Olaparib for maintenance treatment of *BRCA* 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy: A Single Technology Appraisal

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Contributions of authors

Sue Harnan summarised and critiqued the clinical effectiveness data reported within the company's submission. Ruth Wong critiqued the company's search strategy. Shijie Ren critiqued the statistical analyses undertaken by the company. Clara Mukuria advised on the company's use of health utility mapping. Paul Tappenden and Praveen Thokala critiqued the health economic analysis submitted by the company. Paul Tappenden and Shijie Ren undertook the ERG's exploratory analyses. Clare Green, Simon Pledge and 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
ANZCTR	Australian and New Zealand Clinical Trials Registry
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
b.i.d	*Bis in die* (twice daily)
BER	Base excision repair
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOADICEA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
BRCA	Breast cancer susceptibility gene
BRCAm	Breast cancer susceptibility gene-mutated
CA-125	Cancer antigen-125
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Complications and comorbidities
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CG	Clinical guideline
CMU	Commercial Medicines Unit
CR	Complete response
CS	Company's submission
CSE	Crossover sites excluded
CSR	Clinical Study Report
CT	Computerised tomography
CTCEA	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DSU	Decision Support Unit
ECOG	Eastern Co-operative Oncology Group
EMA	European Medicines Agency
EMBASE	Excerpta Medica Database
eMit	Electronic Marketing Information Tool
EPAR	European Public Assessment Report
EQ-5D	Euroqol 5-Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FIGO	International Federation of Gynaecology and Obstetrics
FOSI	FACT/NCCN Ovarian Symptom Index
FST	First subsequent therapy
GCIG	Gynaecologic Cancer InterGroup
GDG	Guideline Development Group
GFR	Glomerular filtration rate
HAS	Haute Autorité de Santé
HERC	Health Economics Research Centre
HR	Hazard ratio
HRD	Homologous-recombination-deficient
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life

HRR	Homologous recombination repair
HSUV	Health state utility value
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform Search Portal
IPCW	Inverse Probability of censoring weights
IPD	Individual patient-level data
IPE	Iterative parameter estimation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	Intention-to-treat
IVRS	interactive voice response system
LYG	Life year gained
MDS	Myelodysplastic syndromes
MEDLINE	Medical Literature Analysis and Retrieval System Online
MRI	Magnetic resonance imaging
NA	Not applicable
NCI	National Cancer Institute
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NOMA	Norwegian Medicines Agency
NR	Not reported
OC	Ovarian cancer
OLS	Ordinary least squares
OR	Objective response
ORR	Objective response rate
OS	Overall survival
P/C	Paclitaxel plus carboplatin
PARP	Poly ADP ribose polymerase
PARPi	Poly ADP ribose polymerase inhibitor
PBAC	Pharmaceutical Benefits Advisory Committee
pCODR	pan-Canadian Oncology Drug Review
PF	Progression-free
PFS	Progression-free survival
PHARMAC	Pharmaceutical Management Agency
PLDH	Pegylated liposomal doxorubicin hydrochloride
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSR	Platinum-sensitive relapsed
PSS	Personal Social Services
PTAC	Pharmacology and Therapeutics Advisory Committee
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RMSE	Root mean squared error
RPSFTM	Rank Preserving Structural Failure Time Model
SAE	Serious adverse event
SE	Standard error
SGO	Society of Gynaecological Oncology
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Serous ovarian cancer
SST	Second subsequent therapy

TA	Technology appraisal
TFST/D	Time to first subsequent therapy or death
TLV	Tandvårds- och läkemedelsförmånsverket (Swedish Dental and Pharmaceutical Benefits Agency)
TOI	Trial Outcome Index
TSD	Technical Support Document
TSST/D	Time to second subsequent therapy or death
TTD/D	Time to treatment discontinuation or death
TTE	Time-to-event
TTP	Time to progression
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WTP	Willingness to pay

1 SUMMARY

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

The population considered by the company in this assessment, that is, people with *BRCA1/2*-mutated, platinum-sensitive relapsed (PSR) ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy, matches that defined in the final scope issued by the National Institute for Health and Care Excellence (NICE). The intervention considered in the company's submission (CS), that is, olaparib monotherapy, also matches the final NICE scope. According to its current marketing authorisation, the recommended dose of olaparib is 400mg (eight 50mg capsules) taken twice daily, equivalent to a total daily dose of 800mg. The CS defines the comparator for olaparib as routine surveillance, also referred to as "watch and wait", which typically involves 3-monthly outpatient appointments. This is in line with the final NICE scope. Bevacizumab was not listed as a comparator within the NICE scope. The CS notes that whilst evidence exists to support the use of bevacizumab as maintenance therapy following use in combination with chemotherapy in the first-line setting, or in the first PSR ovarian cancer setting, neither approach has been recommended for use by NICE. The CS further notes that following the January 2015 Cancer Drugs Fund (CDF) evaluation, bevacizumab is no longer routinely available through the CDF in the relapsed setting. Clinical advisors to the Evidence Review Group (ERG) agree that bevacizumab should not be considered as a comparator for this appraisal. The outcomes considered within the CS are in line with the final NICE scope (overall survival [OS], progression-free survival [PFS], PFS on the second line of therapy [PFS2], time to next line of therapy, adverse events [AEs] of treatment and health-related quality of life [HRQoL]), except that time to second subsequent therapy or death (TSST/D) is presented as a proxy for PFS2. The ERG notes that whilst the company's health economic analysis generally reflects the decision problem set out in the NICE scope, the available data on OS (from randomisation) and PFS are not used within the company's model. In line with the current marketing authorisation for olaparib, the CS focusses on the available evidence for the *BRCA1/2*-mutated subgroup of the intention-to-treat (ITT) population within Study 19.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company submitted an unpublished systematic review with a wider scope than the decision problem for the assessment. One study that was relevant to the decision problem, Study 19, was identified by the review. This was a Phase II, double blind randomised controlled trial (RCT). The study recruited 265 patients with a histological diagnosis of recurrent serous ovarian cancer (including primary peritoneal or fallopian tube cancer) that was platinum-sensitive (progression >6 months) as determined by response to the most recent round of chemotherapy and at least one previous round (not necessarily sequential rounds).

The study recruited patients regardless of *BRCA* mutation status. Patients were randomised by an interactive voice system to 400mg olaparib (8 *x* 50mg capsules), twice daily or matched placebo. The primary outcome was PFS. Secondary outcomes that were pre-specified and relevant to the final NICE scope included OS, AEs and HRQoL by the Trial Outcome Index (TOI), the Functional Assessment of Cancer Therapy - Ovarian (FACT-O) and the FACT/NCCN Ovarian Symptom Index (FOSI). *Post hoc* exploratory analyses performed in the safety population included time to treatment discontinuation or death (TTD/D), time to first subsequent therapy or death (TFST/D) and TSST/D. These were presented to investigate whether the treatment effect was sustained into subsequent rounds of chemotherapy in the absence of mature OS data. Study 19 did not include the use of a preference-based measure of HRQoL.

A subgroup analysis of BRCA-mutated (*BRCAm*) patients was performed. The subgroup was added to the statistical plan more than one year after the study commenced, and approximately one month before the PFS data cut-off (DCO) point was reached (June 2010). Initially, the study had not been designed to test for patients' *BRCAm* status. However, once the initial analysis was performed, the study was redesigned to include testing of all patients for germline and tumour (spontaneously occurring) *BRCA* mutations. This increased the sample size. Additional analyses of all other clinical end points were added to the analysis plan after the DCO, in consultation with the European Medicines Agency (EMA). Changes were also made to the timing of OS analyses. In the whole population analysis, OS was analysed at two main points: (i) at the same time as the PFS analysis, and; (ii) at an interim point when the data were 58% mature. [redacted]

In the whole population analysis, the primary end point of the study was met, with a hazard ratio (HR) for PFS of 0.35 (95% c.i. 0.25 to 0.49, $p<0.01$) for olaparib versus placebo; this indicates a statistically significant improvement in PFS for olaparib. Median PFS was 8.4 months for olaparib versus 4.8 months for placebo (95% c.i. not reported [NR]). The *BRCAm* subgroup analysis also showed a benefit for olaparib patients, with a HR for PFS of 0.18 (95% c.i. 0.10 to 0.31, $p<0.0001$) for olaparib versus placebo; median PFS was 11.2 months for olaparib (95% c.i. 8.3 to "not calculable") versus 4.3 months for placebo (95% c.i. 3.0 to 5.4). An interaction test to demonstrate that the subgroup was statistically significantly different to the rest of the group was not presented within the CS but was reported in the Clinical Study Report (CSR); the results of this test appear inconclusive.

Within the whole population, OS between the two treatment groups was not statistically significantly different at either analysis point. The HR for death was 0.94 (95% c.i. 0.63 to 1.39; *p*=0.75) for olaparib versus placebo (median OS 29.7 months versus 29.9 months respectively, 95% c.i. NR) at the DCO June 2010. At 58% OS data maturity (November 2012), the HR for death was 0.88 (95% c.i. 0.64 to 1.21, *p*=0.44) for olaparib versus placebo, with a median survival of 29.8 months (95% c.i. 27.2 to 35.7) in the olaparib arm versus 27.8 months (95% c.i. 24.4 to 34.0) in the placebo arm.

For the *BRCAm* subgroup, OS was only reported at the second DCO (November 2012), when OS maturity was 52%. The HR for death was 0.73 (95% c.i. 0.45 to 1.17, *p*=0.19) for olaparib versus placebo. Median OS was 34.9 months in the olaparib group and 31.9 months in the placebo group. A crossover analysis within the *BRCAm* group was reported in the CS to adjust for potential confounding of OS for patients in the placebo arm who went on to receive subsequent poly ADP ribose polymerase (PARP) inhibitor treatment. The crossover analysis excluded sites where crossover occurred and a statistically significant difference in OS was reported for olaparib versus placebo (HR=0.52, 95% c.i. 0.28 to 0.97, nominal *p*=0.039). In the crossover site excluded analysis, median survival was 34.9 months in the olaparib arm and 26.6 months in the placebo arm. A second crossover analysis using the Rank Preserving Structural Failure Time Model (RPSFTM) approach, reported as part of the company's clarification response, produced HRs ranging from [redacted] to [redacted] (*p*-value NR). Neither crossover analysis included an attempt to correct for patients in the olaparib arm who continued to receive olaparib beyond disease progression.

HRQoL was presented as "best response" scores only. It was reported that there was *"no significant difference in improvement rates or time to worsening of TOI, FOSI or Total FACT-O"* and it was concluded that HRQoL was not negatively impacted during the therapy.

All the *post hoc* exploratory outcomes, TTD/D, TFST/D and TSST/D, were statistically significant for both the whole population analyses and the *BRCAm* subgroup analyses. In the whole population, the HR for TTD/D was 0.39 (95% c.i. 0.30 to 0.51) for olaparib versus placebo. In the *BRCAm* subgroup, the HR for TTD/D was similar at 0.36 (95% c.i. 0.24 to 0.53) for olaparib versus placebo; median TTD/D was reported to be 11.0 months in the olaparib arm versus 4.6 months in the placebo arm. In the whole population, the HR for TFST/D was 0.41 (95% c.i. 0.31 to 0.54) for olaparib versus placebo. In the *BRCAm* subgroup, the HR for TFST/D was 0.33 (95% c.i. 0.22 to 0.50) for olaparib versus placebo; median TFST/D was reported to be 15.6 months in the olaparib arm versus 6.2 months in the placebo arm. In the whole population, the HR for TSST/D was 0.54 (95% c.i. 0.41 to 0.72) for

olaparib versus placebo. In the *BRCAm* subgroup, the HR for TSST/D was 0.44 (95% c.i. 0.29 to 0.67) for olaparib versus placebo; median TSST/D was 23.8 months in the olaparib arm versus 15.2 months in the placebo arm.

AEs occurred more often in the olaparib group, but were largely minor and manageable with dose reductions or interruptions. A greater proportion of patients in the olaparib arm than the placebo arm suffered from severe AEs such as fatigue, anaemia and neutropenia. Serious adverse events (SAEs) occurred in 21.6% of olaparib patients versus 9.7% of placebo patients. These included anaemia, small bowel obstruction, dyspnoea and gastritis. Mortality was slightly higher in the olaparib group than the placebo group, although the study sample size was too small to conclusively identify any difference in mortality.

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

The ERG has a number of concerns relating to the evidence submitted by the company. In terms of conventional standards of evidence-based medicine, the ERG considers the evidence base to be weak and at a high risk of bias. There are also a number of confounding factors and methodological issues that have not been addressed.

Adaptations to the systematic review were made by the company to bring it in line with the final NICE scope. These were poorly reported in terms of study selection criteria and processes. Clarifications from the company suggest however that the review was well conducted. The ERG believes that all relevant evidence was identified.

Study 19, the only study included in the company's review, has a number of limitations, both methodologically and in terms of its relevance to the decision problem.

Methodological problems include:

- Errors with the interactive voice randomisation system (IVRS) which led to mis-stratification of patients and may account for observed and potentially unobserved imbalances in known and unknown prognostic factors between groups.
- The continuation of some olaparib patients on treatment after disease progression, which contravenes the marketing authorisation for olaparib and would therefore be unlikely to occur in usual practice. This could introduce bias and is likely to confound results for all end points except PFS.

- Multiple amendments to the OS analysis plan in terms of interim analyses being added and removed.
- PFS2 was not measured, though this was defined in the final NICE scope and is recommended in EMA guidelines to provide supporting evidence of the persistence of treatment effects in the long-term.
- *Post hoc* addition of a long-term OS analysis leading to the potential introduction of bias.
- *Post hoc* addition of TTD/D, TFST/D and TSST/D leading to the potential introduction of bias.
- Use of the safety analysis dataset rather than the ITT analysis dataset for TDD/D, TFST/D and TSST/D.
- *Post hoc* addition of *BRCA* testing for all patients, including the addition of tumour *BRCA* testing, leading to the potential introduction of bias.
- Crossover of placebo group patients to subsequent PARP inhibitor treatments, leading to the potential introduction of confounding and bias. This issue was addressed in additional analyses provided by the company during the clarification process.
- A lack of clarity regarding when and under what circumstances patients were treated with subsequent chemotherapy after progression.
- The small sample size of the *BRCAm* subgroup, which is reduced further within the crossover analysis which excludes study sites that allowed placebo group crossover.
- Interaction tests were not presented in the CS, and appear to be inconclusive as to whether the *BRCAm* subgroup is statistically significantly different to the rest of the study population.

Problems with relevance to the decision problem and clinical practice in England include:

- The study used both germline (blood test) and tumour (tissue sample test) *BRCA* mutation testing to select patients. These tests are not routinely performed in England. It is unclear whether tumour testing will be possible in England on a large scale. As such, the population who would be treated may differ from that analysed in the subgroup analysis, leading to potential problems with generalisability. It is unclear whether results would have been biased, and if so, whether they would be biased in favour or against olaparib with respect to this issue.
- The study did not use CA-125 to assess progression. This is likely to have lengthened PFS in comparison to practice in England, where CA-125 is used to assess progression in some centres. The extent of the impact of this bias is unknown. It may also mean that patients in England would receive treatment for a shorter amount of

time on average compared with patients in Study 19. This may impact on both costs and effectiveness in usual clinical practice.

- The lack of clarity concerning when and under what circumstances patients were treated with subsequent chemotherapy after progression means that TFST/D and TSST/D may not reflect usual clinical practice in England. This may shorten or lengthen the observed TFST/D and TSST/D estimates, though clinical advice received by the ERG suggests that it is more likely that it will shorten estimates, and may affect comparative estimates between study arms.

Given that these biases and relevance issues may operate in unknown directions and to unknown extents, together with the small sample size of the study and subgroup analyses, the results of this study are associated with a high degree of uncertainty in relation to their accuracy and generalisability to practice in England. To compound these issues further, the history of changes to the study protocol and the fact that the subgroup was not defined at the study outset and did not conclusively pass interaction tests means that the hypothesis that olaparib has superior efficacy in *BRCAm* patients compared with other patients has not been robustly tested or proved. A subsequent Phase III trial would be very useful to ascertain the validity of these results; the ERG notes that a Phase III trial of olaparib in *BRCAm* ovarian cancer patients after complete or partial response to platinum chemotherapy is ongoing (clinicaltrials.gov identifier - NCT01874353). Additionally, Study 19 relies on what is essentially a proxy outcome (PFS), though this has become an acceptable outcome in studies where OS follow-up will be lengthy. The lack of conclusive and mature evidence to support an OS advantage for olaparib does not detract from the benefits inherent to a postponement of PFS, but does make it difficult to conclude whether the treatment confers a survival benefit or not. This has important implications for the approach taken within the company's health economic analysis.

