years and a lognormal distribution post-24 months in both arms. This was made on the basis of the relative goodness of fit, the prediction of the SOLO1 Kaplan-Meier and the prediction of data in the Edinburgh Ovarian Cancer Database. The company stated that relevant alternatives were a generalised gamma distribution fitted to the entire dataset and a piecewise model with a log-logistic distribution fitted to data post-24 months. The company was asked to justify why their curves were considered plausible in clarification question B7, but no rationale was provided as to why other distributions were not plausible.[2]

To reflect long-term survival, PFS seven years after randomisation was set equal to all-cause mortality rates for persons with a BRCA mutation that have no evidence of cancer. This was estimated using general mortality, adjusted using a hazard ratio of 1.26 from Mai *et al*, [37] to account for the fact that these patients had a BRCA mutation. This change in the hazard was made on the basis of the hazards for relapse observed in the Edinburgh Ovarian Cancer Database and expert clinical input stating that people who do not progress within five years are exceptional responders who are highly unlikely to experience a relapse event, and that their risk of death would approach that of the age- and gender-matched general population. On this issue, the ERG's clinical advisors broadly agreed with the company's experts. However, they could not rule out the possibility that receiving a PARP inhibitor, such as olaparib, could delay future recurrences. Consequently, the point at which patients in the olaparib arm were at a very low risk of recurrence could be after the 5-year time point assumed in the model.

Overall survival

Kaplan-Meier curves for OS for patients receiving olaparib and routine surveillance were obtained from the SOLO1 study.[21] The Kaplan-Meier plot is provided in Figure 4 and is marked commercial-in-confidence by the company. OS was defined as the interval from the date of randomisation to the date of death. Standard parametric distribution functions, including the exponential, Weibull, Gompertz, log-logistic, lognormal and generalised gamma distributions were fitted separately to the olaparib and routine surveillance data. In response to a request for clarification from the ERG (clarification response,[2] question B11), the company stated that fitted curves for spline models were included in

Figure 24 of the CS as standard output from the statistical program used to analyse the data, but were not considered when choosing the best fitting model. Other potentially plausible distributions (e.g. a generalised F distributions) and more flexible models such as fractional polynomials were not considered.

Two approaches to fitting the curves were taken. In the first approach the distributions were fitted to the entire dataset. In the second approach, the distributions were fitted to the post-2 years after randomisation, with the Kaplan-Meier curves used to estimate OS between randomisation and two years after randomisation. The rationale for the second approach is the same as was given for using this approach to model PFS (see above).

Figure 4: The Kaplan-Meier curves for overall survival in SOLO1 (reproduced from Clarification response,[2] question B6)

The company did not estimate an OS curve for routine surveillance arm from the SOLO1 data, for the following reasons. Firstly, the company considers that "*An unusual plateau is observed between from Month 30 to Month 36, which would suggest a hazard rate of death near zero*" (Clarification response[2], question B6). Secondly, from "… *[m]onth 36, the level of censoring becomes too high for the data to be informative*"(Clarification response,[2] question B6). Thirdly, the company believed that the OS Kaplan-Meier "… *showed uncharacteristic flattening of the OS curve from approximately 3-years which is clinically implausible*"(CS[1], page 88). Finally, the data from the SOLO1 routine surveillance

arm does not appear to match data from the University of Edinburgh Ovarian Cancer Database or the expectation of two UK clinical experts of median OS in the UK population.(CS[1], Appendix M).

To obtain an OS curve for routine surveillance, the company used PFS2 as a surrogate for the effect of routine surveillance compared to olaparib on OS. This is because the company considered the data and the fitted models to be "*…clinically implausible…*".(CS[1], page 87) Standard distributions (exponential, Weibull, Gompertz, log logistic, log normal and generalised gamma) were fitted to the PFS2 data. Similar to the modelling of OS for olaparib, two approaches were taken to fitting distributions to the PFS2 data. In the first approach the distributions were fitted to the entire dataset. In the second approach, distributions were fitted to data two years post-randomisation and the Kaplan-Meier curves were used up to two years post-randomisation. These treatment effects were then applied to the matching OS curve for olaparib. For example, if an exponential curve was fitted to the full dataset to estimate OS for olaparib, then OS curve for routine surveillance was obtained by applying a treatment effect, which was estimated using an exponential distribution fitted to both arms and the full data set for PFS2, to the olaparib OS curve. The ERG notes that the process of fitting distributions separately to data from different treatment groups ignores correlation between parameters, although the ERG does not routinely support the use of proportional hazards or constant acceleration factors when fitting curves.

The ERG disagrees with the rationale for using the company's approach (further details of which are given in Section 5.3.4). for the following reasons: (1) the Kaplan-Meier curve is estimated from the observed data and, as such, cannot be implausible; (2) the ERG considers that there are a sufficient number of events in the routine surveillance arm to estimate the curve up to month 42 albeit with uncertainty (Figure 4); (3) if the change in hazard is caused by subsequent chemotherapies and PARP inhibitor use, then these should be explicitly modelled. Consequently, the ERG believes that the company's approach to estimating OS in the routine surveillance arm is not justified because it ignores actual OS data from SOLO1.

To assess the goodness-of-fit of different models the company: (1) generated AIC and BIC for the olaparib treatment arm; (2) visually assessed the parametric curves against the Kaplan-Meier curve; (3) compared the routine surveillance extrapolation to the BRCA mutated subgroup of the Edinburgh Ovarian Cancer Database; and (4) sourced clinical opinion.

The AIC and BIC statistics for the olaparib OS curves are provided in Table 25 of the CS.[1] On the basis of the AIC and BIC statistics the company preferred the log-logistic distribution when the distributions were fitted to the entire dataset, although the log-normal and Weibull distributions provided equally good fits. When the models were fitted to the 24 months' post randomisation dataset, the best fitting

distribution was the exponential, although there was not strong evidence to rule out other distributions being plausible based on BIC values.

The predictions of cumulative OS with olaparib from the various OS curves were compared with the available Kaplan-Meier data from SOLO1 in Table 28 of the CS.[1] Predictions within 1% of the Kaplan-Meier were coloured green, within 1% to 3% of the Kaplan-Meier predictions were coloured amber and greater than 3% difference from the predictions were coloured red.

Clinical opinion sought by the company from two UK clinical experts provided an estimate of median OS of [redacted] for people receiving routine surveillance. The median OS values predicted from the extrapolations were compared with this estimate. In response to clarification question B8, the company stated that their clinical experts believe that the "*hazard rate of death to increase over time, as the likelihood and duration of response to chemotherapy diminishes with each subsequent line*". From the CS and clarification responses, it is unclear if this expert opinion was used in the company's model selection process.[1, 2]

On the basis of the criteria used, the company selected using the Kaplan-Meier curve for the first 24 months and the log-logistic distribution post-24 months. In response to clarification question B7, the company stated the lognormal and Weibull distributions provided plausible extrapolations.[2] It is unclear whether any criteria other than AIC or BIC (relative goodness to the SOLO1[2] data) were used to determine if the extrapolated parts of the curves were considered to be plausible. It is also unclear on what basis the other curves were considered implausible. The base case curve is presented in Figure 5, which is marked as CIC by the company.

Figure 5: Illustration of the company's base case deterministic curve choice compared to the SOLO1 data (reproduced from CS,[1] page 98, Figure 27)

The ERG believes that the company's generation of the curves for the routine surveillance arm lacks face validity because it does not match the Kaplan-Meier curve from SOLO1. As Figure 5 shows, the OS curve for routine surveillance clearly diverges from the corresponding Kaplan-Meier curve at approximately [redacted] months, at which point [redacted] patients remain in the comparator arm. A full critique of this issue is provided in Section 5.3.4.

Treatment discontinuation or death - olaparib

Kaplan-Meier curves for TTD for patients receiving olaparib was obtained from the SOLO1 study.[21] The Kaplan-Meier plot is provided in Figure 11 of the CS.[1] TTD was defined as the interval from the date of randomisation to the first of the date of death or the date at which olaparib treatment was discontinued. In the company's submitted economic model all patients are assumed to discontinue olaparib treatment after 51 months. In response to clarification question B20 the company stated that, if the olaparib treatment is discontinued at 2 years post treatment initiation, then the patient is not recorded as discontinuation until their next study visit (on average 30 days later).[2] This provides the rationale for the shape of the curve in which [redacted].

Subsequent use of PARP inhibitors

The use of subsequent PARP inhibitors was included in the company's model separately from the main partitioned survival structure. It was operationalised in three steps: (1) the proportion of people receiving subsequent PARP inhibitors was estimated; (2) the time until these people received a subsequent PARP inhibitor was estimated; (3) the time that they spent on subsequent PARP inhibitors was estimated.

The company estimated the proportion of people receiving a subsequent PARP inhibitor using the SOLO1 data, separately for each arm of the study ([redacted] in the olaparib arm and [redacted] in the placebo arm).[1]

Time to subsequent PARP inhibitor use was estimated using the SOLO1 data for those patients who received a PARP inhibitor. Time to subsequent PARP inhibitor use was defined as the time from randomisation until a patient received a subsequent PARP inhibitor. Kaplan-Meier curves were fitted separately to each trial arm (CS,[1] Figure 28). Due to the population of SOLO1 included in this analysis, the Kaplan-Meier curves were complete.

The average time spent on subsequent PARP inhibitors was estimated using data from Study 19. In brief, Study 19 was a, double blind, randomised controlled trial which compared olaparib with placebo for patients with relapsed, high-grade serous ovarian cancer who had received two or more platinum-based chemotherapy regimens and had had a partial or complete response to their most recent platinum-based chemotherapy regimen.[6, 45] In Study 19, data on BRCA mutation status was collected retrospectively using germline and somatic testing. Time spent on subsequent PARP inhibitors was defined as the time from randomisation in Study 19 until they stopped receiving their olaparib treatment. A 1-knot spline model was selected to estimate the time spent on treatment within the company's submitted model. The company states that this was the best fitting curve out of multiple parametric models. However, exactly which parametric models were considered and how the relative goodness-of-fit of the models were assessed is unclear.