1.4 Summary of cost-effectiveness submitted evidence by the company

The CS includes a systematic review of published economic studies of treatments for ovarian cancer together with a *de novo* model-based economic evaluation to assess the incremental cost-effectiveness of olaparib versus routine surveillance in women with *BRCA1/2* mutated (germline and/or somatic), PSR high-grade serous ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy.

The company's review identified one previously published economic evaluation of olaparib (with or without prior *BRCA* mutation testing) versus routine surveillance in patients with PSR high-grade serous ovarian cancer after a partial or complete response to a platinum-

containing regimen (Secord *et al*). Within this analysis, the incremental cost-effectiveness ratio (ICER) for *BRCA1/2* mutation testing followed by olaparib treatment for *BRCA* mutation carriers compared with routine surveillance was reported to be $193,442 per progression-free life year saved (PFLYS). This study is however subject to a number of limitations including the use of a short time horizon, the use of PFS as the metric of health benefit, and the omission of downstream health benefits associated with platinum-based chemotherapies.

The company developed a *de novo* health economic model to assess the cost-effectiveness of olaparib versus routine surveillance in patients with *BRCAm* PSR ovarian cancer. The health economic analysis contained within the CS is comprised of two economic evaluations:

(i) The base case economic evaluation of olaparib maintenance treatment versus routine surveillance in patients with *BRCAm* PSR ovarian cancer. This analysis excludes the costs of *BRCA* mutation testing and considers costs and benefits relating to the index *BRCAm* ovarian cancer patient only.

(ii) A broader economic evaluation that also accounts for: (a) the costs of *BRCA* mutation testing in PSR ovarian cancer patients, and; (b) the costs and benefits of expanding *BRCA* mutation testing to family members of relapsed *BRCAm* ovarian cancer patients undergoing *BRCA* mutation testing as a prerequisite in consideration of olaparib as a potential treatment option. This analysis considers costs and benefits relating to the index *BRCAm* ovarian cancer patient and family members.

The company's base case analysis adopts a semi-Markov approach and evaluates costs and benefits from the perspective of the NHS and Personal Social Services (PSS) over a 15-year time horizon. The model includes five health states: (i) progression-free (on maintenance treatment); (ii) progression-free (discontinued maintenance treatment); (iii) first subsequent chemotherapy (on treatment or discontinued); (iv) second subsequent chemotherapy (on treatment or discontinued), and; (v) dead. Clinical input parameters were estimated using data from the *BRCAm* subgroup within Study 19. For the progression-free states, health utilities were mapped from the FACT-O to the EQ-5D using a published algorithm; other utilities were taken from the manufacturer's submission for NICE Technology Appraisal (TA) 222. Resource use estimates were taken from Study 19, previous NICE appraisals, guidelines, other literature and assumptions. Unit costs were derived from standard sources. The additional costs and benefits of *BRCA* mutation testing within the wider secondary economic analysis were taken from the cost-effectiveness review report published as part of NICE Clinical Guideline (CG) 164 for familial breast cancer.

The probabilistic version of the company's base case analysis suggests that olaparib is expected to produce an additional 0.90 quality-adjusted life years (QALYs) at an additional cost of £72,232 compared against routine surveillance; therefore, the probabilistic ICER for olaparib versus routine surveillance is expected to be £79,953 per QALY gained. The deterministic version of the model yielded an ICER for olaparib versus routine surveillance of £81,063 per QALY gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately zero. Assuming a willingness to pay threshold of £50,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately 0.05. The company's secondary analysis, which includes the costs and benefits of *BRCA* mutation testing applied to five family pedigrees, suggests a lower average deterministic ICER for *BRCA* mutation testing plus olaparib versus routine surveillance without *BRCA* mutation testing of £61,159 per QALY gained.

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

The ERG critically appraised the company's economic analysis and double-programmed the company's health economic model. The ERG's rebuild of the company's economic model did not reveal any significant programming errors. However, the ERG has several concerns regarding the model and the evidence used to inform it. The most pertinent of these relate to: concerns regarding the company's model structure and use of outcomes data from Study 19 (particularly the exclusion of outcomes relating to time from randomisation to death and PFS); the potential confounding of end points used in the company's model; concerns regarding the methods for modelling of time-to-event outcomes; discordance between model predictions and observed data from Study 19, and; concerns regarding the nature of the comparison made within the company's secondary analysis. Overall, the ERG has concerns that the assumptions employed within the company's model are likely to overestimate the incremental health gains for olaparib versus routine surveillance.

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

The ERG considers the clinical evidence base to be weak and open to extensive criticism under the conventional precepts of evidence-based medicine and clinical trial science. The *BRCAm* subgroup was not defined before the study commenced, and Study 19 is only a Phase II clinical trial, albeit one conducted as an RCT, making sample sizes in subgroup analyses small. Interaction tests to demonstrate that the *BRCAm* subgroup is different to the rest of the study group were apparently inconclusive. Whilst the primary end point of PFS in the whole population was met, other outcomes were subject to a number of changes after the study

commenced, and in some cases apparently after data analysis had taken place (e.g. TTD/D, TFST/D and TSST/D), thus leaving them open to the introduction of bias. The generalisability of the study results was unclear due to differences across England in the use of CA-125 testing, a lack of clarity regarding when and under what circumstances subsequent chemotherapy treatment commenced and concerns about whether tumour *BRCA* testing could be implemented as a routine test in England.

The ERG believes that the company's health economic model does not adopt a structure that allows for an appropriate synthesis of the available evidence from Study 19, nor does it appropriately adjust for the potential confounding and bias resulting from the design of the trial. Overall, the ERG does not consider the company's estimates of the cost-effectiveness of olaparib versus routine surveillance to be reliable.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

As the relevance of the review to the decision problem could not be initially ascertained from the CS, the ERG conducted a focussed search of RCTs relating to olaparib and consulted the European Public Assessment Report (EPAR). The list of excluded studies provided by the company was also checked by the ERG to ascertain whether adaptations to the original review protocol were carried out in accordance with the scope of the decision problem. No additional studies were identified through any of these methods.

In order to further explore the likely magnitude of potential biases in the company's approach to synthesising evidence from Study 19 to estimate survival benefits for olaparib and routine surveillance, the ERG requested patient-level data (IPD) from the *BRCAm* subgroup within Study 19 with the intention of re-fitting the time-to-event curves, taking into account the exclusion of crossover sites and avoiding the company's assumption of proportional hazards between treatment groups. The company declined the ERG's data request. Instead, the ERG replicated the IPD from the *BRCAm* subgroup within Study 19 using methods reported by Guyot *et al.* and fitted a range of potential candidate survivor functions to the replicated IPD on: (i) TTD/D; (ii) TFST/D; (iii) OS adjusted using RPSFTM methods, and; (iv) OS adjusted by excluding crossover sites. These analyses were used to address two questions: (1) What is the expected incremental survival gain for olaparib versus routine surveillance? (2) What is the expected incremental QALY gain for olaparib versus routine surveillance? With respect to the first question, the ERG used a restricted means approach to estimate the area under the curve (AUC) using the ERG-fitted parametric models of crossover-adjusted OS for olaparib versus placebo. With respect to the second question, the ERG developed a simple four state partitioned survival model in which OS was directly informed by parametric curves fitted to

the crossover-adjusted Kaplan-Meier curves provided in the company's response to clarification questions.

The most optimistic estimate of undiscounted incremental survival for olaparib versus routine surveillance produced by the ERG's restricted means analysis was 0.68 life years gained (LYGs), based on the log normal curve for the crossover sites excluded (CSE) OS dataset. This estimate is considerably lower than the estimated 1.36 incremental undiscounted LYGs for olaparib versus routine surveillance generated by the company's base case model. This analysis suggests that it is highly likely that the company's model substantially overestimates the incremental survival benefits associated with olaparib.

The ERG's partitioned survival model suggests that the most optimistic discounted incremental QALY gain for olaparib versus routine surveillance is approximately 0.52 QALYs. This scenario is based on the generalised gamma distribution for TTD/D, the log normal distribution for TFST/D and the log normal distribution for CSE-adjusted OS. The most favourable QALY estimate generated by the ERG's model is considerably lower than the estimated 0.90 discounted incremental QALYs generated by the company's model. Assuming that the incremental costs of olaparib versus routine surveillance estimated by the company's model, which are largely comprised of the acquisition costs of the drug, are reasonable, this implies that the ICER for olaparib versus routine surveillance is likely to be in excess of £145,000 per QALY gained, but may be considerably higher. Based on the preferred survivor functions selected by the clinical advisors to the ERG, together with the company's estimated incremental costs of olaparib, the implied ICER for olaparib versus routine surveillance is estimated to be, at best, £191,979 per QALY gained. One clinical advisor stated a preference for a combination of survivor functions which led to olaparib being dominated by routine surveillance.

2. BACKGROUND

This chapter presents a brief commentary on the company's interpretation of the underlying health problem and the nature of current service provision.

2.1 Critique of the company's description of the underlying health problem

The ERG considers that the descriptions of ovarian cancer pathophysiology, epidemiology and prognosis detailed in Section 2 of the CS[1] appear reasonable. The CS[1] cites an Australian observational study in which a median OS of 21.9 months was observed for patients with *BRCAm* PSR ovarian cancer who were not treated with a PARP inhibitor. The ERG notes that this study is small (n=41) hence the estimates drawn from it are subject to considerable uncertainty. Clinical advisors to the ERG indicated that the estimate observed within the placebo group of Study 19[1] (unadjusted median survival = 31.9 months) is broadly reflective of the prognosis of patients typically seen in usual clinical practice in England. Overall, the ERG considers the company's discussion of the context of the appraisal to be relevant to the decision problem under consideration.

2.2 Critique of company's overview of current service provision

Overall, the company's description of current service provision for patients with ovarian cancer is reasonable. The CS[1] asserts that in order to maintain quality of life, treatment with an effective and well-tolerated maintenance therapy can delay disease progression and the requirement for subsequent chemotherapy and may ultimately prolong survival. The CS highlights that there are currently no licensed or recommended maintenance treatments or treatments specific to the *BRCAm* ovarian cancer population. The CS also states that chemotherapy treatment has a detrimental impact upon patients' HRQoL, based on the ADVOCATE study in advanced ovarian cancer,[2] noting "bothersome" side effects of cytotoxic treatment for patients including fatigue, hair loss and constipation. Within this survey-based study, the majority of patients valued HRQoL equally or above prolongation of life, thereby suggesting that optimal treatment strategies should aim to minimise exposure to chemotherapy whilst also delaying disease progression.[1]

Section 2.5 of the CS[1] details the following recommendations from NICE for second- and subsequent-line chemotherapy treatments for ovarian cancer:

- NICE TA 91. Paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin) is recommended as an option for the second-line (or subsequent) treatment of women with platinum-sensitive or partially platinum-

sensitive advanced ovarian cancer, except in women who are allergic to platinum-based compounds.[3]

- NICE TA 91. Single-agent paclitaxel is recommended as an option for the second-line (or subsequent) treatment of women with platinum-refractory or platinum-resistant advanced ovarian cancer, and for women who are allergic to platinum-based compounds.[3]
- NICE TA 91. Pegylated liposomal doxorubicin hydrochloride (PLDH) is recommended as an option for the second-line (or subsequent) treatment of women with partially platinum-sensitive, platinum-resistant or platinum-refractory advanced ovarian cancer, and for women who are allergic to platinum-based compounds.[3]
- NICE TA 91. Topotecan is recommended as an option for second-line (or subsequent) treatment, only for those women with platinum-refractory or platinum-resistant advanced ovarian cancer, or those who are allergic to platinum-based compounds, for whom PLDH and single-agent paclitaxel are considered inappropriate.[3]
- NICE TA 222. Trabectedin in combination with PLDH is not recommended for the treatment of women with PSR ovarian cancer.[4]
- NICE TA 285. Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for treating people with the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.[5]

The CS[1] states that the main comparator for olaparib is routine surveillance ("watch and wait") and that there are no relevant active comparators for olaparib within the indication under review. The CS[1] suggests that in usual clinical practice, outpatient consultations take place approximately every three months. Clinical advisors to the ERG consider this to be accurate. The ERG's clinical advisors also noted that the use of CA-125, a serum tumour marker for relapse in ovarian cancer, is variable across centres in England. This view is supported in the literature by an RCT which compared early treatment based on elevated CA-125 with later treatment based on clinical or symptomatic indicators.[6] This study concluded that early treatment based on CA-125 levels conferred no survival advantage, and therefore routine CA-125 monitoring was unnecessary.

The CS[1] notes that bevacizumab has recently been granted marketing authorisation by the EMA for use in combination with first-line, platinum chemotherapy or second-line (if not used as a first-line treatment), and for continued use as a maintenance monotherapy after chemotherapy.[7] The therapeutic indications for bevacizumab in the treatment of ovarian cancer, as listed in the Summary of Product Characteristics[7] (SmPC), are presented in Box 1.

Box 1: EMA-recommended therapeutic indications for bevacizumab in ovarian cancer

(i) *Front-line treatment:* Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. The recommended dose of Avastin is 15mg/kg of body weight given once every 3 weeks as an intravenous infusion.

(ii) *Treatment of platinum-sensitive recurrent disease:* Avastin is administered in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of Avastin as single agent until disease progression. The recommended dose of Avastin is 15mg/kg of body weight given once every 3 weeks as an intravenous infusion.

(iii) *Treatment of platinum-resistant recurrent disease:* Avastin is administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of Avastin is 10mg/kg of body weight given once every 2 weeks as an intravenous infusion. When Avastin is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of Avastin is 15mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that treatment be continued until disease progression or unacceptable toxicity.

The CS[1] notes that bevacizumab is not recommended for use by NICE[5] (see above) and is not licensed specifically for maintenance treatment in *BRCAm* PSR ovarian cancer patients. The CS also highlights that, following the January 2015 CDF evaluation, bevacizumab is no longer routinely available through the CDF.[1] Clinical advisors to the ERG agree that bevacizumab should not be considered as a comparator for olaparib.

The CS[1] highlights that there is considerable variation in the availability of *BRCA* mutation testing, suggesting that whilst NICE CG 164[8] recommends that women with ovarian cancer in whom the risk of harbouring a germline *BRCA* gene mutation is ≥10% should have a genetic test, this recommendation has been implemented only in a small number of centres in the UK. Clinical advisors to the ERG agree that the availability of *BRCA* mutation testing is subject to geographical variation in England. The CS highlights that, subject to a positive

recommendation for olaparib, the need for genetic tests is likely to be higher initially due to the prevalent pool of patients not previously tested, whilst testing at diagnosis for incident ovarian cancer patients will be an ongoing need.[1] In order to assist with managing this increased need for *BRCA* mutation testing, the company is developing an interim testing service through UK NHS laboratories to support the testing of the prevalent pool of patients with high-grade serous, PSR ovarian cancer.[1] In response to a request for clarification on this testing service, the company stated:

[redacted] (clarification response[9] question 1).

The CS[1] highlights that in addition to prerequisite *BRCA* testing for patients to be considered eligible for olaparib treatment, a routine monthly clinic appointment and blood test is expected to be required to monitor patients during the first 12 months of treatment, with less frequent visits thereafter. Blood tests for full blood count, liver and renal function tests and CA-125 are anticipated to be carried out. The CS suggests that the provision of olaparib is anticipated to require an additional two appointments and blood tests per quarter for patients receiving the drug.

In Study 19, patients were tested for both germline and tumour (somatic) mutations and patients with either type of mutation were included in the analysis. The company's interim testing service does not appear to provide testing of tumour samples for mutation status, nor does the CS provide any information relating to the existence of such testing services in England at present.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1]

A summary of the decision problem as outlined in the final NICE[10] scope and addressed in the CS[1] is presented in Table 1.