5.2.5.2 Health related quality of life

The health state utility values for the progression free and progressed disease health states were calculated using the EQ-5D-5L collected during the SOLO1 studies. As recommended by NICE, EQ-5D-3L utilities were calculated from the EQ-5D-5L data using the van Hout *et al* crosswalk algorithm.[32] The mean utilities for people who have progressed disease and those in PFS were calculated using data from the SOLO1 trial. Excluding the effects of adverse events, utility in each state was assumed independent of treatment arm. The utility was estimated to be [redacted] for patients who were in PFS and [redacted] for patients with progressed disease.

The utility values estimated from the SOLO1 trial data were adjusted to take into account ageing. The utility values for PFS and progressed disease were reduced each cycle by values calculated from the formula published by Ara and Brazier to estimate the average utility score based on age and sex.[35]

QALY decrements were applied to each treatment arm to incorporate the effect of anaemia, neutropenia and diarrhoea. The absolute decrements are based on values in the literature whilst the duration of events is based on previous NICE appraisals and assumptions with an unclear source. The utility loss incurred per adverse event and the duration of each adverse event are provided in the CS, page 106, Table 34.[1] The incidence of each of these adverse events by treatment arm are provided in the CS, page 101, Table 32.[1] The decrements for each of the adverse events, in each arm of the company's model, are summarised in Table 7.

Table 7: QALY decrements applied in the deterministic analyses due to incidence of adverse events in each treatment arm

Adverse event	QALY decrement per event	Total QALYs lost due to adverse events		Sources
		Olaparib	Routine Surveillance	
Anaemia	0.0023	0.00125	0.00005	Swinburn[38], Nafees[39], NICE,[40] assumption, SOLO1[21]
Neutropenia	0.0017	0.00022	0.00007	
Diarrhoea	0.0009	0.00007	0.00000	

QALY, quality adjusted life years; NICE, National Institute For Health and Care Excellence

5.2.5.3 Resource use and costs

The costs and resource use included in the base case model consisted of: drug acquisition costs; drug administration costs; disease monitoring costs; AE costs; and, end of life care costs. Additional BRCA testing costs were included within a scenario analysis.

Drug acquisition costs

The drug acquisition costs included those related to: maintenance olaparib after response to first-line platinum chemotherapy; the costs of subsequent chemotherapy regimens after progression; and the cost of subsequent PARP inhibitors.

The cost of olaparib is £2317.50 per 56 tablet (14 day) pack. The BNF indicates that this cost is same regardless of whether the pack contains 150mg or 100mg tablets. Based upon the average daily olaparib

dose observed in the SOLO1 data, patients receive [redacted] of olaparib each day. This reduction in dose from the licenced 600mg each day is due to: (1) interruptions of olaparib treatments due to the occurrence of adverse events; and, (2) reductions in dose to 500mg or 400mg each day to manage adverse events. This gives a per cycle acquisition cost for [redacted] of olaparib per day of a minimum of [redacted]. The acquisition cost would be increased if the reduced dosage observed in SOLO1 was due to planned decreases in dose, rather than to temporary interruptions of treatment. This is because the per cycle cost for 400mg, 500mg and 600mg of olaparib per day is the same, regardless of the dose.

The subsequent chemotherapies assumed to be used in the company's economic model were: carboplatin, doxorubicin, paclitaxel, docetaxel, and cisplatin. The unit costs for these chemotherapies were obtained by the company from the BNF and commercial medicines unit (CMU) drugs and pharmaceutical electronic market information tool (eMIT). The recommended doses of the chemotherapies were sourced from the Yorkshire Cancer Network treatment guidelines. Details of the cost of each chemotherapy and the dose of each regimen are provided on page 37 of the CS (Table 37 and Table 38 respectively).[1] The future use of chemotherapy lines has been calculated although the ERG does not believe the methodology used is appropriate. For both arms of the model: 96.20% of patients who relapse receive a platinum-based chemotherapy regimen (platinum chemotherapy plus non-platinum chemotherapy) and that 33.15% of patients who relapse receive a non-platinum-based chemotherapy regimen alone. The data source for these proportions are unclear and the proportions add up to greater than 100%. It is further assumed that all regimens consist of three lines of subsequent therapy, with the rationale and source for this assumption being unclear. The assumed proportions of patients receiving the different chemotherapies are provided in Table 8. It is unclear where the proportions in Table 8 have been obtained.

Table 8: The proportion of patients receiving the different chemotherapy regimens upon relapse within the company's submitted model

Chemotherapy	Percentage receiving chemotherapy upon relapse
Platinum-based	
Carboplatin	50%
Cisplatin	50%
Non-platinum-based	
Doxorubicin	33%
Paclitaxel	33%
Docetaxel	33%

Patients could receive PARP inhibitors after relapse. All patients were assumed to receive 300mg daily of niraparib, as their subsequent PARP inhibitor. The acquisition cost of niraparib was obtained from the BNF and was £4500 for a pack of 56 100mg niraparib tablets. The ERG was not provided with details on any managed access agreement for niraparib in this setting.

The use of subsequent PARP inhibitors was estimated using the following data: 1) the proportion of patients who relapse and received a subsequent arm inhibitor; 2) the time to subsequent PARP inhibitor therapy; and 3) the time spent on treatment. Details of these data sources are provided in the section on the subsequent PARP inhibitors, starting on page 33 of this report.

Chemotherapy and PARP inhibitor administration costs

The cost of administering chemotherapy was obtained from NHS reference costs. Different costs were used for first (£173.99) and subsequent attendances (£205.09). No additional administration costs, above those associated with patients' monthly visits to consultants, were applied to the use of PARP inhibitors as they are administered orally.

Disease monitoring costs

The company principally used the British Gynaecological Cancer Society guidelines to determine the follow up schedule for patients in the model.[46] The key difference between the resource use in the olaparib and routine surveillance arm is that during the first two years in the progression free state, patients in the olaparib arm receive a more intense follow up comprising monthly outpatient visits and blood tests. After the first two years, resource use in the progression free health state and at any time in the progressed disease health state is assumed to be the same in both arms. Details on the costs and monthly resource use is given in Table 9.

Table 9: The monthly resource use and associated costs used within the company's model

	Unit cost	RS - PF, first two years	Olaparib - PF, first two years	PF, after two years	PD	Source
Outpatient Visit	103.30	0.3	1.0	0.3	1.0	NHS reference costs 2016-17[47], BGCS[46], CS[1]
Blood count	3.06	0.3	1.0	0.3	0.3	
CT scan	102.09	0.3	0.3	0.3	0.3	
RS, routine surveillance; PF, progression free; PD, progressed disease; BCGS, British Gynaecological Cancer Society; CS, Company's submission.						

Adverse Event costs

The costs of adverse events in each model arm and the associated unit costs are provided in Table 10.

Table 10: The cost of each included adverse event

Adverse event	Cost per event (£)	Total cost incurred due to adverse events (£)		Sources
		Olaparib	Routine Surveillance	
Anaemia	£620.18	341.10	12.40	NHS reference costs, CS[1]
Neutropenia	£464.53	60.39	18.58	
Diarrhoea	£485.50	38.84	0	

CS, company's submission

End of life care costs

The company's model applies a one off cost of £7638.51 upon death from Guest *et al*. to reflect the cost of terminal care.[48]

5.2.6 Model validation and face validity check

The company state that they chose the model structure on the basis of a review of NICE technology appraisals in oncology. The selected approach was a three-state partition survival model, comprising of progression free, progressed disease and death health states. Reasons for this choice was that the approach "*makes the best use of the evidence available, captures clinically important aspects of this disease, and is aligned with the stated preference of evidence review groups (ScHARR and BMJ-TAG) for a partitioned survival approach to predict lifetime costs and health effects of treatment. This modelling structure and approach have been used extensively and validated in previous NICE oncology technology appraisals*"(CS[1], page 129). ScHARR-TAG, however, notes that its preference is very much decision-problem orientated and would caution about the automatic selection of a partition survival approach for various reasons including that it ignores correlation between outcomes.

The company states that the model structure and approach was reviewed by a UK expert in health economics; it is not stated whether the expert provided comments on the results of the curve fitting to the data in SOLO1.

The face validity of the model was reviewed by two health economists at AstraZeneca who were not involved in the submission and an external health economist. Clinical outcomes predicted by the model

were compared to real-world clinical data from the UK and with clinical opinion; the company did not comment on the face-validity of the model outputs to the observed data in SOLO1.

The implementation of the model was checked through logical tests and extreme value testing and review of macros within the model structure. Data in the model relating to costs and utilities were stated to be checked against the source data and the stated values in the CS.[1]

5.2.7 Cost effectiveness results

In the CS, the company discounts both costs and QALYs at a rate of 1.5% per annum.[1] The reason for this is that the company believes that criteria in Section 6.2.19 of the NICE methods guide apply, as olaparib "*... demonstrates that patients in this setting are highly likely to have long term health benefits (i.e. >30 years…"* (CS, page 64).[1, 23] The ERG notes that these criteria have three conditions, which are: (1) that people receiving standard care (routine surveillance) would otherwise die or have a very severely impaired quality of life; (2) that treatment (olaparib) restores people to full or near full health over a very long period (usually at least 30 years); and, (3) that the committee believes that the treatment (olaparib) would not commit the NHS to irrecoverable costs.[23] The ERG has concerns about whether all of these are criteria are met, further details of which are given in Section 5.3.4.

For completeness, the ERG presents the company's base case analysis both when using the company's preferred 1.5% discount rate for both costs and QALYs and when using a 3.5% discounting discount rate as per the NICE Reference Case.[23]

Table 11 shows the results of the company's base case analysis in both the deterministic analysis and the PSA analysis when costs and QALYs are discounted at 1.5%. The PSA results are based on the ERG rerunning the PSA with 1,000 iterations. Based on the probabilistic version of the model, olaparib is expected to generate [redacted] additional QALYs at an additional cost of [redacted], compared with routine surveillance. The corresponding ICER is £12,007 per QALY gained. The deterministic version of the company's model produces a similar ICER of £11,830 per QALY gained. The corresponding cost-effectiveness plane (CEP) and cost-effectiveness acceptability curve (CEAC) for the ERG's rerun of the company's base case are presented in Figure 6 and

Figure 7 respectively.