Table 1: Statement of the decision problem (reproduced from CS[1] page 50)

	Final scope issued by NICE[10]	**Decision problem addressed in the CS[1]**	**Rationale if different from the scope**
Population	People with *BRCA1/2*-mutated, PSR ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy	As per scope	
Intervention	Olaparib	As per scope	
Comparator(s)	Routine surveillance	As per scope	
Outcomes	The outcome measures to be considered include: • OS • PFS • PFS2 (i.e. PFS on next line of therapy) • Time to next line of therapy • AEs of treatment • HRQoL	As per scope, except that time to second subsequent therapy (TSST) is presented as a proxy of PFS2	In the absence of follow-up for PFS2 by RECIST criteria, TSST is a reasonable proxy for clinical progression
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a NHS and Personal Social Services perspective.	As per scope	
Subgroups to be considered	Not specified	As per scope	
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 in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. The use of olaparib is conditional on the presence of *BRCA1/2*m. The economic modelling should include the cost associated with the diagnostic testing for *BRCA1/2m* in people with ovarian cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See Section 5.9 of the 'Guide to the methods of technology appraisal.'	As defined in the final scope, the economic modelling includes the cost associated with the diagnostic testing for *BRCA1/2*m and the health-related benefits linked to testing	

3.1 Population

The population defined in the final NICE scope[10] relates to *"people with BRCA 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy."* This reflects the *BRCAm* subgroup within Study 19 which forms the main basis of the evidence presented within the CS.[1]

3.2 Intervention

The intervention considered within the CS is defined as olaparib; this matches the final NICE scope.[10] Olaparib (Lynparza®) is a potent inhibitor of PARP-1, PARP-2 and PARP-3, which has been shown to inhibit the growth of selected tumour cell lines *in vitro* and tumour growth *in vivo* either as a standalone treatment or in combination with established chemotherapies.[11] PARP are required for the efficient repair of deoxyribonucleic acid (DNA) single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thereby blocking repair.[11] An important repair pathway of these double-strand breaks is homologous recombination repair (HRR). Mutations in the *BRCA1/2* genes result in a deficiency in the HRR pathway, and therefore accumulation of double-strand DNA breaks. Olaparib is the first in class PARP inhibitor to exploit this novel mechanism of action. In cells with deficiency in homologous recombination due to a *BRCA* gene mutation, the introduction of a PARP inhibitor, causing increased double strand DNA breaks, combined with an inability to repair these by HRR, results in cell death; this process is known as "synthetic lethality." This deficiency is only present in cancer cells, resulting from mutations in both copies of the *BRCA* gene, whilst non-tumour cells retain a functional copy of the *BRCA* gene. PARP inhibition therefore selectively targets tumour cells by exploiting their intrinsic DNA repair deficiency.[1]

Olaparib monotherapy has a therapeutic indication for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCAm*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.[11]

As of March 2015, olaparib had not been listed on the British National Formulary (BNF).[12] According to the CS,[11] the NHS list price is £3,950.00 per pack of 448 capsules.

Olaparib is available as hard capsules, each containing 50mg of olaparib. Each pack consists of four plastic bottles each containing 112 olaparib capsules (448 capsules per pack). This is equivalent to 28 days' supply. The recommended dose of olaparib is 400mg (eight 50mg capsules) taken twice daily, which is equivalent to a total daily dose of 800mg. Patients should take olaparib at least one hour after food, and should refrain from eating preferably for up to 2 hours afterwards. Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered. The recommended dose reduction is to 200mg twice daily, equivalent to a total daily dose of 400mg. If required, a dose reduction to 100mg twice daily, equivalent to a total daily dose of 200mg may be considered.[11]

According to the SmPC,[11] patients should start treatment with olaparib no later than 8 weeks after completion of their final dose of the platinum-containing chemotherapy regimen. Patients should continue to be treated with olaparib until progression of the underlying disease. A definition of progression is not provided in the SmPC. The SmPC notes that there are no data on retreatment with olaparib following subsequent relapse.

The SmPC[11] notes that no adjustment in starting dose is required for elderly patients but highlights that there are limited clinical data in patients aged 75 years or over. The SmPC also notes that the effect of renal impairment on exposure to olaparib has not been studied. Olaparib can be administered in patients with mild renal impairment but is not recommended for use in patients with moderate renal impairment (creatinine clearance <50ml/min) or severe renal impairment (creatinine clearance <30ml/min). The SmPC states that olaparib may only be used in patients with moderate or severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and AEs. The SmPC[11] states that the effect of hepatic impairment on exposure to olaparib has not been studied, hence it is not recommended for use in patients with hepatic impairment (serum bilirubin greater than 1.5 times the upper limit of normal [ULN]). In addition, there are very limited clinical data available in patients with performance status 2 to 4 and there are currently no data relating to the safety and efficacy of olaparib treatment in paediatric patients.

Contraindications to olaparib include hypersensitivity to olaparib or any of its excipients, and women who are breast-feeding during treatment and 1-month after the last dose.[11]

The SmPC[11] notes the following special warnings and precautions for use: haematological toxicity, Myelodysplastic syndrome (MDS)/Acute Myeloid Leukaemia (AML), pneumonitis and embryofoetal toxicity.

The SmPC[11] states that patients should not start treatment with olaparib until they have recovered from haematological toxicity caused by previous anticancer therapy. Baseline testing followed by monthly monitoring of complete blood counts is recommended for the first 12 months of olaparib treatment and periodically thereafter to monitor for clinically significant changes in any parameter during treatment. If patients develop severe haematological toxicity or blood transfusion dependence, olaparib treatment should be interrupted and haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of olaparib dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.[11]

The incidence of MDS/AML has been reported in a small number of patients who received olaparib alone or in combination with other anticancer drugs. The SmPC[11] notes that the majority of these cases have been fatal. If MDS and/or AML are confirmed whilst on treatment with olaparib, it is recommended that the patient be treated appropriately. If additional anticancer therapy is recommended, olaparib should be discontinued and not given in combination with other anticancer therapy.[11]

Pneumonitis has been reported in a small number of patients receiving olaparib. The SmPC[11] notes that some of these cases have been fatal. If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or if a radiological abnormality occurs, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient should be treated appropriately.[11]

The SmPC[11] also notes that PARP inhibition could cause foetal harm when administered to pregnant women.

3.3 Comparators

The CS defines the comparator for olaparib as routine surveillance, also referred to as "watch and wait." This is in line with the final NICE scope.[10]

The CS notes that whilst evidence exists to support the use of bevacizumab as a maintenance therapy following use in combination with chemotherapy in the first-line setting, or in the first

PSR ovarian cancer setting, neither approach has been recommended for use by NICE.[5,13] As discussed in Section 2.2, following the January 2015 CDF evaluation, bevacizumab is no longer routinely available through the CDF in the relapsed setting.[1] Bevacizumab was not listed in the final NICE scope.[10] Clinical advisors to the ERG agree that bevacizumab should not be considered as a comparator for this appraisal.

3.4 Outcomes

The CS reports on the following clinical outcomes where data were available:

- OS
- PFS
- TTD/D
- TFST/D
- TSST/D
- AEs of treatment
- HRQoL

The CS[1] states that the outcomes are in line with the final NICE scope[10] except that TSST/D is presented as a proxy for PFS2. TTD/D was not listed as an outcome in the final scope.

3.5 Economic analysis

The company submitted a fully executable model to assess the incremental cost-utility of olaparib versus routine surveillance for the treatment of women with *BRCA1/2m*, PSR ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy. The company's model is detailed and critiqued in Chapter 5. The ERG notes that whilst the company's model reflects the scope set out in the company's definition of the decision problem, the available data on OS (from the point of randomisation) and PFS for the *BRCAm* subgroup within Study 19 are not used to inform the company's model parameters.

3.6 Subgroups

The CS focusses on the available evidence for the *BRCA1/2*-mutated subgroup of the ITT population within Study 19.[14] Limited data are presented for the ITT population of Study 19.

3.7 Special considerations including issues related to equity or equality

The company's health economic analysis includes two evaluations:

(i) The base case economic evaluation of olaparib maintenance treatment versus routine surveillance in patients with *BRCAm* PSR ovarian cancer. This analysis excludes the

costs of *BRCA* mutation testing and considers costs and benefits relating to the index *BRCAm* ovarian cancer patient only.

(ii) A broader economic evaluation that also accounts for: (a) the costs of *BRCA* mutation testing in PSR ovarian cancer patients, and; (b) the costs and benefits of expanding *BRCA* mutation testing to family members of relapsed *BRCAm* ovarian cancer patients undergoing *BRCA* mutation testing as a prerequisite in consideration of olaparib as a potential treatment option. This analysis considers costs and benefits relating to the index *BRCAm* ovarian cancer patient and family members. This appears to be a secondary analysis within the CS, and is referred to as such throughout the remainder of this report.

The ERG notes that the cost of *BRCA* mutation testing is not included in the company's base case analysis. In addition, the final NICE scope[10] does not request an analysis of the potential health benefits associated with expanding *BRCA* mutation testing to include family members of *BRCAm* ovarian cancer patients.

No equality concerns are raised within the CS.

4. CLINICAL EFFECTIVENESS

This section presents a summary and critique of the clinical evidence contained within the CS.[1]

4.1 Critique of the methods of review(s)

The CS presents an unpublished systematic review that originally had a wider scope than the decision problem. The CS states that *"In order to focus only on relevant information, studies within the scope of the original systematic review, but outside the scope of this NICE submission were excluded (with accounted reasons)."* (see CS[1] page 52). In doing so, a number of irregularities and omissions are present in the reporting and potentially the conduct of the systematic review.

4.1.1 Searches

4.1.1.1 Description of company's searches

The company's searches for clinical effectiveness studies were clearly reported in the submission (see CS[1] pages 52-53). The company reported that the searches comprised a comprehensive search of major biomedical databases, searched from 1st January 1998 to 13th June 2014, but also stated that the review covered the last 15 years. The ERG notes that this minor discrepancy may be due to subsequent search updates.

The company's search strategy including searching of the following databases:

- Excerpta Medica Database (EMBASE®)
- Medical Literature Analysis and Retrieval System Online (MEDLINE®) including MEDLINE In-Process
- Cochrane Central Register of Controlled Trials (CENTRAL).

Abstracts from relevant conference proceedings were also hand-searched for the past three years, including:

- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- Society of Gynaecological Oncology (SGO).

In addition, the following trial registries were screened for ongoing trials:

- Clinicaltrials.gov
- International Clinical Trials Registry Platform Search Portal (ICTRP)
- Australian and New Zealand Clinical Trials Registry (ANZCTR)
- EU Clinical Trials Register
- PharmNet.Bund (Klinische Prüfungen).

Supplemental searching included bibliographical searching of relevant systematic reviews and meta-analyses.

4.1.1.2 Critique of the company's search strategy for clinical effectiveness studies

Published and unpublished but completed studies were searched in the relevant databases, conference proceedings websites and several clinical trials registries. The applied restrictions were justified in the CS. Search strategies for both the original and updated search were transparent and fully reported in Appendix 10.2 of the CS.[1] The original search and updated search strategies contained a comprehensive list of known drug therapies for the treatment of ovarian cancer, although these were not comparators to olaparib. The keywords used in the additional searches of conference proceedings were not reported and hence searches were not replicated by the ERG.

On 6th February 2015, the ERG re-ran the company's clinical effectiveness review search (see CS[1] Table A9) in PubMed for studies published since April 2014. A total of 30 records were retrieved and considered; no further relevant studies were identified. However, it should be noted that the ERG did not attempt to repeat all of the company's searches due to time constraints.

4.1.2 Inclusion criteria and study selection

4.1.2.1 Inclusion criteria

The inclusion criteria for the company's review are listed in Table 6.1 of the CS and are reproduced in Table 2. In relation to the decision problem, the following observations can be made:

- The selection criteria do not match the decision problem or the studies selected. The criteria presented relate to a review that was designed to answer a wider review question. Criteria are not presented for how these were adapted to the decision problem. As such, it is unclear whether the review appropriately selected studies. For example, five studies were excluded because they addressed induction therapy with olaparib followed by maintenance therapy with olaparib. This does not appear in the list of inclusion and exclusion criteria. Conversely, of the two studies listed as being relevant (Study 19 and Study 41), Study 41[15] was a study which addressed induction with olaparib followed by maintenance with olaparib. In addition, four studies were maintenance studies but were not judged to be relevant to the decision problem; the reasons underpinning this judgement were unclear.
- Studies in patients with Stage I disease only were excluded from the company's review. The rationale given is that *"About 75% of OCs are diagnosed at a late*

stage.[16] *Generally, patients receiving chemotherapy in first-line setting or above are in advanced disease stage."* (see CS[1] page 54). The final NICE scope[10] does not exclude patients with Stage 1 disease. It is also not clear how the company dealt with studies that included all disease stages, as the inclusion criteria states "Stages II to IV." However, clinical advisors to the ERG suggest that very few Stage 1 patients would in fact be eligible for olaparib, as few are offered chemotherapy, fewer relapse and even fewer would be *BRCAm*. As such, this exclusion is unlikely to represent a significant problem.

- Only one study is listed as meeting the inclusion criteria in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram and the text of the CS, [1] but two studies are listed as relevant RCTs in Table 6.2 of the CS.[1]
- Very little information was provided about the intervention. It was not clear if studies where olaparib was used in combination with other treatments would be included. It was also unclear which doses of olaparib were included.
- It is not clear whether studies that recruited patients who had combination therapies during their induction chemotherapy were eligible for inclusion.
- Only English language publications were included, hence there is a risk that relevant non-English language data are missing from the review.

4.1.2.2 Study selection

Study selection was conducted by two reviewers independently; disagreements were reconciled by a third reviewer. The ERG considers this to be a high quality methodology. However, the documentation of study selection in terms of study flow was very poor in the CS.[1] Consequently, the ERG requested clarification on the company's process of study selection. Issues and omissions that prevented the ERG from assessing and validating whether study selection had been appropriate were:

- The citations and reasons for the exclusion of full-text articles were not provided in the CS.[1] The ERG sought clarification on this and was provided with a full list of excluded studies. The ERG consulted this list and was satisfied that selection was appropriate to the decision problem.
- Of the 4 studies addressing a maintenance therapy, it was reported that only one study addressed a maintenance treatment relevant to the decision problem set out in the final NICE scope.[10] However, it was not apparent in what way the others did not meet the decision problem. This was later clarified by the company and was judged by the ERG to be acceptable as the other studies were not testing olaparib (see clarification response[9] question A4).

- The PRISMA flowchart (see CS[1] Figure 6.1) was not constructed appropriately in that it did not provide reasons for the exclusion of 163 publications which simply disappear from the diagram. The company provided a revised flow chart in their clarification response[9] (see Appendix 1).

Overall, the ERG considers the inclusion criteria and study selection process to have been poorly reported to the extent that the relevance of the review to the decision problem could not be adequately determined. Responses to the ERG's request for clarification indicate that the results are probably relevant to the decision problem.

Additional work conducted by the ERG (see Section 4.5) suggests that Study 19 was the only RCT study that is directly relevant to the decision problem.