Table 11: Company's base case results, assuming a discount rate of 1.5% for Costs and QALYs (adapted from CS,[1] Table 45)

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)	Probability that the intervention is the most cost-effective at a MAICER of:	
				£20,000 per QALY gained	£30,000 per QALY gained
Probabilistic sensitivity analysis – based on a rerun by the ERG					
Olaparib	[redacted]	[redacted]	-	0.93	0.99
RS	[redacted]	[redacted]	-	0.07	0.01
Incremental	[redacted]	[redacted]	£12,007	-	-
Deterministic					
Olaparib	[redacted]	[redacted]	-	-	-
RS	[redacted]	[redacted]	-	-	-
Incremental	[redacted]	[redacted]	£11,830	-	-

ICER, incremental cost-effectiveness ratio; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality adjusted life year; RS – Routine surveillance

Figure 6: Company's base case cost-effectiveness plane based on the ERG's rerun of the PSA, using a 1.5% discount rate for costs and QALYs

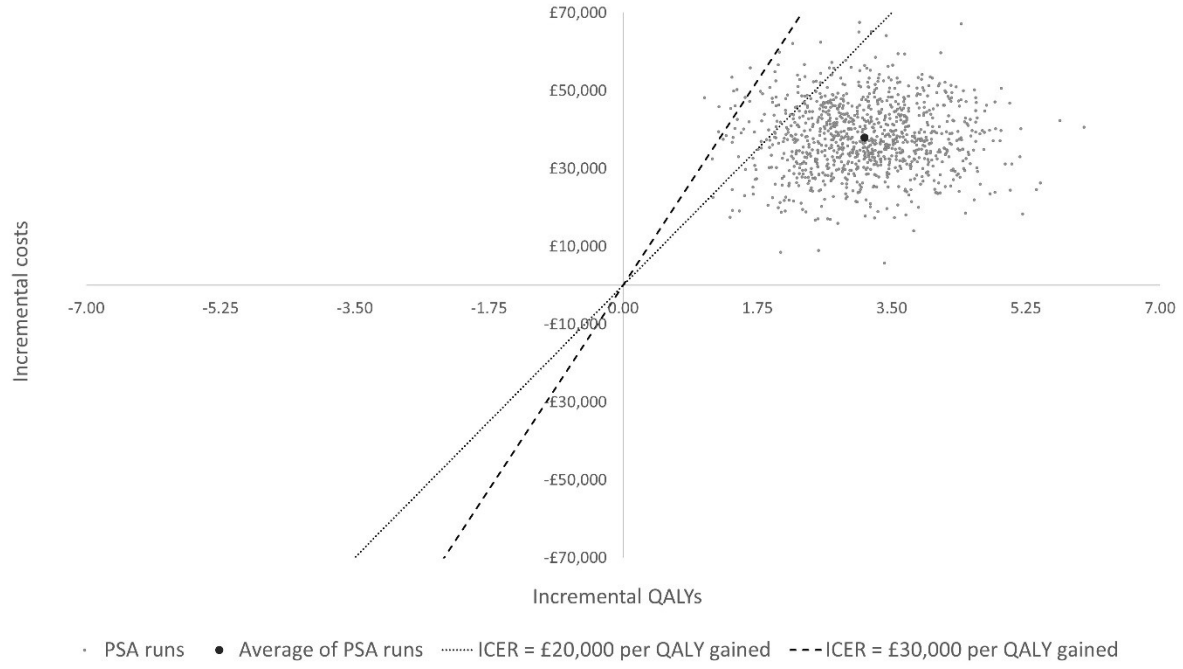
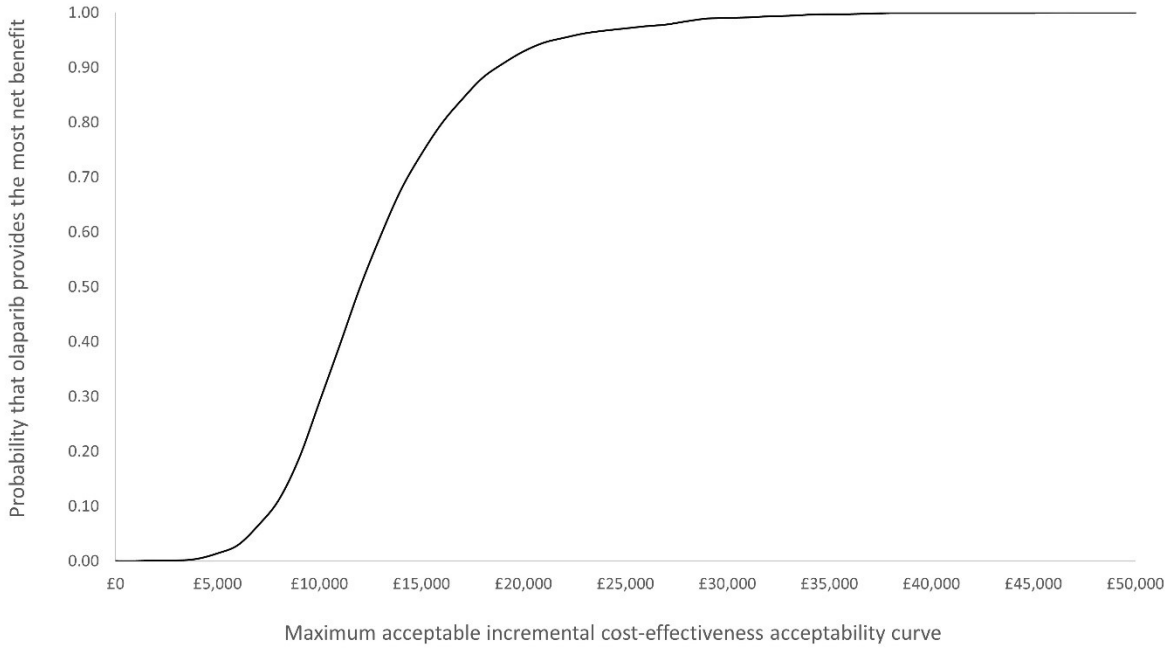


Figure 7: Company's base case cost-effectiveness acceptability curve based on the ERG's rerun of the PSA, using a 1.5% discount rate for costs and QALYs



5.2.8 Sensitivity analyses

The sensitivity analyses were conducted using a discount rate of 1.5% for costs and QALYs.

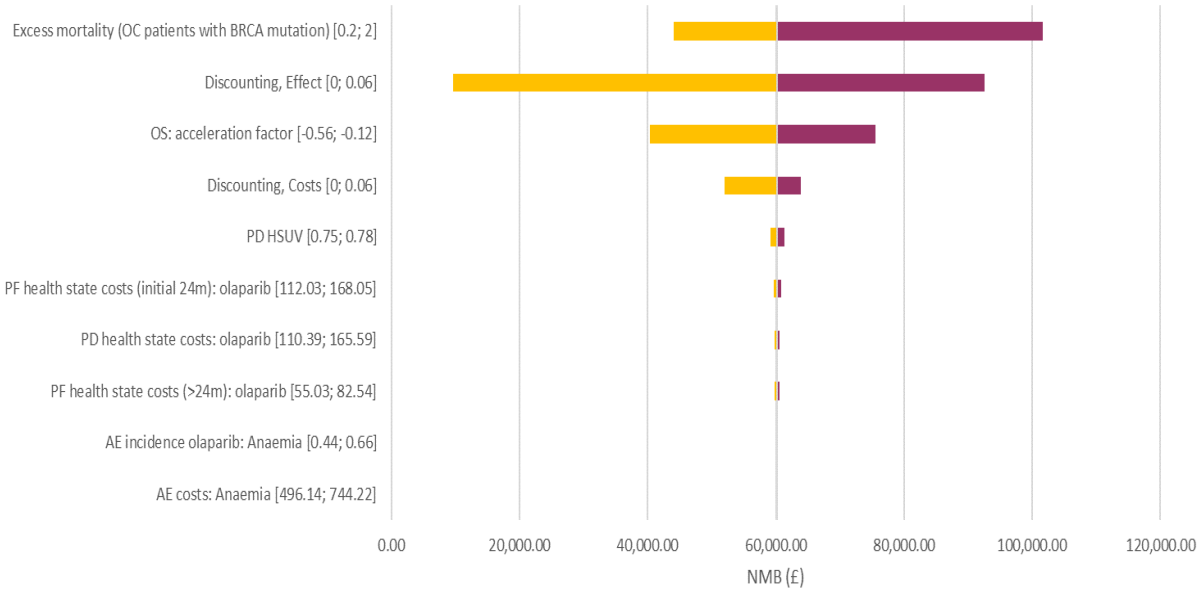
The company conducted a range of sensitivity analyses, which included: (1) a tornado diagram presenting the impact changing parameters from their upper and lower limits; and (2) a range of scenario analyses, which included the effects of alternative assumptions and data on the results.

5.2.8.1 Tornado diagram

The company's tornado diagram is presented in Figure 33 of the CS.[1] It shows the ten most influential parameters in terms of net monetary benefit (NMB). In response to clarification question C5, the company established that the maximum acceptable ICER (MAICER) used to calculate the NMB was £30,000 per QALY gained.[2] Within the tornado diagram, parameters were varied between the upper and lower bounds of the 95% CIs of each parameter. With the discount rate, the parameter was changed to a 0% and a 6% discount rate. The company's tornado plot, showing the 10 most influential parameters on net monetary benefit (calculated using a maximum acceptable ICER of £30,000 per QALY gained) is given in

Figure 8.

Figure 8: A tornado diagram showing the ten most influential parameters on the ICER, when changed between lower and upper bounds (reproduced from CS,[1] Figure 33)



5.2.8.2 Scenario analyses

The company undertook several scenario analyses, which are presented in the CS, Table 47.[1] The most influential parameter on the base case ICER was the discount rate. When the discount rate was set at 3.5%, as in the NICE reference case, the company's base case ICER increased from £11,830 per QALY gained to £18,356 per QALY gained.[23]

5.2.8.3 Updated model results following the clarification process.

In response to a minor issue raised by the ERG during the clarification process, the company updated their base case model results. This amended the method used to adjust annual probabilities to monthly probabilities from dividing the annual probability to adjusting the probability using the formulae for converting probabilities into rates in Briggs *et al*.[49] This method assumes that there is an underlying exponential distribution when converting the probabilities. The updated results produced a very similar deterministic base case ICER, the revised ICER is £11,910 compared to the original base case ICER of £11,830. The full set of updated scenario analysis results, but not the PSA or tornado diagram, are provided in response in clarification question B2.[2]

Furthermore, in response to clarification question B2, the company provided the deterministic base case and the results of the scenario analyses when the discount rate was 3.5% for both costs and QALYs.[2] However, the tornado diagram and PSA were not provided. The ERG undertook a PSA using the

company's base case assumptions with the exception of using a discount rate of 3.5% for both costs and QALYs. The company's updated model was not provided in the company's clarification response; therefore, the PSA results do not incorporate the change relating to calculating monthly mortality probabilities. However, as shown previously, addressing these minor issues changed the ICER by less than £100.