Table 2: Eligibility criteria used in search strategy (reproduced from CS[1] Table 6.1)

Criteria	Inclusion	Exclusion	Rationale
Study design	RCTs (irrespective of blinding status)	Studies other than RCTs, i.e. non-randomised trials, prospective cohort studies, retrospective cohort studies, single-arm studies, case studies, case reports, case-control, and cross-sectional studies	RCTs are the gold standard of clinical evidence, minimising the risk of confounding factors and allowing for comparison of the relative efficacy of the interventions
Population	Adult women of any race	Studies focusing on children or adolescents only (unless a mixed population with relevant subgroup data is reported)	OC occurs in women and primarily in adults; studies often include patients with different racial characteristics. As treatment is based on mutation status, race is not relevant for the purposes of study selection
Disease	Patients with OC defined as epithelial ovarian, fallopian tube, or primary peritoneal cancer	Any cancer other than OC (unless a mixed population with relevant subgroup data is reported)	Olaparib is licensed for OC
Platinum status	Patients with platinum-sensitive OC (platinum sensitive is defined as relapse ≥6 months after the cessation of prior chemotherapy) AND in complete or partial remission after two or more platinum-based regimens	Studies of platinum-resistant or refractory patients (defined as relapse during prior chemotherapy or within 6 months) will be excluded	Olaparib is licensed as a maintenance treatment for the pre-treated PSR patient population only
Disease stage	Stages II–IV	Studies in disease stage I alone will be excluded	About 75% of OCs are diagnosed at a late stage.[16] Generally, patients receiving chemotherapy in first-line setting or above are in advanced disease stage
Histological subtype	Any histological type of OC	No exclusion based on histological subtype during the screening phase	Approximately 70% of epithelial ovarian carcinomas in the UK are classified as high-grade serous[17]

Mutation status	Any *BRCA1* or *BRCA2* mutation status (present or absent) Any information regarding mutation status (hereditary or acquired) will be captured if reported	No exclusion will be based on expression of allele status	Data for *BRCA1* and *BRCA2* subgroups will be additionally extracted for all the outcomes, where reported
Intervention	Olaparib	Studies investigating the role of other unlicensed treatments, radiotherapy, chemo-radiotherapy, hormonal therapy, or surgery Adjuvant or neo-adjuvant therapy	Olaparib is the intervention for this review as defined by the NICE scope
Comparators	Best supportive care/'watch and wait'	Studies comparing interventions not mentioned in the above list	Currently there is no recommended treatment for maintenance therapy after first-line or subsequent-line chemotherapy in the NHS; these patients are typically monitored over time (a 'watch and wait' strategy)
Line of therapy	Second-line or beyond	Studies investigating first-line maintenance or maintenance immediately following surgery	Patients receiving maintenance therapy in second-line (first relapse) or third- and subsequent-line setting are of interest to the review
Language	Only studies with the full text published in English will be included	Studies with an English abstract where the full text is not in English and that meet the inclusion criteria will be flagged	The vast majority of publications likely to provide data of interest for addressing the objectives of this review will have full texts published in English. Restricting to such publications will therefore be unlikely to exclude useful information
Publication time frame	Last 15 years (1998–2013)	Publications before 1998	Role of maintenance therapy has been explored only in recent years, although no consensus on its benefit has been reached until now

4.1.3 Critique of data extraction

The process of data extraction was poorly described within the CS; it is simply stated that *"data extraction from included studies was carried out in parallel by two independent reviewers, and any discrepancies were reconciled by a third reviewer. Studies with multiple publications were extracted in one grid with multiple publications linked to one another."* (CS[1] page 53). Whilst the ERG considers double independent data extraction to be a high quality methodology, it is not clear which fields were data extracted, how the data extraction form was developed, or whether it was standardised. However, given the data that are presented and that only one study was included in the company's review, it is unlikely that these omissions obscure any methodological bias.

4.1.4 Quality assessment

The process of quality assessment was not well described in terms of how it was done or by whom. It is not clear if quality assessment was checked, and if so, how disagreements were reconciled.

Study quality was assessed using the questions listed by NICE in the submission template and are presented in Table 6.6 of the CS.[1] It is unclear if the quality assessment was conducted against the CSR or against published articles relating to the study. This is particularly important when assessing outcome reporting bias. As would be expected, the quality assessment appears to relate to the whole study population, rather than the subgroup analysis relating to *BRCAm* patients. Quality assessment of the study, undertaken both by the company and by the ERG, is provided in Section 4.2.1.5.

4.1.5 Evidence synthesis

No evidence synthesis plans were presented in the CS,[1] however since there was only one relevant study, a formal synthesis was not required.

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

The review identified one relevant study and excluded eight other potentially relevant studies. These exclusions were appropriate. Details of included studies and excluded studies are provided in Tables 3 and 4, reproduced from the company's clarification response[9] (question A4).

Table 3: List of five studies excluded for addressing induction followed by maintenance treatment (reproduced from clarification response[9] Table A4.1)

Primary publication	Intervention	Title	Publication details	Included?
Approved agent				
Aghajanian 2012[18] (OCEANS study)	Bevacizumab + carboplatin + gemcitabine followed by bevacizumab Carboplatin + gemcitabine followed by placebo	OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer	Journal of Clinical Oncology (2012): 30 (17): 2039-2045	No
Investigational agents				
Kaye 2013[19]	Carboplatin + gemcitabine/ paclitaxel + pertuzumab followed by pertuzumab Carboplatin + gemcitabine/ paclitaxel followed by no therapy	A randomized phase II study evaluating the combination of carboplatin-based chemotherapy with pertuzumab versus carboplatin-based therapy alone in patients with relapsed, platinum-sensitive ovarian cancer	Annals of Oncology (2013): 24 (1): 148-152	No
Oza 2012[20] (Study 41)	Carboplatin + olaparib + paclitaxel followed by olaparib Carboplatin + paclitaxel followed by placebo	Olaparib plus paclitaxel plus carboplatin (P/C) followed by olaparib maintenance treatment in patients (pts) with platinum-sensitive recurrent serous ovarian cancer (PSR SOC): A randomized, open-label phase II study	Journal of Clinical Oncology (2012); 30 (15)	No
Ledermann 2013 (ICON-6 study)	Cediranib + platinum based chemotherapy followed by cediranib Cediranib + platinum based chemotherapy followed by placebo Platinum based chemotherapy followed by placebo	Randomised double-blind phase III trial of cediranib (AZD 2171) in relapsed platinum sensitive ovarian cancer: Results of the ICON6 trial	European Journal of Cancer (2013): 49: S5-S6	No
Vergote 2013	Farletuzumab + carboplatin + paclitaxel/docetaxel followed by farletuzumab (1.25 mg) Farletuzumab + carboplatin + paclitaxel/docetaxel followed by farletuzumab (2.5 mg) Carboplatin + paclitaxel/docetaxel + placebo followed by placebo	Phase 3 double-blind, placebo-controlled study of weekly farletuzumab with carboplatin/taxane in subjects with platinum-sensitive ovarian cancer in first relapse	International Journal of Gynecological Cancer (2013): 23 (8): 11	No

Table 4: List of four studies investigating maintenance therapy alone (adapted from clarification response[9] Table A4.2)

Primary publication	Intervention	Title	Publication details	Included?
Ledermann 2012[14]	Olaparib Placebo	Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer	New England Journal of Medicine (2012); 366 (15): 1382-1392	Yes
Kaye 2012[21]	Vismodegib Placebo	A phase II, randomized, placebo-controlled study of vismodegib as maintenance therapy in patients with ovarian cancer in second or third complete remission	Clinical Cancer Research (2012): 18 (23): 6509-6518	No – not olaparib
Ledermann 2011	Nintedanib Placebo	Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer	Journal of Clinical Oncology (2011): 29 (28): 3798-3804	No – not olaparib
Gray 2014	Cvac Observation	Progression-free survival in ovarian cancer patients in second remission with mucin-1 autologous dendritic cell therapy.	ASCO (2014): Abstract number 5504	No – not olaparib

4.2.1 Study 19

The included trial focussed on in the submission, Study 19,[14,22] was also considered the pivotal trial in the EPAR.[23] This is the most important study in relation to the decision problem.

4.2.1.1 Population

Patient eligibility criteria were provided in Table 6.4 of the CS[1] and are reproduced in Table 5. Baseline patient characteristics for the whole population and the *BRCAm* subgroup were provided in Table 6.4 of the CS[1] and are reproduced in Table 6.

In summary, patients were eligible for inclusion in the study if they had a histological diagnosis of recurrent serous ovarian cancer (including primary peritoneal or fallopian tube cancer) that was platinum-sensitive (progression >6 months) as determined by response to the most recent round of chemotherapy and at least one previous round (not necessarily sequential rounds). The response had to be maintained from the round prior to enrolment at the point of enrolment. Randomisation had to be within 8 weeks of the last dose of chemotherapy. Patients were not enrolled if they had received previous treatment with any PARP inhibitor.

In relation to the decision problem, the following observations can be made:

- The population recruited to Study 19 was wider than the population indicated in the licence and the decision problem set out in the final NICE scope[10] in that it recruited patients of any *BRCA* status.
- In the opinion of the clinical advisors to the ERG, most criteria seem appropriate in relation to the wider population and to the *BRCAm* subgroup. Only patients with Eastern Co-operative Oncology Group (ECOG) performance status ≤2 were recruited; this is not a condition of the marketing authorisation for olaparib.[11] Only patients with a life expectancy >16 weeks were recruited; again, this is not a condition of the marketing authorisation. Clinical advisors to the ERG were not concerned about these restrictions.
- The ERG highlighted to the clinical advisors the criterion which states patients had to be stable according to CA-125 measurements, or below the ULN (see Table 5). A restriction on CA-125 is not listed in the marketing authorisation for olaparib. As such, this criterion may have altered the patient spectrum by enriching stable patients, and removing those patients who may be in the early stages of relapse. However, clinical advisors to the ERG believe that CA-125 is used to monitor response to chemotherapy and so would be known (note, it is not always used in England for ongoing monitoring post-chemotherapy). Two advisors agreed that patients would be selected on the basis of CA-125 levels, so this selection criterion is likely to be representative of clinical practice in England.
- Patient baseline characteristics were fairly well balanced between intervention and placebo groups in both the whole population and the *BRCAm* subgroup (see Table 6.5) except for:
    (i) ECOG performance status, intervention versus placebo, *BRCAm* subgroup. 83.8% of the olaparib group versus 72.6% of the placebo group scored "normal activity", whilst 14.9% of the olaparib group versus 24.2% of the placebo group scored "restricted activity." A similar but less pronounced difference is evident in the full analysis set for the ITT population.
    (ii) Age, *BRCAm* subgroup versus whole group. The *BRCAm* subgroup was generally younger, probably due to the natural history of *BRCA* mutations.
    (iii) Objective response (OR) to most recent platinum-based regimen, intervention versus placebo. More patients had a complete response (CR), and fewer had a partial response (PR), in the placebo arm in both the whole group and the subgroup analyses. The imbalance may be due to protocol deviations (see Section 4.2.1.5). It is unclear whether, or in which direction, such an imbalance would influence the results of the study. These factors were adjusted for in Cox proportional hazards model analyses for all efficacy outcomes in the whole population, though it is less clear if this was also implemented for all outcomes in the *BRCAm* subgroup analyses.

(iv) OR to the most recent platinum-based regimen, *BRCAm* versus whole group. More patients (overall (51.5%) and per study arm) had a CR, and fewer had a PR, in the *BRCAm* subgroup compared against the whole group (45.3% overall). This may reflect the greater propensity for *BRCAm* patients to respond to platinum-based therapy. This factor was adjusted for in Cox proportional hazards model analyses for all efficacy outcomes in the whole population, though it is less clear if this was also implemented for all outcomes in the *BRCAm* subgroup analyses.

Table 5: Eligibility criteria for Study 19 (reproduced from CS[1] Table 6.4)

Inclusion criteria	Exclusion criteria
▪ Age ≥18 years or older ▪ Histological diagnosis of recurrent serous OC (including primary peritoneal and fallopian tube cancer) ▪ Histological diagnosis of recurrent serous OC (including primary peritoneal and fallopian tube cancer) ▪ Platinum-sensitive disease (defined as disease progression greater than 6 months after penultimate platinum chemotherapy) ▪ Patients had completed ≥2 courses of platinum-based chemotherapy with OR (CR or PR, maintained to permit study entry) ▪ CA-125 measurements below the upper limit of the normal (ULN) range or if above ULN, not significantly rising over time ▪ Normal organ and bone marrow function within 28 days prior to administration of study treatment ▪ ECOG performance status ≤2 ▪ Life expectancy of 16 weeks	▪ Low-grade OC ▪ Drainage of their ascites during the final two cycles of their last chemotherapy ▪ Previous treatment with PARP inhibitors, including olaparib ▪ Second primary cancer ▪ Receiving chemotherapy, radiotherapy (except for palliative reasons) within 2 weeks from study entry ▪ Symptomatic uncontrolled brain metastases ▪ Major surgery within 2 weeks before study ▪ Serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection ▪ Pregnant and breastfeeding women ▪ Hepatitis B or C

Table 6: Patient demographics and baseline characteristics for whole population and according to *BRCA* mutation status (reproduced from CS[1] Table 6.5)

	Full analysis set		***BRCAm***	
	Olaparib 400 mg bid (n=136)	**Placebo (n=129)**	**Olaparib 400 mg bid (n=74)**	**Placebo (n=62)**
Age (years)				
Median (range)	58.0 (21–89)	59.0 (33–84)	57.5 (38–89)	55.0 (33–84)
Age group (years), n (%)				
<50	30 (22.1)	20 (15.5)	19 (25.7)	16 (25.8)
≥50 to <65	61 (44.9)	74 (57.4)	38 (51.4)	35 (56.5)
≥65	45 (33.1)	35 (27.1)	17 (23.0)	11 (17.7)
Ethnic population,* n (%)				
Jewish descent				
No	115 (84.6)	112 (86.8)	60 (81.1)	48 (77.4)
Yes	21 (15.4)	17 (13.2)	14 (18.9)	14 (22.6)
ECOG performance status, n (%)				
(0) Normal activity	110 (80.9)	95 (73.6)	62 (83.8)	45 (72.6)
(1) Restricted activity	23 (16.9)	30 (23.3)	11 (14.9)	15 (24.2)
(2) In bed <50% of the time	1 (0.7)	2 (1.6)	0	1 (1.6)
Unknown	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)
Primary tumour location				
Ovary	119 (87.5)	109 (84.5)	65 (87.8)	54 (87.1)
Fallopian tube or primary peritoneal	17 (12.5)	19 (14.7)	9 (12.0)	8 (12.9)
Time to progression after completion of penultimate platinum-based regimen				
>6 to ≤12 months	53 (39.0)	54 (41.9)	28 (37.8)	26 (41.9)
>12 months	83 (61.0)	75 (58.1)	46 (62.2)	36 (58.1)
OR to most recent platinum-based regimen				
CR	57 (41.9)	63 (48.8)	36 (48.6)	34 (54.8)
PR	79 (58.1)	66 (51.2)	38 (51.4)	28 (45.2)

*Data are median (range) or number (%); *Ancestry was self-reported*

4.2.1.2 Intervention

The intervention assessed within Study 19 was 400mg olaparib, twice daily (8 *x* 50mg capsules).[24] Patients could be discontinued from treatment at any time at the discretion of the investigators. Retreatment was not permitted. Interruptions and dose reductions were permitted to manage toxicity and AEs. All these are in line with the marketing authorisation for olaparib.[25]

Patients were allowed to continue study treatment following objective progression, provided they were still benefitting and did not meet any other discontinuation criteria (see CS[1] page 65). This is not in line with the marketing authorisation, which states that *"It is recommended that treatment be continued until progression of the underlying disease."*[23] As such, data collected beyond PFS within Study 19 may overestimate relative treatment effects for olaparib compared with clinical practice

undertaken in accordance with its licence. This is also likely to have affected the *post hoc* analysis of TTD/D.

However, there is also an issue around what is considered disease progression in clinical practice. This is not defined in the EPAR[23] or the SmPC[11] with respect to when treatment with olaparib should be discontinued. Within the trial, PFS was assessed using Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, progression can also be assessed through CA-125 levels either alone or in conjunction with RECIST (e.g. Study 19 uses this as a secondary outcome). Clinical advisors to the ERG suggested that CA-125 is differentially monitored throughout England, with a substantial minority of patients not receiving this test for monitoring purposes post-chemotherapy. As such, there may be heterogeneity in how "progression" is interpreted in clinical practice. If CA-125 is used as a criterion for assessing progression in clinical practice, this is likely to decrease the duration and potentially the benefit of olaparib treatment. The impact of this potential heterogeneity in clinical practice on the generalisability of the study results is unknown. In addition, it is unclear whether patients in Study 19 received subsequent chemotherapy immediately after progression, or whether, as is usual in England, patients only progressed to subsequent chemotherapy once symptoms required treatment. Clinical advice received by the ERG suggests that international practice may be to treat relapse earlier than in the UK, in response to rises in CA-125 and before symptoms present. As such, the event of TFST may be shorter in Study 19 than would be expected in clinical practice in England.

4.2.1.3 Comparator

The comparator within Study 19 is described as "placebo ('watch and wait')" (see CS[1] page 61). Patients were allowed concomitant medications (except chemotherapy, immunotherapy, hormonal therapy or other novel agents) at the discretion of the investigators (who were blinded to treatment group) regardless of treatment arm. This appears to reflect clinical practice. However, no data are presented on differences between concomitant treatments (e.g. ascite drainage, pain relief) in each group.