The results of the PSA using the company's base case but with discount rates of 3.5% are presented in Table 12, Figure 9, and Figure 10. In summary the PSA base case ICER increases to £18,221 which remains broadly similar to the deterministic ICER (£18,356). The probability that olaparib is cost-effective at MAICERs of £20,000 and £30,000 per QALY gained are 0.641 and 0.955 respectively.

Table 12: Company's base case results, assuming a discount rate of 3.5% for Costs and QALYs

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)	Probability that the intervention is the most cost-effective at a MAICER of:	
				£20,000 per QALY gained	£30,000 per QALY gained
Probabilistic sensitivity analysis – based on a run by the ERG					
Olaparib	[redacted]	[redacted]	-	0.641	0.955
RS	[redacted]	[redacted]	-	0.359	0.045
Incremental	[redacted]	[redacted]	£18,221	-	-
Deterministic					
Olaparib	[redacted]	[redacted]	-	-	-
RS	[redacted]	[redacted]	-	-	-
Incremental	[redacted]	[redacted]	£18,356	-	-

ICER, incremental cost-effectiveness ratio; MAICER, maximum acceptable incremental cost-effectiveness ratio; QALY, quality adjusted life year; RS – Routine surveillance

Figure 9: The cost-effectiveness plane of the ERG's PSA analysis of the company's base case, except a 3.5% discount rate for costs and QALYs is used

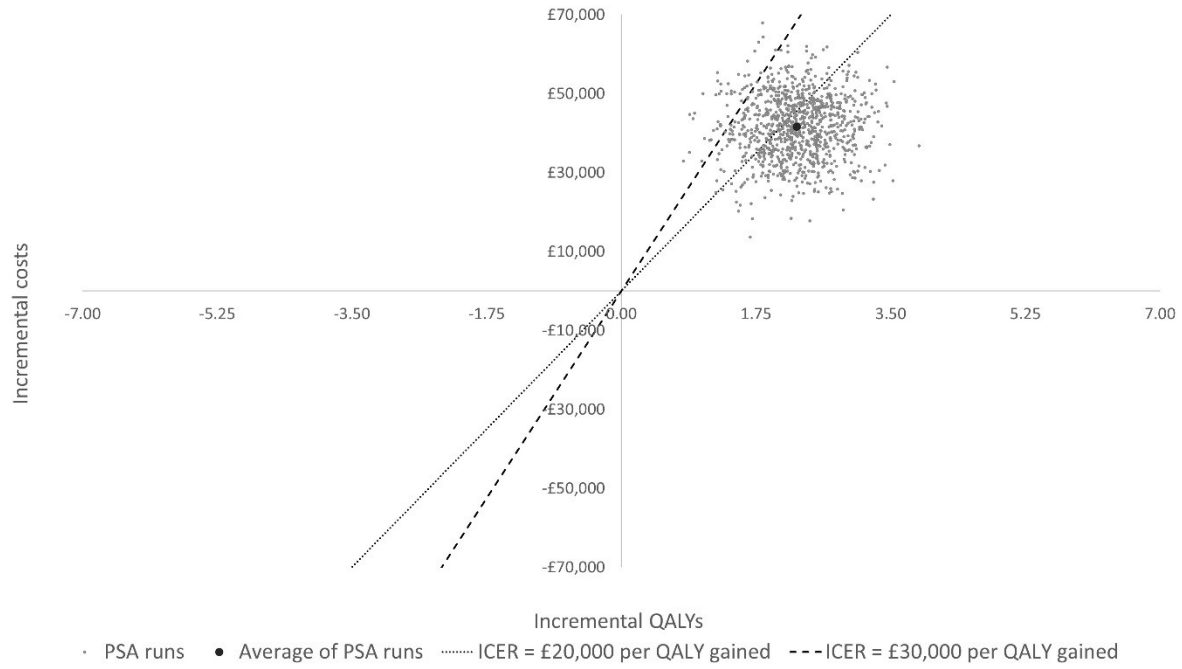
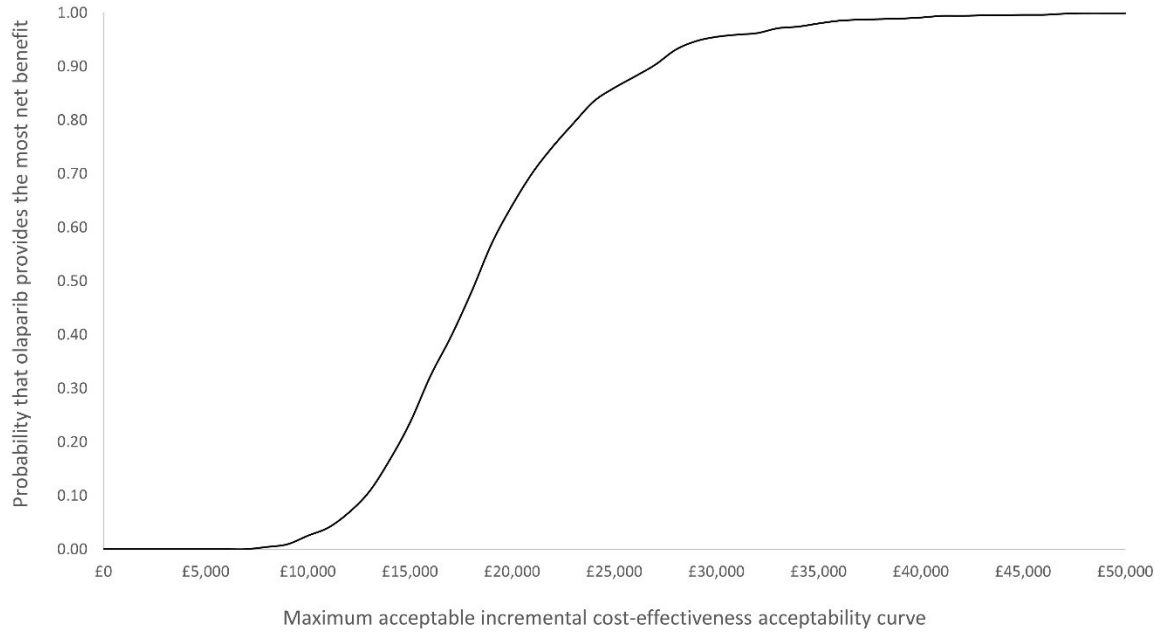


Figure 10: The cost-effectiveness acceptability curve of the ERG's PSA analysis of the company's base case, except a 3.5% discount rate for costs and QALYs is used



5.3 Critique of company's submitted economic evaluation by the ERG

This section presents a critical appraisal of the health economic analyses presented within the CS.[1] Section 5.3.3.1 details the methods used by the ERG to interrogate and critically appraise the company's submitted health economic analyses. Section 5.3.2 discusses the extent to which the company's analysis adheres to the NICE reference case. Section 5.3.3 summarises the ERG's verification of the company implemented model and highlights inconsistencies between the model, the CS, and the sources used to

inform the model parameter values.[1] Section 5.3.4 presents a detailed critique of the main issues and concerns underlying the company's analysis.

5.3.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model and discussion of issues identified amongst the members of the ERG.
- Examination of the correspondence between the description of the model reported within the CS and the company's executable model.
- Rerunning the PSA presented within the CS.
- Where possible, checking the parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.2 Adherence of the company to the NICE reference case

The company's economic evaluation is generally in line with the NICE reference case, details of which are given in Table 13.

Table 13: Adherence of the company's model to the NICE reference case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The ERG notes that patients with FIGO stage II ovarian cancer may be defined as having an advanced ovarian cancer, however they are not included in the company's submission. Furthermore the company's submission only included patients with high grade serous tumours.
Comparator(s)	As listed in the scope developed by NICE	The company's model compares olaparib against routine surveillance. No other comparators were identified in the NICE scope.[4]
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are modelled in terms of QALYs gained
Perspective on costs	NHS and PSS	Costs were considered from an NHS and PSS perspective
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. The results of the analysis are presented in terms of cost per QALY gained for olaparib versus routine surveillance.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company's model adopts a 50-year time horizon. By this point, over 99.9% of patients had died.
Synthesis of evidence on health effects	Based on systematic review	Health outcomes are modelled using the data collected in the SOLO1 randomised controlled trial.[21] It is implicitly assumed that the SOLO1 trial is generalisable to UK clinical practice.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	HRQoL estimates for the progression free and progressed disease health states were derived from EQ-5D-5L data collected in the SOLO1 study.[21] The EQ-5D-5L responses were valued using the van Hout *et al* crosswalk algorithm to the UK EQ-5D-3L valuation set.[32, 50]

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The ERG had no concerns with the company's approach
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	The ERG had no concerns with the company's approach
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gained.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource components included in the company's model reflect those relevant to the NHS and PSS. Unit costs were valued at 2017/18 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 1.5% per annum. The company believes that olaparib meets the criteria listed in Section 6.2.19 of the NICE methods guide.
HRQoL, health related quality of life; PSS, personal social services		

5.3.3 Model verification and correspondence between the model, the CS and parameter sources

5.3.3.1 Model verification

The ERG verified the company's model by checking the formulae in its submitted model. A user defined function was used to produce the PFS and OS curves. The ERG checked that the results of the company's user defined function matched the curves produced by package that the company used to fit the curves (flexsurv Package in R). During this process the ERG only identified one minor, which was addressed by the company in their clarification response (see Section 5.2.8.3)

5.3.3.2 Correspondence between the written submission and the model

The implemented model appears to be generally in line with its description within the CS.[1] As individual patient-level data were not provided by the company, it was not possible for the ERG to fully verify the implementation of the survival models described in the CS.[1]

5.3.3.3 Correspondence of the model inputs and the original sources of parameter values

The ERG found that some NHS reference costs had minor differences from the values reported in the CS.[1] However, as the discrepancies were in the region of 20p the ERG is satisfied that if these costs are errors, they will not significantly impact on the ICER. All other parameters corresponded with their original source values.