4.2.1.4 Outcomes

The outcomes listed in the CS[1] are shown in Table 7. As can be seen from the table, the CS presents additional outcomes that were not included in the final NICE scope[10] and that are not directly suggested in the EMA's guidelines on the evaluation of anticancer medicinal products.[26] The term *"intermediate clinical endpoints"* is used on page 70 of the CS,[1] however the term *"post hoc exploratory analyses"* has instead been used in this report, as the ERG believes that this better represents the nature of these analyses. These analyses were not pre-planned and were not added to the analysis plan until the data for the PFS analyses had already been collected, and possibly analysed. These changes to the protocol and planned analyses are discussed in more detail in Section 4.2.1.5.

The ERG notes also that these *post hoc* outcomes have been used as parameters in the company's health economic model.

Figure 1 shows when outcomes either included in the NICE scope, or which were used in the company's health economic model,[1] were measured. Each outcome represents a different stage in a patient's progression.

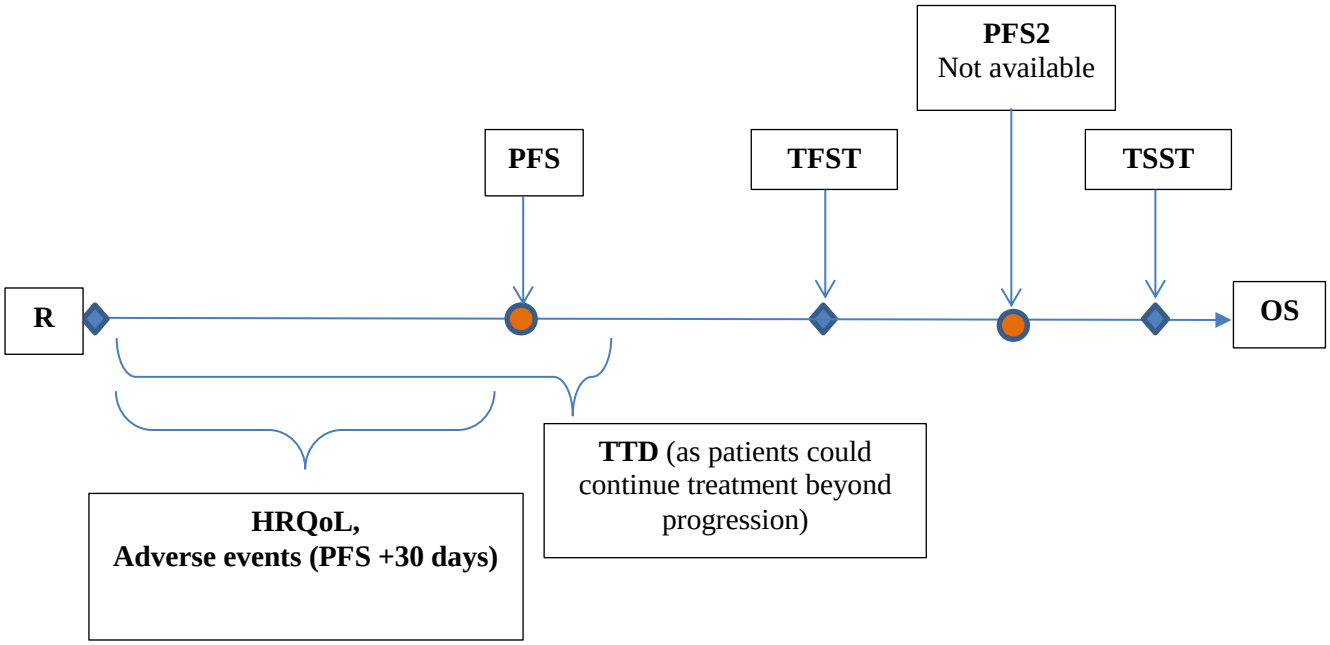
Table 7: Summary of outcomes listed in CS[1] and their relationship to EMA research recommendations,[26] the NICE scope,[10] and the company's health economic model

Outcome	Recommended by EMA?	In NICE scope?	Used in model?	Defined *a priori*?
Primary outcome				
PFS – objective assessment of disease progression according to RECIST guidelines or death. Assessed with computed tomographic scans every 12 weeks, calculated by measuring target and non-target lesions and assessing new lesions. A blinded independent scan was also conducted.[14]	Y	Y	N	Whole population: Y *BRCAm*: N, defined after study commenced but just before DCO June 2010; all patients subjected to *BRCA* tumour and germline testing, which increased sample size.
Secondary outcomes				
Time to progression (RECIST or CA-125, whichever showed earliest progression)	Y	N	N	Whole population: Y *BRCAm*: U*
Objective response rate by RECIST, or by RECIST and CA-125	Y	N	N	Whole population: Y *BRCAm*: U*
Disease-control rate, by RECIST (confirmed complete or partial response, stable disease, or no evidence of disease for at least 23 weeks)	N	N	N	Whole population: Y *BRCAm*: U*
Change in tumour size at weeks 12 and 24	N	N	N	Unclear (part of RECIST)
Overall survival	Y	Y	Not directly	Whole population: Y *BRCAm*: U*
Disease-related symptoms	Y		N	Whole population: Y *BRCAm*: U*
Quality of life	Y	Y	Y	Whole population: Y *BRCAm*: U*
Adverse events measured through monitoring, biochemical tests, vital signs and physical examination.	Y	Y	Y	Whole population: Y *BRCAm*: U*
***Post hoc* exploratory analyses**				
Time to first subsequent therapy or death (TFST/D)	Could be considered "duration of response"**	Y	Y	N
Time to second subsequent therapy or death (TSST/D)	Could be considered "duration of response"	Presented as a proxy for PFS2	Y	N
Time to treatment discontinuation or death (TTD/D)	N	N	Y	N

**Scored as "Unclear" (U) as subject to same problem as PFS, and page 72 of CS[1] states that "full analyses" were conducted "after discussion with the regulator" in the BRCAm population "based on the significant additional benefit in the BRCA population…" suggesting not all outcomes were added to the analysis plan before the June 2010 DCO*

*** EMA research guidelines (page 11)[26] list this as an outcome, but a definition is not given. It is unclear if TFST and TSST are a measure of duration of response.*

Figure 1: Outcome measurement in Study 19



R - randomisation; PFS - progression-free survival; TFST - time to first subsequent therapy; PFS2 - second progression-free survival interval; TSST - time to second subsequent therapy; OS - overall survival; HRQoL – health-related quality of life; TTD - time to treatment discontinuation.

Primary outcome

The primary outcome was PFS, which is a proxy for harder clinical endpoints such as OS, but has some therapeutic merit as an outcome in its own right. PFS was measured from the point of randomisation to the point of objective progression by RECIST criteria.

Secondary outcomes

Several secondary outcomes were recorded in Study 19, as shown in Table 7. Those not listed in the final NICE scope[10] will not be discussed further. The following outcomes were listed in the NICE scope and were reported in the CS[1] as secondary outcomes:

- OS – defined as the time from randomisation to death by any cause
- AEs on treatment – collected from consent to 30 days after the last dose of study treatment.
- HRQoL – measured using the TOI, the FACT-O and the FOSI.

Post hoc exploratory outcomes

All *post hoc* exploratory outcomes were performed on the safety population, not the ITT population as *"as only patients who received a randomised treatment were able to discontinue treatment and thus have any subsequent therapies."* (Page 55, CSR) One of the *post hoc* outcomes was listed in the NICE scope:[10]

- Time to next line of therapy, or time to first subsequent therapy or death (TFST/D) as it is referred to in the CS – defined as the time from randomisation to the start of the first subsequent cancer treatment given after discontinuation of study treatment, or to death.

A further outcome which was not listed in the NICE scope is reported within the CS:

- Time to second subsequent therapy or death (TSST/D) – defined as the time from randomisation to the start of the second cancer therapy treatment given after discontinuation of study treatment, or to death. The company asserts that TSST/D can be considered to be a proxy for PFS2 (which was listed in the final NICE scope, see Table 1).

The third *post hoc* analysis related to:

- Time to treatment discontinuation or death (TTD/D), defined as time from randomisation to discontinuation of study treatment, or death.

Critique of primary outcome

The EMA research guidelines state that for Phase II, single agent therapeutic exploratory studies which are investigating non-cytotoxic compounds (such as Study 19), objective response rate (ORR) is considered to be a convincing measure of anti-tumour activity, and PFS is considered *"a function of underlying tumour growth rate and the activity of the anti-tumour compound."*[26] The primary endpoint would therefore seem appropriate and has clinical merit as an end point in its own right. In terms of measuring the impact of a treatment on survival, PFS is a proxy: OS would be the most clinically relevant primary outcome.

Critique of secondary and post hoc exploratory outcomes

OS, TFST/D and TSST/D

As Study 19 is being used to provide pivotal evidence of efficacy, it is reasonable to argue that it should be subjected to the same standards as required for Phase III confirmatory trials. According to the EMA guidelines for Phase III confirmatory trials,[26] PFS is an acceptable endpoint, but OS should be reported as a secondary outcome and should show a trend towards superiority (assuming that the available data are immature). For maintenance interventions such as olaparib, ideally a survival benefit should be demonstrated, as treatment effects may not persist beyond a single cycle (i.e. progression is delayed, but death is not). Where OS cannot be ascertained within feasible timescales, outcomes such as PFS2 or time on next-line therapy can be substituted, as these give some indication of whether treatment effects persist beyond the progression-free interval.

Where toxicity is expected to be increased, as is likely for olaparib given that the alternative is watchful waiting, PFS is required at the least, and survival data should be made available at the time of submission, with long-term follow-up post-approval. However, it is also acknowledged that alternative endpoints may be more appropriate in certain situations.[26]

- OS data are provided up to November 2012, however the latest figures are not provided. The final DCO for OS has not yet been reached [redacted].[9]
- It appears that within Study 19, the EMA guidelines[26] have been adhered to in other respects, and it is likely that the use of TFST/D and TSST/D constitute "alternative endpoints" mentioned above. The CS[1] states that the EMA were consulted in the process of preparing their data for submission. Additionally, clinical advisors to the ERG suggest that TFST/D and TSST/D are clinically relevant outcomes. This is because patients with ovarian cancer in England often only receive subsequent treatment after progression once their symptoms have become problematic. The rationale for this, according to the ERG's clinical advisors, is that the longer the gap between chemotherapies, the better the outcome in terms of patients' quality of life and recovery from toxicity. A rough rule of thumb is that if treatments are given at <6 month intervals, they are less likely to be effective, and that it does not matter at which point in tumour progression any given round of chemotherapy is administered, as it will have the same effect on OS. As such, it could be argued that TFST/D and TSST/D are more clinically relevant than PFS.

However, there are issues with TFST/D and TSST/D specifically in the context of Study 19:

- These analyses were *post hoc*, and were only added once the study results were known.
- Patients were allowed to continue with olaparib after progression at the discretion of the clinician. As noted previously, this contravenes the marketing authorisation for olaparib. As such, estimates of TFST/D from Study 19 may overestimate relative treatment effects compared with the use of olaparib in accordance with its license. The ERG requested clarification on this issue from the company. Data were provided for the *BRCAm* subgroup only,[9] and are summarised in Table 8. These data indicate that a significant proportion of patients in the olaparib group [redacted] This could result in an overestimation of treatment effect as measured by PFS, TFST/D, TSST/D and OS compared against what would be expected in usual clinical practice. Data relating to TFST/D, the interval from first subsequent therapy to second subsequent therapy (for the olaparib group only), and survival (conditional on the point in the pathway rather than

according to the point of randomisation) have been used in the company's health economic model (see Chapter 5).

- Patients were allowed to crossover to receive a PARP inhibitor once the study treatment period was completed. [redacted]. For OS, this was investigated in sensitivity analyses, but was not addressed in the analyses of TFST/D and TSST/D. The ERG sought clarification regarding the potential for crossover to confound these outcomes. The company explained that treatment with a PARP inhibitor would constitute "subsequent therapy", and would therefore not confound TFST/D. However, it is unclear whether treatment with a PARP inhibitor was triggered according to the same clinical criteria as treatment with subsequent chemotherapy. As such, counting PARP as a subsequent therapy could potentially truncate or elongate the period of time between progression and first subsequent therapy, as compared against usual clinical practice. Only [redacted], hence the impact on TFST is likely to be small.
- For TSST/D, the company note "[redacted]" (see clarification response[9] question A2). Overall, the extent, direction and importance of this potential confounding remain unknown.
- It is unclear whether subsequent chemotherapy was administered immediately following progression. In England, clinical practice tends to only re-commence chemotherapy once symptoms dictate the need, whereas clinical advice to the ERG suggests in international practice, therapy may be re-commenced more quickly. As such, the outcomes of TFST/D and TSST/D may represent underestimates of the time to subsequent therapies in comparison to usual clinical practice in England.

In addition to the above, it should be noted that the outcomes can only loosely be considered as a measure of "duration of response" as mentioned in the EMA guidelines.[26]

Table 8: Summary of patients who continued to receive treatment after progression (adapted from clarification response[9] Table A3.1)

[redacted]	[redacted]	[redacted]

	[redacted]			[redacted]			[redacted]	

TTD – time to treatment discontinuation or death

Time to treatment discontinuation

TTD/D was also added to the analysis plan after the study results were known. This outcome was not specified in the final NICE scope,[10] nor was it listed in the EMA research guidelines. This outcome is used in the company's health economic model (see Chapter 5). The ERG notes that:

- Treatment was sometimes discontinued before progression, which reflects the marketing authorisation for olaparib.
- Treatment was sometimes continued beyond disease progression, which contravenes the marketing authorisation for olaparib.

As such, it is unclear what this outcome can usefully provide in terms of clinical efficacy or cost-effectiveness estimations. It is not a surrogate for progression nor is it an accurate representation of drug use in a real-world setting.

Adverse events

The method of AE measurement was not clearly described in the CS.[1] The original journal article was also unclear,[14] but the *BRCAm* subgroup journal article (Ledermann *et al*, 2014)[22] states that *"Adverse events and laboratory parameters were recorded throughout the trial and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0."* From this information, it remains unclear whether AE rates were actively elicited from patients through direct questioning at follow-up visits, or whether AEs were only recorded if the information was volunteered by patients. The study protocol[27] (Section 7.7.3.2) states that both methods were performed. The protocol also defines SAEs as any event that: results in death; is immediately life-threatening; requires in-patient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital abnormality or birth defect; is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above. Severity was judged according to the NCI-CTCAE, version 3, or if not listed there, according to a scheme presented in Appendix 2. Clinicians were asked to determine causality with the question *"Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"* The ERG considers these methods for AE data collection to be acceptable.

Quality of life

Quality of life was measured only during the treatment phase of the study. As such, there are no long-term data available on the impact of olaparib on HRQoL. Two of the three measures reported, TOI and FOSI, are subsets of questions from the third measure reported, FACT-O. FOSI focusses on patients' symptoms and whether these have changed. TOI compiles the physical well-being, functional well-being and "additional concerns" subscales. FACT-O is a validated measure of HRQoL in ovarian cancer. EMA guidance on measuring HRQoL in oncology[28] is not specific about which

instrument should be used. However, FACT-O appears to be a well-established HRQoL measure and is commonly used.[29] The ERG notes the following:

- HRQoL appears to have been measured using appropriate questionnaires, although the study did not include the use of a preference-based measure of HRQoL
- There are no data on the long-term impact of olaparib on HRQoL.

4.2.1.5 Study design

The study was an RCT which randomised 265 eligible patients to treatment with olaparib or placebo. The study methodology was detailed in Table 6.3 of the CS[1] and is reproduced in Table 9. The ERG notes two major problems with the study design: (i) it is only a Phase II trial, and; (ii) the only data available are from an analysis of a subgroup that was defined after the study commenced. These problems mean that the data are somewhat isolated in that the study did not set out to test the hypothesis that *BRCAm* patients are a clinically valid subgroup who will gain a greater advantage from treatment. As this is only a Phase II trial, there are also currently no subsequent Phase III data to confirm the findings of the subgroup data from this trial. The ERG notes that a Phase III trial of olaparib in *BRCAm* ovarian cancer patients after complete or partial response to platinum chemotherapy is ongoing (clinicaltrials.gov identifier - NCT01874353).