5.3.4 Main issues identified within the critical appraisal

The ERG has a key concern about the company's choice of OS curves within their model. In short, the ERG considers that the fitted OS curves lack face validity, and consequently any ICERs generated from the model are unreliable. The ERG identified multiple other issues. Each of these issues are summarised and addressed in detail in this section of the report

Box 2: Summary of the main issues identified within the company's health economic model

Overall Survival and model structure issues.

1) Concerns regarding the face validity of the company's selected OS curve for routine surveillance
2) Further concerns regarding the company's curve fitting
3) Unrealistic treatment pathway
4) Exclusion of PFS2 from the economic model

Other identified issues

5) Whether olaparib meets the criteria in Section 6.2.19 of the NICE methods guide for discounting costs and QALYs at a rate of 1.5% per annum
6) Populations in the final scope not included in the model
7) The implementation of dose reductions within the company's estimates of the cost of olaparib
8) The inability to remove the effects of niraparib maintenance therapy from the company's model
9) The use of subsequent PARP inhibitors by people receiving olaparib
10) The PSA results lack face validity

(1) Concerns regarding the face validity of the company's selected OS curves for routine surveillance

As initially identified in Section 5.2.5.1, the ERG believes that the company's OS curves for the routine surveillance arm do not exhibit face validity. The key reason for this is that the company's OS extrapolation for routine surveillance begins to diverge from the observed Kaplan-Meier curve at approximately [redacted] months resulting in a large discrepancy between the observed data and the modelled data at [redacted] months.

The ERG agrees with the company that the OS Kaplan-Meier curve for routine surveillance plateaus after 30 months. Figure 4 shows that the numbers of patients at risk are [redacted] (out of an initially 260) prior to month 45 in the olaparib arm and [redacted] (out of an initially 131) in the routine surveillance arm. At month 39,

[redacted]. The ERG believes that these are sufficiently high numbers of patients at risk to not be dismissed. Furthermore, the ERG does not believe the routine surveillance OS data can be clinically implausible given that it was observed in SOLO1. In addition, The ERG believes that: 1) using a surrogate outcome to estimate OS, which in the company's model is PFS2, is inappropriate given the availability of OS data, and 2) generating a curve for routine surveillance using a hazard ratio applied to the olaparib hazard function ensures that a benefit of olaparib will be generated over the lifetime of patients in spite of the possibility that curves may not remain separated over the lifetime of patients.

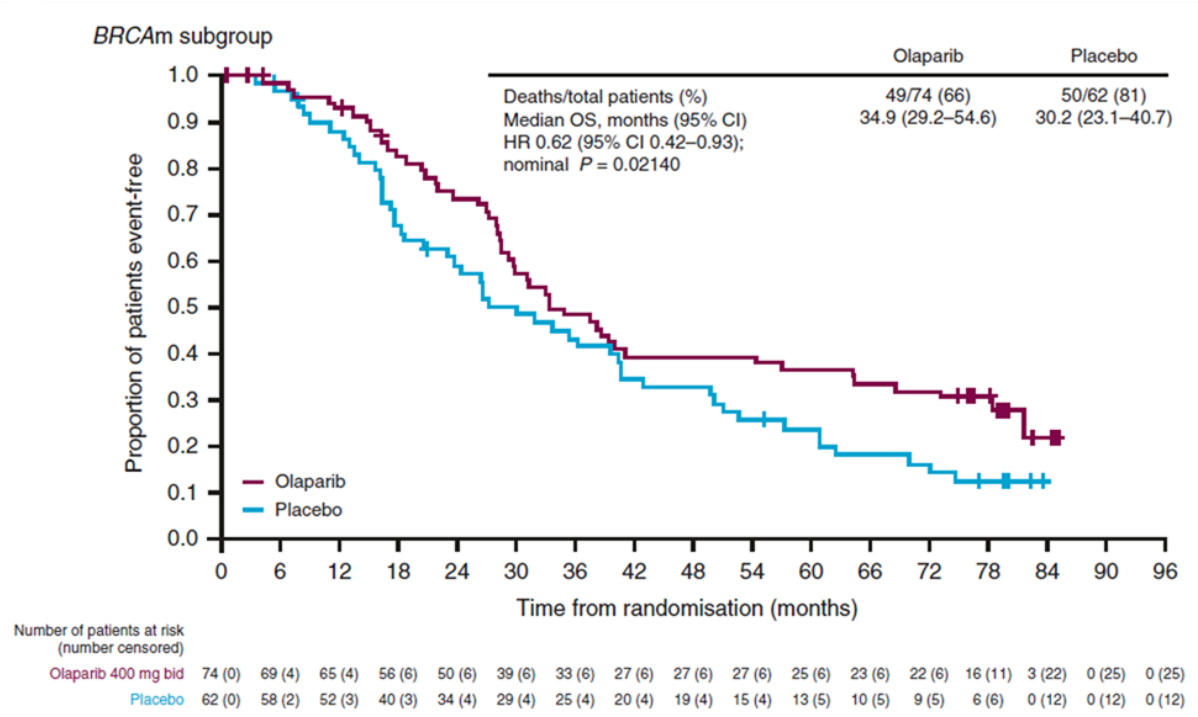
The ERG accepts that it is plausible that olaparib may have survival benefits beyond the time horizon of the SOLO1 study, but maintain that the company's modelled estimates should broadly follow the curves estimated using SOLO1 data up until at least 45 months. The ERG has two reasons for believing that a gain in OS associated with olaparib use could be plausible: the first relates to the use of subsequent PARP inhibitors; and the second relates to observed data in Study 19. However, without further data, it is also plausible that olaparib does not generate any further survival benefits than those observed in SOLO1 given that most patients discontinued first line olaparib 24 months post-randomisation in SOLO1.[21]

PARP inhibitors are available in the current treatment pathway to some people in the routine surveillance in model. A detailed description of the treatment pathway is provided in Section 2.2. In summary, if patients with advanced ovarian cancer respond to two lines of platinum-based chemotherapy, then they can currently receive niraparib maintenance treatment through the CDF, if they respond to a third-line of platinum-based chemotherapy, then they can receive olaparib through

routine commissioning.[18, 20] The ERG expects that these maintenance treatments will bolster OS, but not PFS, in this population.

The OS Kaplan-Meier curve in Study 19 for the BRCA-mutated subgroup (see Figure 11) showed that olaparib produced an initial overall survival benefit starting at around 12 months which then diminishes to very little remaining benefit at approximately 39 months and then there is a longer term OS benefit from month 42 onwards, albeit estimated from small patient numbers of less than 30 in each arm. The ERG believes that pattern in OS observed in Study 19 is potentially relevant to this appraisal. It may be the case that a similar pattern on OS is observed when olaparib is used as a maintenance treatment after response to 1st line chemotherapy.

Figure 11: Overall survival in patient with BRCA mutated subgroup of Study 19 (reproduced from Clarification Response, Question B6)[2, 43]



The company's curves for OS from SOLO1 are provided in Figure 12. As the company selected the piecewise approach for OS, the Kaplan-Meier curves were used up to 24 months post-randomisation, with later time periods using the curves. All of the extrapolated curves clearly diverge from the routine surveillance Kaplan-Meier curves. Consequently, the ERG considers none of the chosen curves in the company's base case analysis are reliable for decision making.

Figure 12: Overall survival observed in the routine surveillance arm of SOLO1 and the extrapolations used for overall survival in the company's model

The ERG believes that given the lack of plausible OS curves that would predict a long-term OS benefit the company should have considered alternative modelling approaches. Specifically, a sequenced economic model could have been reconsidered by the company. The company's rationale for initially not adopting this approach is given in response to clarification question B1.[2] The sequenced economic model would, at a minimum include: a different health state for each chemotherapy line and subsequent maintenance treatment or routine surveillance and a death state. This type of model would require data to be used from multiple studies to populate the parameters, as data would need to be obtained for patients at each available therapy line. The advantage of this model structure is that it could potentially produce estimates of OS that are closer to the data observed in SOLO1, compared to the OS estimates generated by the company for the control arm.

(2) Further concerns regarding the company's choice of curves

The ERG had three further concerns relating to the company's fitted survival, which are: (1) the relevance of using the Edinburgh Ovarian Cancer Database to validate OS outcomes; and, (2) the justification for using a piecewise approach to fitting curves. These are addressed in turn.

To justify the choice of curve selection for the routine surveillance arm, the company uses the Edinburgh Ovarian Cancer Database. This database contains information collected prospectively on every patient with epithelial ovarian cancer patients treated in south east Scotland from 1974 to 2018. Of the patients in the database, 160 patients have a BRCA-mutated high grade serous ovarian carcinoma. No information in the CS is presented on what year patients with a BRCA-mutated high serous ovarian carcinoma presented; however, for all patients with a high serous ovarian carcinoma: >1% of patients

were recruited in the 1970s; 9% of patients were recruited in the 1980s; 22% were recruited in the 1990s; 30% were recruited in the 2000s; and 38% were recruited in the 2010s.[1] In response to clarification question B6, the company presented an analysis of OS in this dataset.[2] The ERG considers that these analyses may not be informative of the expected OS curve for routine surveillance in the target population because the majority of patients appear to have been recruited prior to January 2016 when NICE approved olaparib for these patients after response to three lines of platinum-based chemotherapy; and, July 2018 when niraparib was approved for use in the CDF for these patients if they responded to two lines of platinum-based chemotherapy. The introduction of subsequent olaparib and niraparib use is expected to improve the survival of patients receiving routine surveillance compared with patients in the Edinburgh Ovarian Cancer Database. Consequently, the ERG does not believe that it is valid to consider the OS from this dataset for validation purposes for the OS extrapolations. Given how recently olaparib and niraparib have enter the treatment pathway in the UK, the ERG does not expect that datasets will be available to validate expected survival for patients receiving routine surveillance after responding to first line platinum based chemotherapy

Concerns about the justification of using a piecewise modelling approach

The company conducts a piecewise approach to modelling PFS and OS, with a justification relying on plausibility. The company also believe that it would be appropriate as most patients discontinue olaparib at two years, if they haven't discontinued earlier. The ERG believes that the company's underlying rationale for a change in the hazard of PFS and OS events in the olaparib arm of SOLO1 is sound, however the ERG would preferred that the company demonstrated that the empirical hazard changed at approximately two years to justify this approach.