Table 9: Methodology of Study 19 (reproduced from CS[1] Table 6.3)

Trial no.	**Study 19**
Location	Australia, Europe, Canada, USA, Russia, Ukraine, Israel
Design	Double-blind, randomised, placebo-controlled, multicentre, phase II international study
Method of randomisation	Eligible patients were randomised in a 1:1 (olaparib:placebo) ratio using a randomisation scheme. A blocked randomisation was generated and all centres used the same list to minimise possible imbalances in the number of patients assigned to each treatment group. The randomisation was stratified based on the time to disease progression from completion of the penultimate platinum-containing therapy prior to enrolment, OR to the last platinum-containing regimen therapy and the patient's ethnicity
Method of blinding (care provider, patient and outcome assessor)	The active and placebo capsules were identical and presented in the same packaging to ensure blinding of the study medication and the blind was appropriately maintained for the duration of the study in order to protect the robustness of the final OS analysis. Un-blinding was only permitted if knowledge of the treatment assignment was necessary for the management of medical emergencies or if the patient was considered for enrolment into a study in which prior PARP therapy was not allowed
Intervention(s) (n=) and comparator(s) (n=)	Olaparib = 136 patients (74 *BRCAm* patients) Placebo = 129 patients (62 *BRCAm* patients)
Primary outcomes (including scoring methods and timings of assessments)	PFS assessed by the site investigator and defined as the time from randomisation (on completion of chemotherapy) until objective assessment of disease progression according to RECIST guidelines or death (from any cause in the absence of progression of disease). CT scans were performed every 12 weeks to assess PFS. PFS was calculated based on measurements of target and non-target lesions, as well as assessment for new lesions as recorded by the investigators. A blinded independent central review of tumour scans was performed retrospectively
Secondary outcomes (including scoring methods and timings of assessments)	To determine the efficacy of olaparib (capsule formulation) compared to placebo by assessment of OS, best overall response, disease control rate, duration of response, change in tumour size, CA-125 response (Gynaecologic Cancer InterGroup [GCIG] criteria), time to progression by CA-125 (GCIG criteria), or RECIST. Tumour assessments were done every 12 weeks until week 60 and every 24 weeks thereafter until objective disease progression or withdrawal of patient consent. To determine the safety and tolerability of olaparib (capsule formulation) compared to placebo. Adverse events were collected from the time of consent throughout treatment, up to and including 30 days post study follow up period (i.e. last dose of treatment). To determine the effects of olaparib (capsule formulation) compared to placebo on disease-related symptoms. To determine the QoL of patients treated with olaparib (capsule formulation) compared to placebo. Patient health-related QoL and disease-related symptoms were evaluated by questionnaire at baseline and every 28 days until progression using the following standardised tools: Functional assessment of cancer therapy ovarian (FACT-O), FACT/NCCN Ovarian Symptom Index (FOSI) and Trial Outcome Index (TOI).

Quality assessment of the study design

The CS provides a critique of the design of Study 19 in the form of a quality assessment. This is reproduced in Table 10, which also provides details of the ERG's critique of both the quality

assessment performed in the CS, and the quality of the study itself. As shown in Table 10, the ERG agreed with the CS in 4 cases, but disagreed in 3 cases.

- Allocation concealment, imbalances in dropouts between groups, outcome reporting bias and analysis methods were all scored low risk by both the ERG and the company.
- Randomisation was scored as low risk by the company, but high risk by the ERG as reference to the EPAR[23] and CSR[24] revealed that problems with the IVRS resulted in the mis-stratification of some patients. This has the potential to affect the distribution of both known and unknown confounders.
- The similarity of the groups at baseline with reference to known prognostic factors was a potential source of risk of bias in the opinion of the ERG (see Section 4.2.1.1), but not in the opinion of the company. The proportion of patients who exhibited a CR or PR in both the whole population and in the subgroup of *BRCAm* patients did not appear balanced, and, as a potential prognostic factor for response, could have an impact on study results. Whilst it is clear from the CSR that all analyses in the whole study population corrected for known imbalances, it is less clear whether this was done for all *BRCAm* analyses. The ERG notes that the analysis of PFS by subgroup for patients with *BRCAm* (see CS[1] Figure 6.6) shows that the point estimate for CR patients is marginally worse than for PR patients (though both with wide and overlapping confidence intervals, data presented graphically). There were more CR patients in the placebo group than the olaparib group (55% versus 49%, respectively), hence there is the potential for this imbalance to have operated in favour of olaparib. It remains unclear whether the observed non-statistical difference in PFS between CR and PR patients would be reflected in other outcomes, however there remains a risk. In addition, ECOG performance status, which was better in the olaparib group than the placebo group, was not adjusted for in analyses, and may have biased results.
- Based on the description of blinding given in the CS,[1] a "low risk" score was appropriate. However, there was the option for emergency un-blinding. The ERG requested clarification on the extent of un-blinding in the study (see clarification response[9] question A5). In total, 56 patients were un-blinded (21.1%). Thirty nine of these (14.7% of the total population) were un-blinded after their PFS event, 17 (6.4%) before documented progression though not all before the DCO for PFS.
    - Given the reasonably objective nature of PFS and the timing of un-blinding, this outcome is unlikely to have been affected.
    - However, TFST/D and TSST/D may have been influenced by a clinician's knowledge of previous treatment. For the most part, the reason for un-blinding was to allow patients to potentially enrol in subsequent trials of PARP inhibitors. According to the company's clarification response[9] (question A4), patients in the intervention group

would be ineligible for enrolment as prior PARP treatment was an exclusion criteria in all known PARP trials. For placebo group patients, un-blinding will have resulted in some patients enrolling in a subsequent PARP trial, and therefore receiving a treatment. This could conceivably have shortened their TFST/D and TSST/D, thus biasing results in favour of olaparib. It is unclear how many patients were unblinded before TFST/D and TSST/D.

- Un-blinding itself is unlikely to affect OS, though subsequent treatment with a PARP inhibitor might. This has been explored in crossover analyses (see Section 4.2.1.6)
- The effect of un-blinding on other outcomes listed in the final NICE scope (HRQoL and AEs) is unclear as the exact time of un-blinding in relation to measurement of the outcomes is not reported within the CS.[1]

Table 10: Quality assessment results for Study 19 (adapted from CS[1] Table 6.6)

Study question	How is the question addressed in the study?	Grade*	ERG critique – Full population	ERG score*
Was randomisation carried out appropriately?	Eligible patients were randomised in a 1:1 ratio using an IVRS. The investigators/ sites determined the appropriate stratification variables for each patient at the time of randomisation. A blocked randomisation was generated and all centres used the same list in order to minimise imbalance in numbers of patients assigned to each group.	Yes	The randomisation plan was appropriate, as stated in the CS[1] However, it is evident from the CSR that the randomisation process was not performed as planned, due to mis-stratification by the IVRS.	No (High risk)
Was the concealment of treatment allocation adequate?	The active and placebo capsules were identical and presented in the same packaging to ensure blinding of the study medication.	Yes	Inappropriately scored and supported. Allocation concealment is only partly assured by identical treatment presentation. Data from Ledermann *et al*, 2014[22] confirms that concealment of treatment allocation was adequate.	Yes (Low risk)
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The demographic characteristics of the *BRCAm* patients were generally consistent with the overall population and the two treatment groups were well balanced in terms of age, race and ethnicity. The age distribution of the *BRCA* population was younger than the overall population but this is consistent with the hereditary nature of *BRCAm*. At diagnosis, the majority of patients had a tumour that was FIGO Stage IIIC (59%). There was a slight imbalance between groups in a number of patients with ECOG PS 0 or 1. For response to previous platinum therapy, a lower percentage in the olaparib compared with placebo group had a CR, and vice versa for PR.	Yes	Inappropriately scored and supported. Imbalances in treatment arms are described and may have confounded results. Some analyses included adjustments for the three stratification factors, but not for other imbalances.	No (high risk)

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 impact on the risk of bias (for each outcome)?	Blinding was maintained throughout the study unless in the case of medical emergency, where un-blinding was necessary. The active and placebo capsules were identical and presented in the same packaging. Un-blinding did not occur until after all planned analyses.	Yes	21.1% of patients in total were unblinded. In some cases, this may have affected outcome measurement.	No (High risk)
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances in dropouts between treatment groups.	No	Appropriately scored and justified.	No (Low risk)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes measures are accounted for.	No	The statement that *"all outcome measures are accounted for"* does not directly answer the question of whether they were reported. In the context of the NICE scope,[10] all outcomes that were measured were reported.	No (Low risk)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy data from this study was summarised and analysed on an ITT basis using randomised treatment. Analyses were undertaken for the overall study population and for patients with *BRCA*-mutated ovarian cancer.	Yes	An ITT analysis was performed according to patient randomisation. Patients who withdrew consent were censored and early censoring was balanced between groups.	Yes (Low risk)

**Grade scored as yes/no/not clear or N/A*

Other sources of bias

Changes to the study protocol and statistical analysis plan

Study 19 has undergone a number of changes to its protocol throughout its history; the main changes are listed on pages 90 to 91 of the EPAR.[23] Many of these changes were made after the first patient was recruited (28th August 2008), some after the primary analysis DCO (30th June 2010) and some at the same time as the "58% interim overall survival" analysis cut-off (26th November 2012). The last patient was recruited on 9th February 2010. As such, these amendments have the potential to introduce bias to the conduct of the trial. The amendments that the ERG considers to be most relevant to this assessment are summarised below.

- *Interim OS analysis.* This was initially planned to occur with the PFS analysis. However, after the DCO was reached, the decision was taken to abandon the interim OS analysis and to analyse OS only once, when there were a similar number of OS events as PFS events in the primary analysis (~60% maturity, the ERG assumes that this is the 58% maturity interim OS analysis referred to elsewhere in the EPAR). However, on 5th November 2011, a decision was made to re-introduce an interim OS analysis, this time after approximately 100 deaths, in order to support the initiation of a Phase III study. The plan for the later (58% maturity) analysis was maintained. On 17th October 2012, a further OS analysis at 85% maturity was also planned (see EPAR[23] page 90). It is unclear why these changes were made, but they have the potential to have prevented the publication of unfavourable results at key moments in the development of this intervention, and/or to have allowed data to mature to a point at which it was favourable. Reasons may equally have been related to the small number of events at earlier time points. Regardless of any reasons, known or otherwise, this constitutes outcome reporting bias at the least.
- *Post hoc addition of exploratory analyses, TFST/D and TSST/D.* The exploratory analyses of TFST/D and TSST/D were added to the analysis plan after the PFS analysis was conducted and at the time of the 58% interim OS analysis (26th November 2012 – see EPAR[23] page 82). The DCO for this analysis was around the same time (November 2012). As such, there is considerable potential for these analyses to be subject to outcome reporting bias based on their results.
- *Post hoc addition of germline BRCA mutations to the subgroup analysis.* The EPAR[23] (page 88) states that *"In the original CSR the sub-group analysis by BRCA status was based on gBRCA status recorded on the CRF at entry to the study, whilst the current analysis additionally considers both germline and tumour BRCA status at entry and hence the sample size for the current analyses by BRCA status was larger than in the original CSR."* Both the CS[1] and the journal article[22] relating to the *BRCAm* subgroup describe this as a "pre-planned" analysis, which is not entirely accurate. The addition of tumour (somatic) *BRCA* patients to

the analysis was not pre-planned, and as such all *BRCA* analyses could be considered to be *post hoc* analyses.

- *Post hoc addition of outcomes to BRCA subgroup analysis*. In addition, the CS states that not all end points were initially planned for the subgroup analysis: *"Based on the significant additional benefit observed in the pre-specified subgroup of BRCA-mutation positive patients, full analyses of all endpoints were conducted after discussion with regulatory agencies within this subgroup."* (see CS[1] page 72).
- *Interim PFS analysis*. On 14th May 2009, an interim analysis of PFS was added to the statistical plan. This was removed again a year later (17th May 2010) because it was *"no longer required"* (see EPAR[23] page 90). The justification for the removal of this analysis from the statistical analysis plan is unclear.
- *HRD patients*. The trial was adapted to incorporate two primary analysis sets on 27th November 2008: (i) the full patient population, and; (2) patients with homologous-recombination-deficient (HRD) tumours only. However, a test to identify HRD patients was not available in time, and so this analysis was removed on 17th May 2010 (see EPAR[23] page 90).

Protocol deviations

The EPAR[23] lists a number of protocol deviations:

"A total of 52.8% patients (57.4% olaparib versus 48.1% placebo) were defined as having "important" deviations in the study that could potentially have influenced the assessment of efficacy with a total of:

- 79 patients (29.8%) were mis-stratified in the interactive voice response system (IVRS) by study sites, with a larger proportion of patients in the olaparib group compared with the placebo group (35.3% olaparib vs 24.0% placebo). The randomisation was stratified by 3 factors and the majority of the discrepancies between data recorded on the IVRS and the CRF were due to Time to Penultimate Platinum disease progression (22 patients were entered into the IVRS as having 6-12 months to penultimate progression but as >12 months on the CRF, the converse for 14 patients) and Response to prior disease (28 patients were recorded on the IVRS as being in complete response but had disease at baseline according to RECIST, the converse for 21 patients);

- 34.0% of patients had "important" deviations other than IVRS mis-stratifications (33.8% olaparib vs 34.1% placebo). Only a minority were considered to have the potential to impact the overall efficacy conclusions.

The other "important" deviations are considered to be unlikely to have affected the efficacy analyses." (EPAR[23] page 91)

In relation to the mis-stratification error, the ERG notes that the baseline data for time to progression (TTP) seem fairly well balanced between arms (see CS[1] Table 6.5). However, the baseline data for OR to previous chemotherapy are less well balanced in both the full population and the *BRCAm* subgroup; the errors in stratification discussed in Section 4.2.1.5 may explain this imbalance.

The other deviations are listed in the CSR[24] (Table 11.1.6.1.c.). Of these, several related to errors in eligibility testing, meaning that a proportion of patients who should have been excluded were included, and a proportion of patients underwent tests at the wrong time. However, the numbers were small. The deviation which occurred most often was *"RECIST: Scans performed outside of the scheduled window on more than two occasions"*, with 16.2% in the comparator arm, and 10.1% in the placebo arm. The impact of such a deviation is difficult to assess.

4.2.1.6 Critique of subgroup analysis

The salient issue here is whether the *BRCAm* subgroup is truly different to the whole population, and whether different treatment decisions can be made upon that basis. The majority of the data presented in the CS[1] relate to the subgroup of *BRCAm* patients, rather than the total population. There are well-documented reasons why subgroup analyses should be treated with caution.[30;31] Rothwell[31] proposes a number of items to be considered when assessing subgroups. These items have been applied by the ERG to assess the reliability of the evidence for the *BRCA* subgroup presented in the CS[1] (see Appendix 3). Study 19, as reported in the CS,[1] did not fully and unequivocally meet any of the criteria proposed by Rothwell.[31] In summary, the following major problems were identified:

- The subgroup was not defined before data collection commenced, and can only loosely be considered a pre-planned analysis in that it was added to the statistical analysis plan a few weeks before the primary DCO in June 2010. It is not clear if any blinded analyses had been conducted at this point, though un-blinding had not taken place.
- No rationale was given for the subgroup being formed in the protocol,[32] and the expected direction of effect was not pre-specified.
- The subgroup was not clearly defined. In the June 2010 PFS subgroup analysis, only germline *BRCA* patients, and only those with a known *BRCA* status at recruitment, were to be included. The study protocol[32] specifically notes that *BRCA* mutation testing was not to be conducted for the study. In the final analysis presented in the CS,[1] germline and tumour *BRCA* testing had been conducted on all available patient samples, and *BRCAm* patients were added to the subgroup, presumably to increase the sample size.

- Interaction tests were not provided in the CS. These are considered the only reliable statistical approach.[30,31] Statistical testing of subgroup data alone is very prone to spurious positive results, and as such it is recommended that interaction tests are conducted to check whether the subgroup data are actually different to the rest of the trial group. Without this level of statistical testing, conclusions can be invalid.[30,31] This is especially important where the results for the whole population have produced a statistically significant effect, as is the case in Study 19. The ERG found reference to interaction tests performed for PFS for the *BRCAm* group in the CSR[24] and the EPAR.[23] These two sources differ slightly, but both report a significant interaction test for *BRCAm* (p=0.030 or p=0.025 respectively) when considered alone, but a non-significant interaction (p=0.15647 or p=0.142 respectively) when a global test adding treatment interaction terms for all 5 non-treatment covariates was performed (see CSR[23] page 1596). The interaction test that considers only *BRCA* may be confounded by other factors, and the global test may be underpowered (the study was not powered for an interaction test). As such, the results of the interaction test appear inconclusive, making it unclear whether the *BRCAm* subgroup is statistically distinct from the whole population. As this has not been demonstrated with certainty, it is possible to argue that there is not a difference in efficacy for the subgroup compared against the remainder of the whole population and the results for the whole population may be considered the most plausible estimate of efficacy. This would present an interesting situation with regard to the marketing authorisation for olaparib, which includes only *BRCAm* patients.

The identification of this subgroup could be considered to have been a clinically relevant consideration, added shortly prior to the June 2010 DCO, nevertheless it remains subject to a considerable risk of bias.

Regardless of all of the above, the most convincing evidence of a subgroup effect is for it to be reproduced in subsequent trials. This evidence does not yet however exist.

4.2.1.6 Results

Progression-free survival

The results for PFS for the whole population and the *BRCAm* subgroup are presented in Table 11; the Kaplan-Meier PFS curves for the *BRCAm* population are presented in Figure 2. As can be seen from Table 11, the primary study objective was met, with a reported HR for olaparib versus placebo of 0.35 (95% c.i. 0.25 to 0.49, p<0.01). Median PFS for the olaparib and placebo groups was reported to be 8.4 months and 4.8 months, respectively (95% c.i. not reported). This result was confirmed by independent central review. When the *BRCAm* subgroup is considered alone, the HR for olaparib versus placebo is estimated to be 0.18 (95% c.i. 0.10 to 0.31, p<0.0001) with a median PFS of 11.2

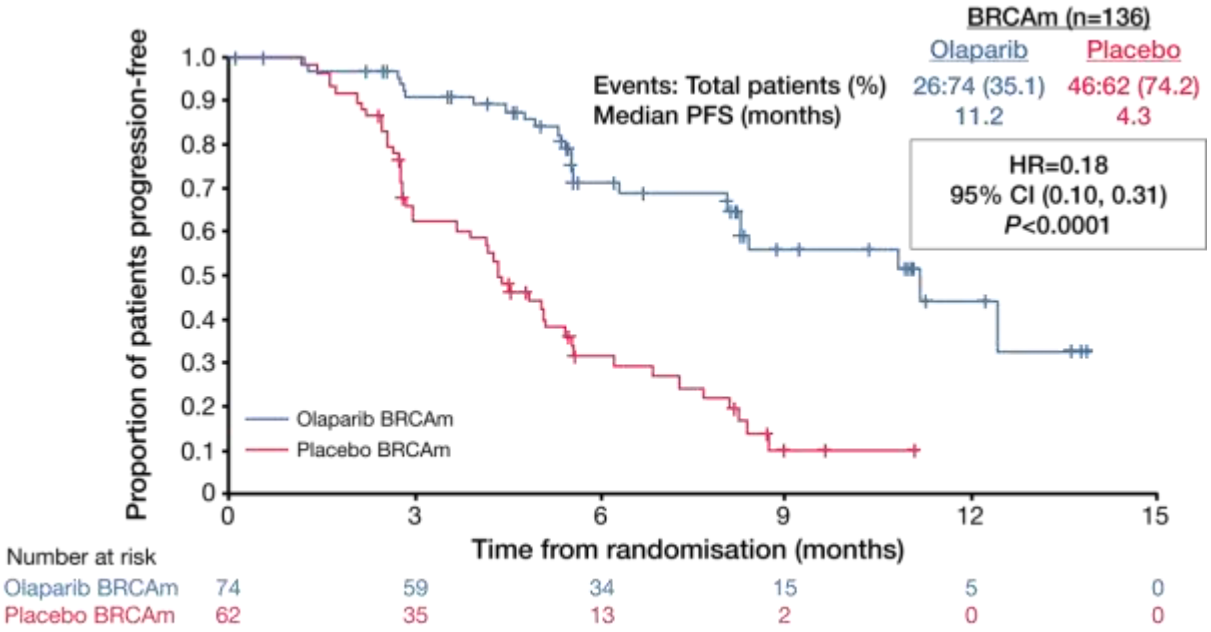
months for the olaparib group (95% c.i. 8.3 to "not calculable") versus 4.3 months for placebo (95% c.i. 3.0 to 5.4). As previously stated, the interaction tests for treatment effects in the *BRCAm* subgroup were inconclusive. The blinded independent review confirmed that the primary end point was met and reported a HR of 0.22 for olaparib versus placebo in the *BRCAm* subgroup (95% c.i. 0.12 to 0.40, $p<0.0001$).

Table 11: PFS data for whole population, *BRCAm* and *BRCA* wild type subgroups

Outcome	Population	Olaparib Median, months (95% c.i.)	Placebo Median, months (95% c.i.)	Comparison HR (95% c.i.)	Notes
PFS (DCO June 2010)	Whole population	8.4	4.8	0.35 (0.25 to 0.49, $p<0.001$)	Primary end point was met Subgroup analyses all showed lower risk of progression in olaparib group, though not statistically significant in those ≥65 years
	BRCAm (g & t)	11.2 (8.3 to not calculable)	4.3 (3.0 to 5.4)	0.18 (0.10 to 0.31, $p<0.0001$) Blinded independent review confirmed primary end point: HR 0.22 (0.12 to 0.40, $p<0.0001$) Log rank test (stratified by randomisation factors) HR: 0.18 (0.13 to 0.25, $p<0.0001$)	Subgroup analyses all showed statistically significantly lower risk of progression in olaparib group
	BRCA wild type	7.4 (5.5 to 10.3)	5.5 (3.7 to 5.6)	0.54 (0.34 to 0.85, $p=0.0075$)	
	gBRCA				"statistically significant benefit in PFS"[24]

BRCA – breast cancer susceptibility gene; g- germline; t – tumour; PFS – progression-free survival; HR – hazard ratio; c.i. – confidence interval; DCO – data cut-off

Figure 2: Kaplan-Meier curve for PFS in the *BRCAm* subgroup (reproduced from CS[1] Figure 6.5)



PFS, progression-free survival; PSR, platinum-sensitive relapsed

Overall survival

The results for OS are presented in Table 12. OS was analysed at two key dates: at the same time as PFS (DCO June 2010), and at 58% maturity (DCO November 2012). As detailed in Section 4.2.1.5, the second "interim" OS analysis was added to the analysis plan after the results of the June 2010 analysis were known. A further 85% maturity analysis was added to the plan in October 2012, one month before the 58% maturity analysis was reached. [redacted] The study was not powered for this outcome.

Table 12: Summary of overall survival results

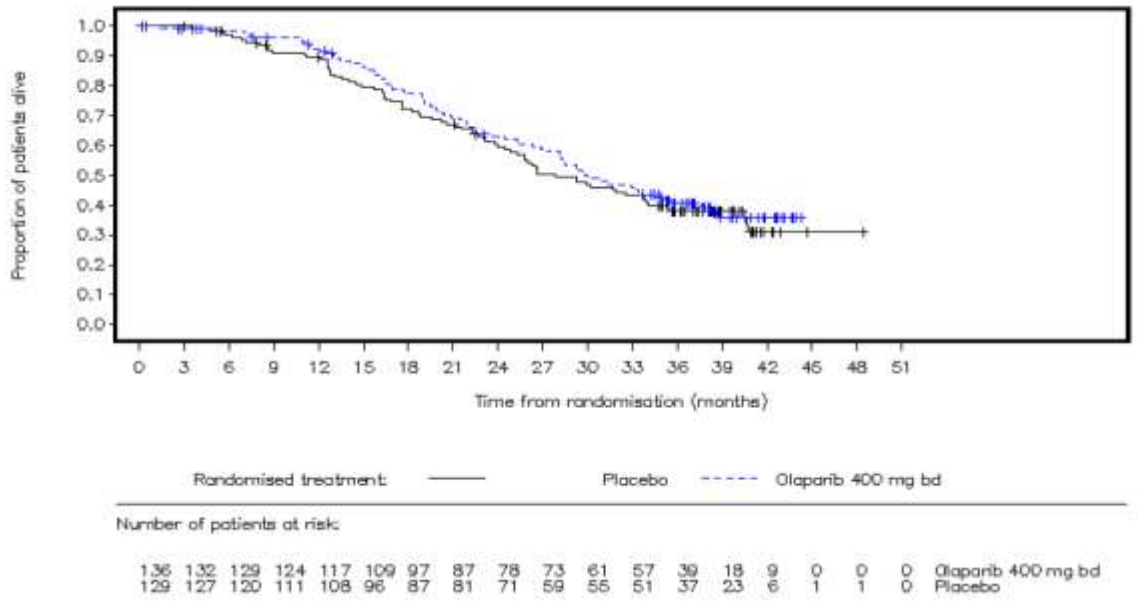
Outcome	Population	Olaparib Median, months (95% c.i.)	Placebo Median, months (95% c.i.)	Comparison HR (95% c.i.)
OS at DCO June 2010	Whole population (38% maturity)	29.7 (NR)	29.9 (NR)	0.94 (0.63 to 1.39; *p*= 0.75)
OS at DCO Nov 2012	Whole population (58% maturity)	29.8 (27.2 to 35.7)	27.8 (24.4 to 34.0)	0.88 (0.64 to 1.21, *p*=0.44)
	gBRCAm (52% maturity)[24]	NR	NR	0.74 (0.46, 1.19; *p*=0.20813)
	BRCAm (52% maturity)	34.9 (29.2 to not calculable)	31.9 (23.1 to 40.7)	0.73 (0.45 to 1.17, *p*=0.19)
	BRCA wild type	24.5 (19.8 to 35.0)	26.2 (22.6 to 33.7)	0.99 (0.63 to 1.55, *p*=0.96)
OS at DCO Nov 2012, excluding crossover sites (25% patients excluded)	*BRCAm* (52% maturity)	34.9 (NR)	26.6 (NR)	0.52 (0.28 to 0.97, nominal *p*=0.039)
OS using RPSFT to adjust for crossover	*BRCAm* (52% maturity)	NR	NR	[redacted]

BRCA – breast cancer susceptibility gene; DCO – data cut-off; HR – hazard ratio; c.i. – confidence interval; NR – not reported

Whole population

As shown in Table 12, none of the analyses conducted for the whole population to date have shown a statistically significant survival benefit. In the whole population analysis performed at the same time as the PFS analysis (OS data 38% mature), the HR was 0.94 (95% c.i. 0.63 to 1.39; *p*= 0.75) for olaparib versus placebo (median OS 29.7 months versus 29.9 months respectively, 95% c.i. not reported). At 58% OS data maturity, the HR was 0.88 (95% c.i. 0.64 to 1.21, *p*=0.44) for olaparib versus placebo, with a median survival of 29.8 months (95% c.i. 27.2 to 35.7) in the olaparib arm, versus 27.8 months (95% c.i. 24.4 to 34.0) in the placebo arm. The Kaplan-Meier curve for the 58% data maturity analysis is presented in Figure 3. It can be seen that the curves did not have a clear separation, in keeping with the HR which showed no significant survival difference between the study groups. The 85% analysis point has not yet been reached, and an analysis correcting for crossover to a PARP inhibitor was not presented for the whole population in the CS.[1]

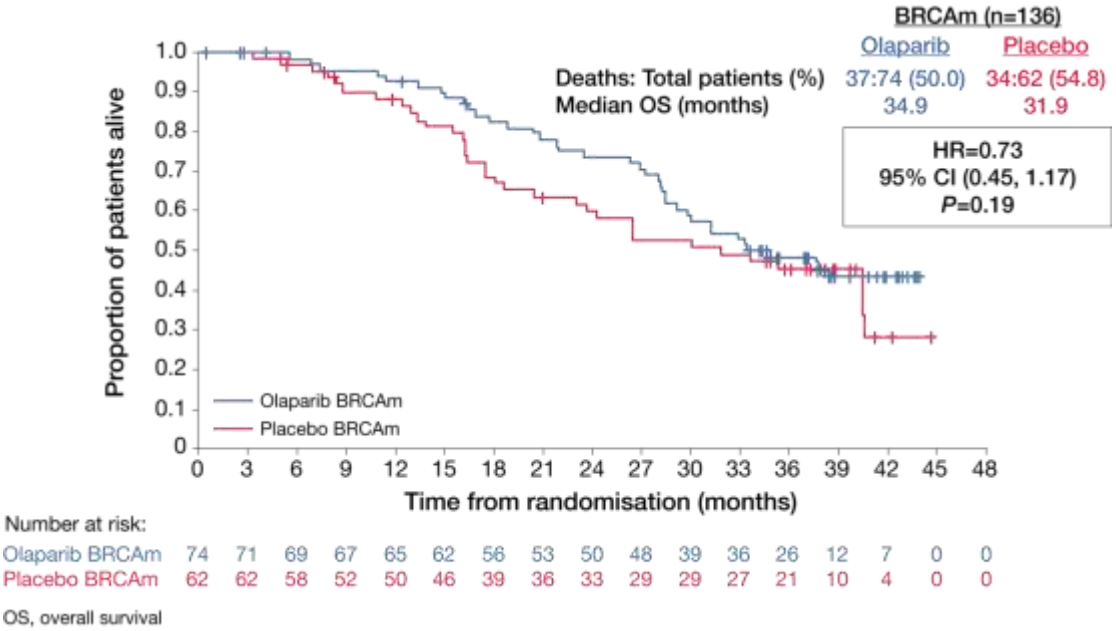
Figure 3: Kaplan-Meier plot of overall survival for the whole population – 58% maturity (reproduced from CSR[24] Figure 7)



BRCAm subgroup

For OS in the *BRCAm* subgroup, it should be noted that whereas it is stated that PFS was added to the statistical plan before the DCO was reached, it is unclear if OS was also added at this point, or whether this analysis was one of the "full analyses of all endpoints" described as having been *"conducted after discussion with regulatory agencies"* (see CS[1] page 72). This would make it a *post hoc* analysis. For the *BRCAm* subgroup, OS at the first DCO (38% maturity) was not reported in the CS,[1] the CSR[24] or in the relevant journal articles.[14,22] At the DCO, data maturity was 52%. Results are presented in the CSR,[24] with a non-statistically significant HR of 0.74 (95% c.i. 0.46 to 1.19, p=0.20813) for olaparib versus placebo, and a median OS of 34.9 months in the olaparib group and 31.9 months in the placebo group. Results presented in the CS[1] differ slightly with a reported HR of 0.73 (95% c.i. 0.45 to 1.17, p=0.19), though median survival in months remains the same. The Kaplan-Meier curve is presented in Figure 4; this shows that the survival curves diverge between approximately 9 months and 34 months, but merge and cross between approximately 36 months and 40 months. Thereafter, the curves appear to be diverging again, but with only a few weeks' data and low numbers of patients at risk, it is difficult to determine whether this is a fluctuation or an emerging trend.