(3) Unrealistic treatment pathway

The company has submitted a three-state model in which patients are either progression free, have a progressed disease or have died. However, in the treatment pathway outlined in Section 2.2, patients can experience multiple disease progressions and if they respond to platinum-based chemotherapy and the time to progression is greater than six months, then they may be eligible to receive a PARP inhibitor (niraparib through the CDF if they respond to two lines of platinum-based chemotherapy and olaparib if they respond to three lines of platinum-based chemotherapy). Capturing such pathways within a single progressed disease health state and using a single PFS curve may not be possible. These issues could be addressed within a sequential model as described in the ERG's first critique point. Furthermore, the ERG believe that it is clinically implausible that every patient who relapses would receive three further lines of chemotherapy and that the proportion of patients who received platinum based chemotherapy and non-platinum-based chemotherapy would be constant across the therapy lines.

(4) Exclusion of PFS2 from the economic model

Data from PFS2 was not used to inform a second progression health state within the company's submitted model. The ERG are concerned about this for two reasons. Firstly, PFS2 was identified as an outcome within the NICE scope, secondly, the ERG would expect the quality of life of patients with a second progression to be lower that the quality of life of women with a first progression. A comparison of the health state utility value of the progressed disease state in this appraisal to the utility values used in NICE TA381, TA528 and ID1296 is presented in Table 14.

Table 14: A comparison of the health state utility values of the progressed disease health state in this appraisal to the values used in NICE TA381, NICE TA528, and NICE ID 1296

Health State in this appraisal	Value	Source	Notes
Progressed Disease	[redacted]	CS[1]	NA
Population in the progressed disease health state who responded to another line of platinum-based chemotherapy	0.77	NICE TA381[20]	This is for patients receiving maintenance therapy
	0.71	NICE TA381[20]	This is for patients not receiving maintenance therapy
	0.801	NICE TA528[18]	
	0.802	NICE ID1296[19]	
Population in the progressed disease health state who responded to another line of platinum-based chemotherapy and experienced another progression	0.68	NICE TA381[20]	
	0.739	NICE TA528[18]	
	0.719	NICE ID1296[19]	

Table 14 shows that the utility in the progressed disease health state [redacted].

Patients who suffered a further progression in previous NICE appraisals had much lower utilities than those patients who are in the progressed disease health state of the current model. As an approximation of the impact of including PFS2 in the company's, the ERG explored the impact of using different utility values in exploratory analyses.

(5) Whether the company's base case meets the criteria for costs and QALYs to be discounted at 1.5%
Section 6.2.19 of the NICE methods guide specifies that three criteria need to be met for the appraisal committee to consider a base case discount rate of 1.5%. These are: (1) people would otherwise die or have a very severely impaired life; (2) the intervention under appraisal restores then to full or near full health, and when this is sustained over a very long period (normally at least 30 years); and, (3) the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs. The ERG were concerned that the company's base case model does not meet criteria (1) or (2) of Section 6.2.19 of the NICE methods guide.[21]

The company provides no evidence that olaparib meets any of these criteria in this indication.

The ERG note that the OS data from SOLO1 suggest that approximately [redacted] of people in the routine surveillance arm are alive after two years. Furthermore the lowest utility in the company's submission is [redacted]. Because of these factors, the ERG believe that patients receiving routine surveillance are not at immediate risk of death or living with a severely impaired quality of life. As such, the ERG believe that the criteria in Section 6.2.19 of the NICE methods guide are not met and consequently, the appropriate discount rate for this appraisal is 3.5% for both costs and QALYs.

(6) Populations in the final scope not included in the model
As mentioned in Section 3.1, patients with FIGO stage II ovarian cancer were not recruited into SOLO1. As a result, the population evaluated in the model does not include these subgroups. Consequently, no estimates of the cost-effectiveness of olaparib in this setting is presented for patients with FIGO stage II ovarian cancer. The draft marketing authorisation, does specifically define advanced ovarian cancer, and as such a recommendation may include patients with stage II disease.

(7) The implementation of dose reductions within the company's estimates of the cost of olaparib
The company's base case costing assumptions reduce the price of olaparib to adjust for the mean dose that people received in SOLO1 (see Section 5.2.5.3). The dose could be reduced for two reasons: (1) olaparib treatment was interrupted due to the incidence of adverse events; and, (2) the dose was reduced, usually due to the incidence of adverse events. The price per tablet of olaparib is the same regardless of dose (either 100mg or 150mg). Consequently, in practice the cost per day of treating a patient on a reduced dose is the same as treating a patient on a full dose of olaparib. The ERG believes that the company's approach to including the cost of olaparib in their model could be an under-estimate. The ERG explored the effect of increasing the dose of olaparib on the ICER in exploratory analyses.

(8) The lack of ability to remove the effects of niraparib maintenance therapy from the company's model

The company's submitted model was used observed data from SOLO1. Patients in both arms were eligible to receive subsequent PARP inhibitors. Consequently, the effects of subsequent PARP inhibitors use are included in the OS curves. [redacted] of patients received a subsequent PARP inhibitor in the olaparib arm and [redacted] of patients received a subsequent PARP inhibitor in the placebo arm. This usage is likely to differ from the UK where niraparib is available after response to two lines of platinum-based chemotherapy (through the CDF) and olaparib is available after response to three lines of platinum-based chemotherapy (through routine commissioning). The ERG cannot assess the effect of changing the use of subsequent PARP inhibitors. It is unclear how changes to subsequent PARP inhibitor use would affect the ICER.

Further, there is uncertainty about whether niraparib will be positioned in the pathway and what this will cost the NHS. It is unclear to the ERG in what direction the ICER would change if niraparib was removed from the pathway. The ICER could increase, as more patients in the routine surveillance arm of the model received a subsequent PARP inhibitor, however, the ICER could decrease as the effect of niraparib on OS would be removed from the economic model.

If the modelled was a sequenced model, see the ERG's first critique point, then the effect of changing subsequent PARP inhibitor use on the ICER could be explored.

(9) The use of subsequent PARP inhibitors by people receiving olaparib

In the model, patients in the olaparib could receive a subsequent PARP inhibitor. This does not match the company's proposed use of subsequent PARP inhibitors in the treatment pathway. A detailed critique of this issue is provided in Section 3.3

(10) The PSA results produce implausible estimates of incremental QALYs

The ERG considers that the PSA results from the company's exhibit a lack of face validity. As shown in Figure 6 and Figure 9, olaparib generated more QALYs than routine surveillance in [redacted] of the PSA runs. While the ERG is not intending to imply that it believes that proportional hazards is appropriate, it notes that the hazard ratio observed in SOLO1 for overall survival was 0.95, with a 95% confidence interval of 0.60 to 1.53. Given that the confidence interval crosses unity and that the confidence interval is reasonably wide, the ERG expects that in a non-negligible proportion of the PSA runs that olaparib would produce fewer QALYs than routine surveillance. It should be noted that OS is only one of the measure of effect used to inform the QALY, and OS data from the SOLO1 study is immature (82/391 events, 21.0% maturity) and uncertain at this time.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

The ERG had concerns regarding the company's overall survival modelling. Therefore the ERG conducted three sets of scenario analyses to explore the impact of alternative OS assumptions on the company's base case ICER. Other ERG exploratory analyses were conducted on the cost of olaparib and the utility for patients in the progressed disease health state. Each of these exploratory analyses are detailed below.

Exploratory analysis 1: Using the SOLO1 OS Kaplan-Meier data and limiting the time horizon to 3.75 years

In the first scenario analysis, the OS Kaplan-Meier curve from SOLO1 was digitised and directly used to estimate within the company's base case model. The time horizon was limited to 3.75 years (45 months) as [redacted]. Furthermore, a threshold analysis was conducted to establish the relationship between additional discounted QALYs which olaparib may accrue and the ICER.

Exploratory analysis 2: Setting the rate of OS events to be the same in the olaparib and routine surveillance arms to be the same after two years.

In the second scenario analysis, patients in the routine surveillance arm of the model were assumed to experience death events at the same rate as patients in the olaparib arm after 2 years; this scenario remains unfavourable to routine surveillance. In this scenario analysis, olaparib still had an OS benefit over routine surveillance due to the assumption in the company's model that OS could not be less than the PFS curve. Given that olaparib was shown to produce a PFS benefit in SOLO1, it has a lower rate of OS events than routine surveillance after approximately [redacted] years.

Figure 13 shows the PFS and OS curves produced in this analysis.

Figure 13: The PFS and OS curves for olaparib and routine surveillance in ERG exploratory analysis 2

Exploratory analysis 3: ERG exploratory analysis 2 and restricting the time horizon so that the PFS and OS curve for olaparib does not cross.

The ERG were concerned that exploratory analysis 2 showed a benefit for olaparib due to the benefits that olaparib has on PFS (see

Figure 13). The ERG conducted the same set of analyses as ERG exploratory analysis 2, but limited the time horizon to [redacted] years. The rational for this analysis is that [redacted] years is just before crossing of the PFS and OS curves cross in the olaparib arm, causing there to be to have a lower rate of OS events in olaparib arm compared to routine surveillance after this time point.

ERG exploratory analysis 4: No reduction in acquisition costs due to dose reductions or interruptions.

Due to ERG's concerns regarding the cost of olaparib in the company's base case model, see Section 5.3.4, the ERG undertook an unfavourable scenario to olaparib with respect to pricing. In this scenario, it was assumed that all dose reductions were planned and that there were no dose interruptions. To implement this, the ERG set the dose of olaparib to the full 600mg per day.

ERG exploratory analysis 5: Lower utility in the progressed disease health state

Due to the ERG's concerns regarding the exclusion of PFS2 from the company's submitted model, the ERG explored the effect of lowering the utility of people in the progressed disease health state to that of a population who had suffered another progression. The ERG looked at NICE appraisals TA381, TA528, ID1296, which were assessing the use of PARP inhibitors in the relapsed population who had responded to two lines of platinum based chemotherapy.[18-20] The utilities in the progressed disease state was obtained from these appraisals and the lowest one was selected (0.68, see Table 14)

5.5 Impact on the ICER of Additional Clinical and Economic Analyses Undertaken by the ERG

The ERG believe that the criteria in Section 6.2.19 of the NICE methods guide are not met, see Section 5.3.4.[23] As such all of the ERG exploratory analyses use the standard discount rate of 3.5% for both costs and QALYs.

A summary of all ERG exploratory analyses is given in

Table 15, details for each of the scenario analysis results are provided in detail below. Due to uncertainties in the most plausible OS extrapolation, the ERG does not have a preferred base case ICER. The ERG believe that it is plausible that the ICER is in excess of £500,000 per QALY gained.

Table 15: A summary of the company's base case ICER, when both costs and QALYs are discounted at 3.5%, and the ERG's exploratory analyses

ERG exploratory analysis	Analysis conducted	ICER
NA	Company's base case, using discount rates of 3.5% for both costs and QALYs	£18,356
1	Using the SOLO1 OS Kaplan-Meier data and limiting the time horizon to 45 months	£660,497
2	Setting the rate of OS events to be the same in the olaparib and routine surveillance arms to be the same, after two years	£27,877
3	ERG exploratory analysis 2 and restricting the time horizon to 9.75 years, so that olaparib does have an OS benefit over routine surveillance due to the olaparib OS curve crossing the olaparib PFS curve.	£201,580
4	No reduction in cost of olaparib due to dose reductions or treatment interruptions	£21,372
5	Lower utility in the PD health state	£16,783
NA	ERG base case	Not calculated. ERG believe that it is plausible that the ICER is in excess of £500,000 per QALY gained

ERG, evidence review group; ICER, incremental cost-effectiveness ratio; NA, not applicable; QALYs, quality adjusted life years; OS, overall survival; ERG, evidence review group; PFS, progression free survival; PD progressed disease

Results of ERG exploratory analysis 1: Using the SOLO1 OS Kaplan-Meier data and limiting the time horizon to 3.75 years

Table 16 shows the result of the ERG's exploratory analysis, when the OS data from SOLO1 was used directly in the company's model and the time horizon was limited to 45 months. In this scenario analysis the ICER increases from £18,356 (company's base case, but with discounting for costs and QALYs 3.5%) to £660,497.

Table 16: The results of restricted mean analysis, using a time horizon of 45 months and probability of death from the digitised OS Kaplan-Meier curves produced by the ERG

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£660,497

ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RS, routine surveillance

Error! Not a valid bookmark self-reference. shows the results of this analysis, olaparib would need to generate an additional 2.25 discounted QALYs over routine surveillance to produce an ICER less than £30,000 per QALY gained. This threshold analysis should be interpreted with some degree of caution, as it does not include any additional future health care costs attributable to more patients in the routine surveillance arm been in the progressed disease state

Table 17: The effect of additional discounted QALYs in favour of olaparib on the ICER presented in

Table 16

Additional Discounted QALYs	0	1.5	1.75	2	2.25	2.5	2.75	3
Incremental QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£ per QALY gained)	£660,497	£43,550	£37,684	£33,210	£29,686	£26,838	£24,489	£22,517
QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio								

Exploratory analysis 2: Setting the rate of OS events to be the same in the olaparib and routine surveillance arms to be the same, after two years

The ERG conducted a second scenario analysis on the OS survival function, in which patients who remained alive in the routine surveillance arm had the same probability of experiencing a death event at any given time as someone who remained alive in the olaparib arm, after two years. The ERG urges caution in interpreting this scenario analysis, as on the basis of the SOLO1 data, it is still unfavourable to routine surveillance (as the probability of dying between 24 months post-randomisation and until 45 months post-randomisation was higher in the olaparib arm than the routine surveillance arm of SOLO1). Also, as shown in Section 5.3.4, olaparib is still associated with a substantial OS benefit over routine surveillance due to the benefits in PFS experienced by patients receiving olaparib and the assumption that OS curve cannot be less than the PFS curve.

Table 18 shows the results of this scenario analysis. Compared to the company's base case ICER (when costs and QALYs are discounted at 3.5%), the ICER has increased from £18,356 to £27,877 per QALY gained.

Table 18: The effect of assuming that the risk of death over time is the same in the olaparib and routine surveillance arms from 2 years onwards

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£27,877
ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; RS, routine surveillance			

Exploratory analysis 3: ERG exploratory analysis 2 and restricting the time horizon so that the PFS and OS curve for olaparib does not cross.

In part c the time horizon was restricted, so that the olaparib OS curve did not cross the PFS curve. In this scenario analysis, the ICER of olaparib compared to usual care substantially increases from £27,877 per QALY gained in ERG exploratory analysis 2 to £201,580 per QALY gained. Full results for this exploratory analysis are provided in Table 19.

Table 19: The effect of assuming that the risk of death over time is the same in the olaparib and routine surveillance arms from 2 years onwards and limiting the time horizon

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£201,580

QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio; RS, routine surveillance

Exploratory analysis 4: No reduction in cost of olaparib due to dose reductions or treatment interruptions

In this scenario analysis, olaparib was costed as though the full dose (600mg) was used per day. This increases the ICER to £21,371 per QALY gained from the company's base case ICER (using 3.5% discount rates for costs and QALYs) of £18,356 per QALY gained. Full results are given in Table 20.

Table 20: The effect of not reducing the price of olaparib, due to dose reductions or interruptions, on the ICER

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£21,372

QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio; RS, routine surveillance

Exploratory analysis 5: Lower utility in the progressed disease health state

In this exploratory analysis, the utility for people in the PFS health state was lowered from [redacted] to 0.68 to explore the effects of subsequent progressions in patients who had progressed. In this scenario analysis, the ICER decreases to £16,783 per QALY gained from the company's base case ICER (using 3.5% discount rates for costs and QALYs) of £18,356 per QALY gained. Full results are given in Table 21.

Table 21: The effect of lowering the utility in the progressed disease health state to 0.68

Treatment	Total QALYs	Total Costs	ICER (£ per QALY gained)
Olaparib	[redacted]	[redacted]	-
RS	[redacted]	[redacted]	-
Incremental	[redacted]	[redacted]	£16,783

QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio; RS, routine surveillance

5.6 Conclusions of the cost effectiveness section

Despite limitations in the review, the ERG were satisfied that no published economic evaluations which were relevant to the scope of this appraisal were excluded.

Based on the probabilistic version of the company's base case model (using a 1.5% discount rate for costs and QALYs, olaparib is expected to generate [redacted] additional QALYs at a cost of [redacted]

compared with standard the care. The corresponding cost effectiveness ratio is £12,007 per QALY gained. The deterministic version of the company's model produces a similar ICER of £11,830 per QALY gained. When a discount rate of 3.5% is used for costs and QALYs, the probabilistic ICER is estimated to be £18,221 per QALY gained and the deterministic ICER is expected to be £18,356 per QALY gained.

The ERG critically appraised the company's economic analysis and checked the implementation of key aspects of the company's model. The ERG's critical appraisal identified 10 issues relating to the company's economic analysis and the evidence used to inform it. These include: (1) concerns regarding the face validity of the company's selected OS curve for routine surveillance; (2) other concerns regarding the company's curve fitting; (3) unrealistic treatment pathway; (4) exclusion of PFS2 from the economic model; (5) whether olaparib meets the criteria in Section 6.2.19 of the methods guide for discounting costs and QALYs at a rate of 1.5% per annum; (6) populations in the final scope not included in the model; (7) the implementation of dose reductions within the company's estimates of the cost of olaparib; (8) the inability to remove the effects of niraparib maintenance therapy from the company's model; (9) the use of subsequent PARP inhibitors by people receiving olaparib; and, (10) the PSA results lack face validity.

The ERG undertook five sets of exploratory analyses using the deterministic version of the company's model, with discount rates of 3.5% for both costs and QALYs. Within the ERG's first exploratory analysis, the OS Kaplan-Meier curves were used and the time horizon was limited to 45 months, this analysis produced an ICER of £660,497 per QALY gained. When the rate of OS events were the same in both arms after two years and the time horizon was limited to [redacted] (so that olaparib did not have a lower rate of OS events than routine surveillance due to the OS curve crossing the PFS curve), the ICER was £201,580 per QALY gained. With a 50 year time horizon, the ICER was £27,877 when the rate of events in the OS curve was the same in both arms. The ERG urges caution when interpreting this analysis, as the rate of OS events is substantially lower in the olaparib arm after [redacted], as after this time point the model uses the event rate from PFS for olaparib. Other analyses demonstrate that the utility of patients in the progressed disease health state and the cost of olaparib had relatively minor effects on the ICER compared to the OS curve. Due to uncertainties in the extrapolation of OS, the ERG does not have a preferred ICER. The ERG believe that it is plausible that the ICER of olaparib compared to routine surveillance is in excess of £500,000 per QALY gained.

The ERG consider that the key uncertainties within the company's economic analysis relate to: the OS curve selected for the routine surveillance arm, which exhibits a lack of face validity when compared to the Kaplan-Meier curve from SOLO1; whether or not the use of subsequent PARP inhibitors in the

placebo arm of SOLO1 are reflective of current UK clinical practice; and, the use of subsequent PARP inhibitors in the olaparib arm of SOLO1.

6 END OF LIFE

The company made no claims that olaparib used as a maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy met NICE's end of life criteria. The ERG believes that this is appropriate as the life expectancy for patients who do not receive olaparib is considerably in excess of 24 months.

7 OVERALL CONCLUSIONS

Clinical-effectiveness

The main evidence in the CS, was derived from one RCT of olaparib as a maintenance treatment after response to first-line chemotherapy. Whilst the study was generally well reported, there are limitations regarding the subsequent treatment pathways in SOLO1. It is unclear to the ERG whether the subsequent treatment pathways reflect UK clinical practice for the placebo arm or the company's proposed pathway for the olaparib arm.

Cost-effectiveness

Due to the uncertainties in the extrapolation of overall survival, the ERG does not have a preferred ICER. The ERG believe it is plausible that the ICER of olaparib compared to routine surveillance is in excess of £500,000 per QALY gained. On the basis of the OS curve and the utilities in the company's submitted economic analysis, the ERG does not believe that people who receive routine surveillance would otherwise die or have a severely impaired quality of life. Consequently, the ERG does not believe that the criteria for 1.5% discounting outlined in Section 6.2.19 of the NICE methods guide are met.[23] Other uncertainties regarding the cost of olaparib and the utility of patients in the progressed disease health state only had a moderate impact on the ICER. The ERG note that there is uncertainty regarding the use of subsequent PARP inhibitors, however the effect of changing the use of subsequent PARP inhibitors on the ICER could not be reliably explored in the company's submitted model.

7.1 Implications for research

The ERG considers that future research should focus on two key uncertainties. Firstly, future research should be conducted on whether olaparib has a long term OS benefit compared to routine surveillance in this population. This should be generated at later data cuts of the SOLO1 study. Secondly, a sequenced economic model should be developed so that two issues can be explored: (1) potentially a more plausible long term extrapolation of OS can be included in the economic model; and, (2) the effects of changing the subsequent use of PARP inhibitors on the ICER can be explored.

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9 APPENDICES

Appendix 1: Technical appendix detailing methods for applying the ERG's exploratory analyses within the company's model

Unless otherwise stated, these steps are all conducted in the company's base case model (submitted on 17th December 2018). With the following two steps applied:

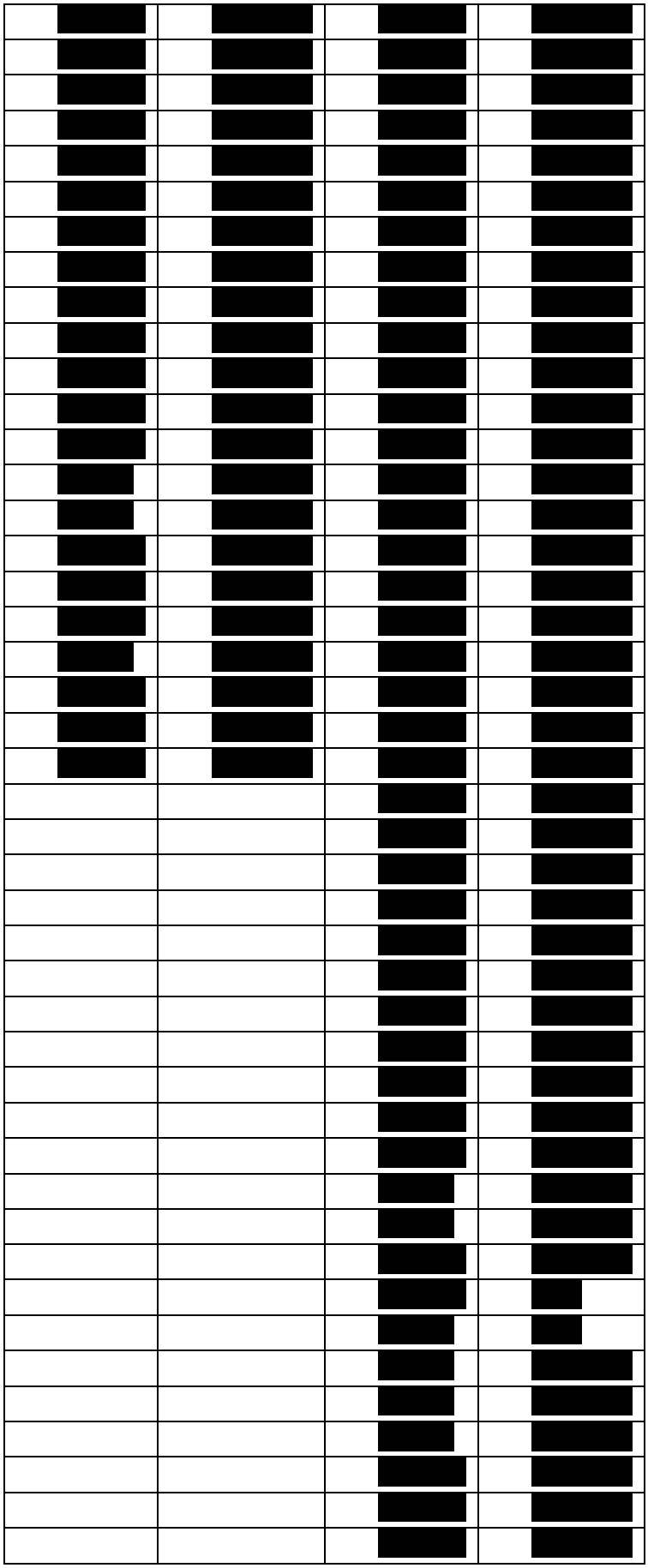
i. Go to the Sheet "Settings", cell D8 and enter 3.5%

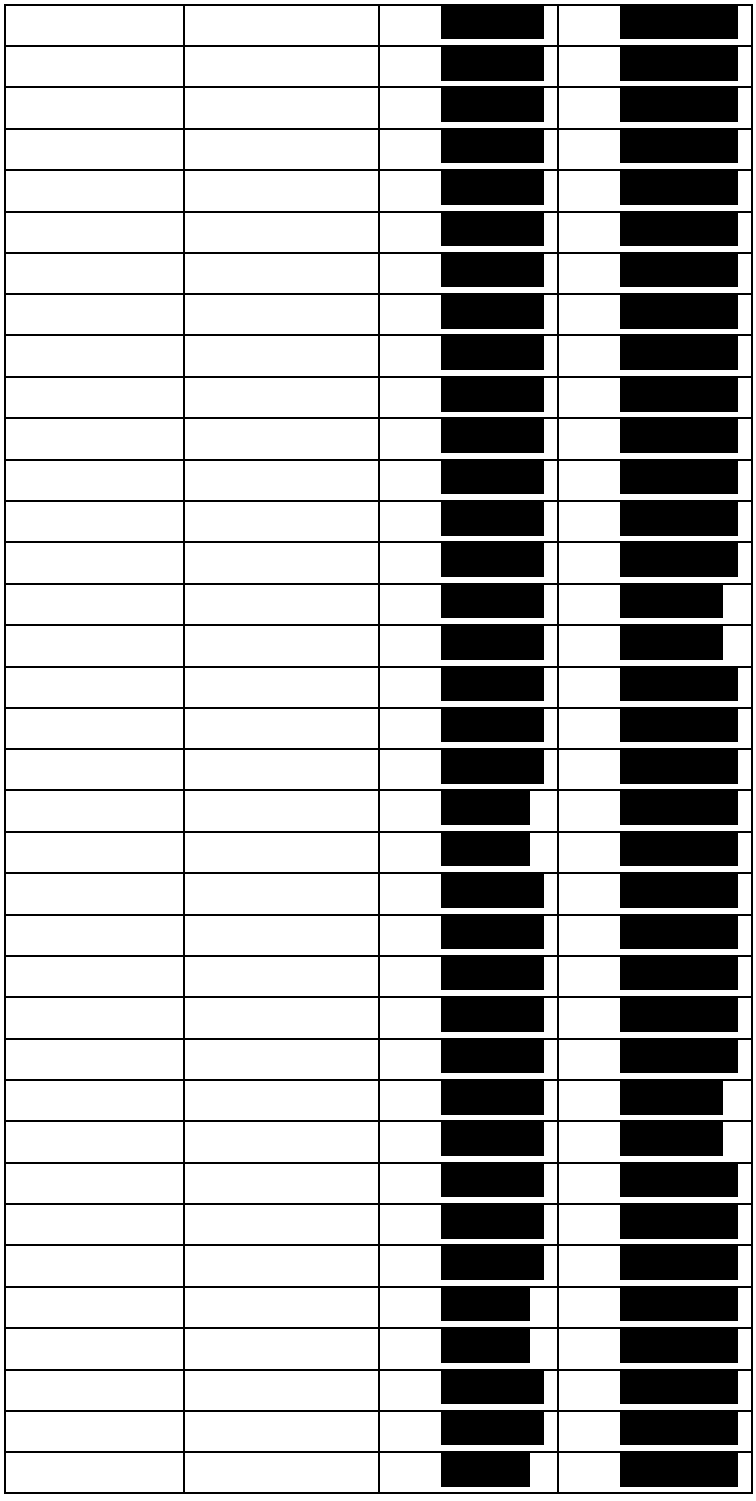
ii. Stay on the same sheet, go to cell D9 and enter 3.5%

ERG exploratory analysis 1: *Using the SOLO1 OS Kaplan-Meier data and limiting the time horizon to 3.75 years*

i. Insert a new sheet called "OS Kaplan-Meier", go to cell A1 and copy in the following data:

Time	RS	Time	Olap
[redacted]			





ii. Go to the sheet “Survival”, cell Z8, delete the array formula and input the following formula “=VLOOKUP($D8,'OS Kaplan-Meier'!$A$2:$B$51,2,TRUE)”

iii. Copy the formula in cell Z8 down to cell Z608

iv. Go to cell AI8, delete the array formula and input the formula “=VLOOKUP($D8,'OS Kaplan-Meier'!$C$1:$D$109,2,TRUE)”

v. Copy the formula in cell AI8 to cell AI608

vi. Go to sheet “Settings”, cell D6 and input the value 3.75

ERG exploratory analysis 2: Setting the rate of OS events to be the same in the olaparib and routine surveillance arms to be the same, after two years

i. Go to Sheet “Survival”, cell AK2, input the value 0

ERG exploratory analysis 3: ERG exploratory analysis 2 and restricting the time horizon so that the PFS and OS curve for olaparib does not cross.

i. Follow the steps in ERG exploratory analysis 2
ii. Go to sheet “Settings”, cell D6 and input the value [redacted]

ERG exploratory analysis 4: No reduction in cost of olaparib due to dose reductions or treatment interruptions

i. Go to the Sheet “Drug costs”, cell K11 and input the value 600

Exploratory analysis 5: Lower utility in the progressed disease health state

i. Go to the Sheet “Utilities and AEs”, cell D8 and input the value 0.68