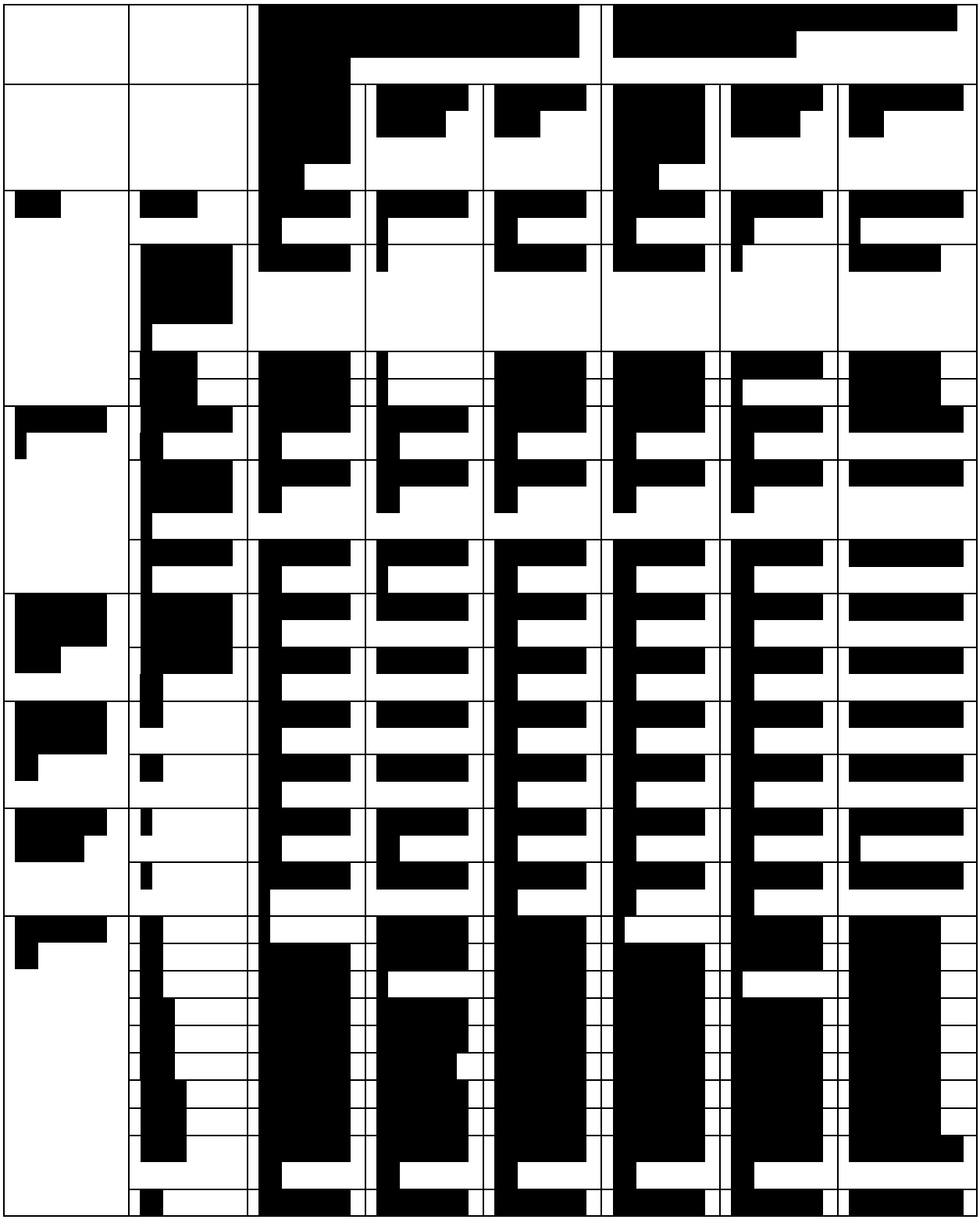
Figure 4: Kaplan-Meier curve for OS in the *BRCAm* subgroup (reproduced from CS[1] Figure 6.7)

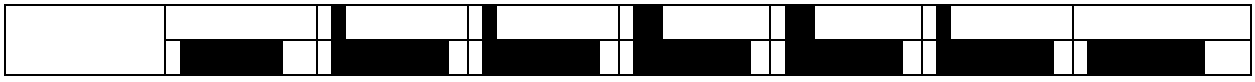


The CS[1] states that patients were not allowed to "cross-over" study arms during the treatment period (this was initially unclear but was later clarified in the company's clarification response,[9] question A2). Patients were, however, allowed to receive subsequent PARP inhibitor therapy after the PFS DCO. As such, all outcomes subsequent to PFS are subject to potential confounding by subsequent PARP therapy. This is likely to operate against olaparib as PARP inhibitors were generally only available through clinical trials, and all trials running at the time excluded patients who had already received a PARP inhibitor. As such, no patients in the olaparib arm received a subsequent PARP inhibitor, but 23% (14 of 62 patients) of the placebo group did. Within the CS,[1] the company presented a [redacted]. In response to a request for clarification[9] (question A2), the company provided a table summarising the baseline characteristics in the crossover-site excluded dataset and the total *BRCAm* subgroup (see Table 13). The company's clarification response states that *"In general, baseline characteristics in the CSE analysis set were balanced or favoured placebo group* [redacted][9] Interestingly, in this clarification, the company failed to report ECOG status which was known to be skewed in favour of olaparib (see Table 6) in the *BRCAm* subgroup, but reported FIGO stages which were not

reported in the CS originally. The ERG notes that the exclusion of crossover sites reduced the overall sample size for the analysis from 136 patients to 97 patients (olaparib n=57; placebo n=40) and led to the exclusion of 4 of the 9 UK centres included in the trial.[9]

Table 13: Patient characteristics in crossover-site excluded analysis versus *BRCAm* population (reproduced from clarification response[9])





The ERG sought clarification regarding why only one method of adjusting for treatment switching had been used when several other methods are available. The company provided an additional analysis using the RPSFTM method in their clarification response.[9] This approach estimates counterfactual survival times in the crossover-affected group that, in theory, would have been observed if no active treatment had been given. The two key assumptions underpinning this method are:

(1) The "common treatment effect" assumption - the treatment effect (an "acceleration factor", or "time ratio") is assumed to be equal, relative to the time for which the treatment is taken, for all patients irrespective of when the treatment is received.
(2) The "exclusion restriction assumption" - the randomisation of the trial means that there is only random variation between treatment groups at baseline, apart from treatment allocated – untreated survival times must be independent of the randomised treatment group.[33]

The company's clarification response also stated that whilst other methods for adjusting for crossover were considered, namely the Inverse Probability of Censoring Weights (IPCW) approach and the 2-stage Weibull approach, these were not considered to be suitable in this instance as the "no unmeasured confounders" assumption is not met due to data collection on the time-dependent factors, which may have affected the decision to crossover, stopping a considerable time prior to the time at which treatment switching occurred.

OS results adjusted for placebo group crossover using the crossover site exclusion method and the RPSFTM approach are summarised in Table 12. As can be seen from Table 12, the analysis where study sites were excluded provides a statistically significant difference in OS between olaparib and placebo for BRCAm patients, with a reported HR of 0.52 (95% c.i. 0.28 to 0.97, nominal p=0.039). Median survival was 34.9 months in the olaparib arm and 26.6 months in the placebo arm." The RPFSTM analysis presented in the clarification response[9] produced *"three plausible outcomes* [redacted], *all generating a numerical improvement in OS HR compared to the ITT for BRCAm population,* [redacted] *The adjusted HR is dependent on both proportion of switchers and the length of the time period the switchers stay on active treatment"* (see clarification response[9] question A2). It is not clear from the data provided if the HRs indicated a statistically significant difference between treatment arms as confidence intervals and *p*-values were not reported. The company notes that the numerical difference in HRs between the original analysis and the RPSFT analysis supports the notion that confounding was introduced by

switching to PARPs from the placebo group. However, the company also notes in the clarification response[9] that *"there remains a large degree of uncertainty in the treatment effect due to the small sample sizes and the data maturity. A further analysis on more mature data would be valuable to confirm these findings."*[9]

The ERG makes the following observations regarding the crossover analyses presented by the company:

- The company's rationale for not pursuing other statistical methods for adjusting for treatment switching, such as the 2-stage Weibull or the IPCW approach, appears reasonable.
- Correction was not made for olaparib patients who continued on treatment beyond disease progression. These patients may have received benefit from continued treatment and this should have been corrected for. This may not be as substantial a source of bias as placebo group patients crossing over, as continuing treatment is unlikely to be as beneficial as an entire course of treatment with a PARP inhibitor (i.e. the benefit gained would probably be less than for the placebo patients who crossed over). However, this correction should have been attempted. As such, the results may be biased in favour of olaparib in both of the crossover analyses presented.
- There is no obvious theoretical reason why the removal of whole study sites where patients were allowed to switch should introduce bias. This is especially the case as the same randomisation schedule was used at all sites. As such, this seems a fair primary analysis to present. However, the already small sample size for the *BRCAm* subgroup was reduced further by this approach.
- Although confidence intervals for the acceleration factors were unobtainable, commonly the ITT *p*-value would be retained for the adjusted HR, so confidence intervals for the adjusted HR could have been presented[34] and would be non-significant.
- The company could have considered alternative methods for applying the RPSFTM (such as a "treatment group" basis) which may have allowed confidence intervals to have been obtained.[33] This would also allow an investigation into the impact of making different assumptions around the durability of the treatment effect.
- Clarification should have been given regarding whether re-censoring was used and results (adjusted HRs and counterfactual survival times) both with and without re-censoring should have been presented. Excluding re-censoring may mean that results are prone to bias from informative censoring; this may operate in either direction. An analysis where re-censoring is performed could also introduce bias which could operate in either direction (e.g. if the treatment effect is not constant over time).

- Overall, the main advantage of the RPSFTM is that it retains patients who would otherwise be excluded using the crossover-site exclusion method, albeit at the cost of making assumptions, particularly around the commonality of the treatment effect.

TTD/D, TFST/D and TSST/D

The results for TFST/D, TSST/D and TTD/D are presented in Table 14. These proxy outcomes were all defined *post hoc*. It is important to note that these analyses, or variants of them, were key inputs to the company's health economic model (see Chapter 5). The nature of the outcomes and the potential for bias has been previously discussed in Section 4.2.1.4.

Time to treatment discontinuation or death

The HR for TTD/D was 0.39 (95% c.i. 0.30 to 0.51) for the whole population, and 0.36 (95% c.i. 0.24 to 0.53) for the *BRCAm* subgroup (median TTD/D was 11.0 months in the olaparib arm versus 4.6 months in the placebo arm). Figure 5 displays the Kaplan-Meier curve for TTD/D, which shows separation between the lines. This outcome may be confounded by patients continuing on treatment after progression and is probably a less reliable outcome than PFS.

Time to first subsequent therapy or death

The HR for TFST/D was 0.41 (95% c.i. 0.31 to 0.54) for the whole population, and 0.33 (95% c.i. 0.22 to 0.50) for the *BRCAm* subgroup (median TFST/D was 15.6 months in the olaparib arm versus 6.2 months in the placebo arm). Figure 6 presents the Kaplan-Meier curve for TFST/D, which shows separation between the lines. This outcome may be confounded by patients continuing on therapy in the olaparib group and by switching of patients from placebo to a PARP inhibitor, which could affect TFST/D in the placebo arm (if treatment was received earlier or later because of the trial protocol), and may bias results in an unknown direction. In the *BRCAm* subgroup, 5 out of the 14 placebo group patients who crossed over received a PARP inhibitor as their first subsequent therapy.[9]

Time to second subsequent therapy or death

The HR for TSST/D was 0.54 (95% c.i. 0.41 to 0.72) for the whole population, and 0.44 (95% c.i. 0.29 to 0.67) for the *BRCAm* subgroup (median TSST/D was 23.8 months in the olaparib arm versus 15.2 months in the placebo arm). Figure 7 presents the Kaplan-Meier curve for TSST/D, which shows separation between the lines. This outcome may be confounded by patients in the olaparib group continuing on treatment and by placebo patients crossing over to receive a PARP inhibitor.

Table 14: Summary of TFST/D, TSST/D and TTD/D outcomes for whole population and *BRCA* subgroups

Outcome	Population	Olaparib Events or median time	Placebo Events or median time	Comparison HR (95% c.i.)	Source
TTD/D (DCO Nov 2012)	Whole population	113/136 (83.1%)	125/128 (97.7%)	0.39 (0.30 to 0.51)	CSR[24]
	BRCAm	11.0 months	4.6 months	0.36 (0.24 to 0.53, nominal p<0.00001)	CS[1]
TFST/D (DCO Nov 2012)	Whole population	95/136 (69.9%)	118/128 (92.2%)	0.41 (0.31 to 0.54)	CSR[24]
	BRCAm	15.6 months	6.2 months	0.33 (0.22, 0.50, nominal p<0.00001)	CS[1]
TSST/D (DCO Nov 2012)	Whole population	88/136 (64.7%)	108/128 (84.4%)	0.54 (0.41 to 0.72)	CSR[24]
	BRCAm	23.8 months	15.2 months	0.44 (0.29 to 0.67, nominal p=0.00013)	CS[1]

BRCA – breast cancer susceptibility gene; DCO – data cut-off; HR – hazard ratio; c.i. – confidence interval; CSR – clinical study report; CS – company's submission

Figure 5: Kaplan-Meier curve for TTD/D in the *BRCA*m subgroup (reproduced from CS[1] Figure 6.9)

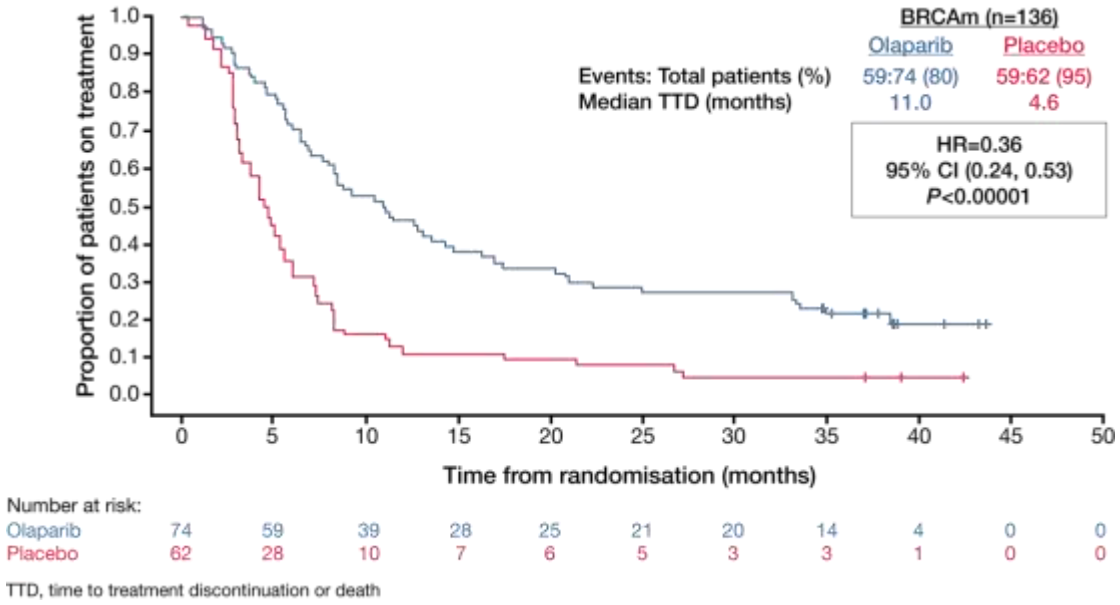
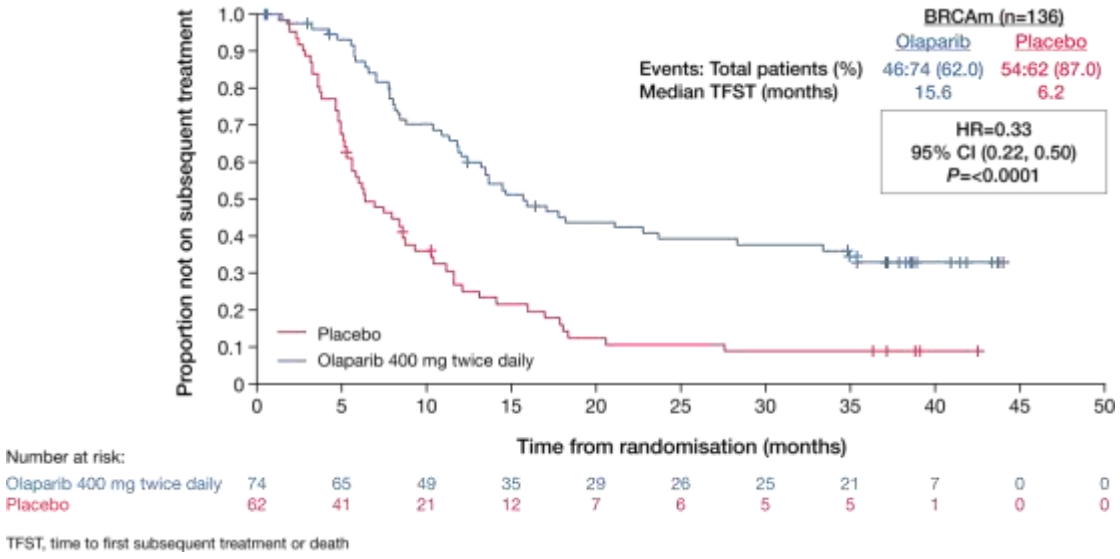
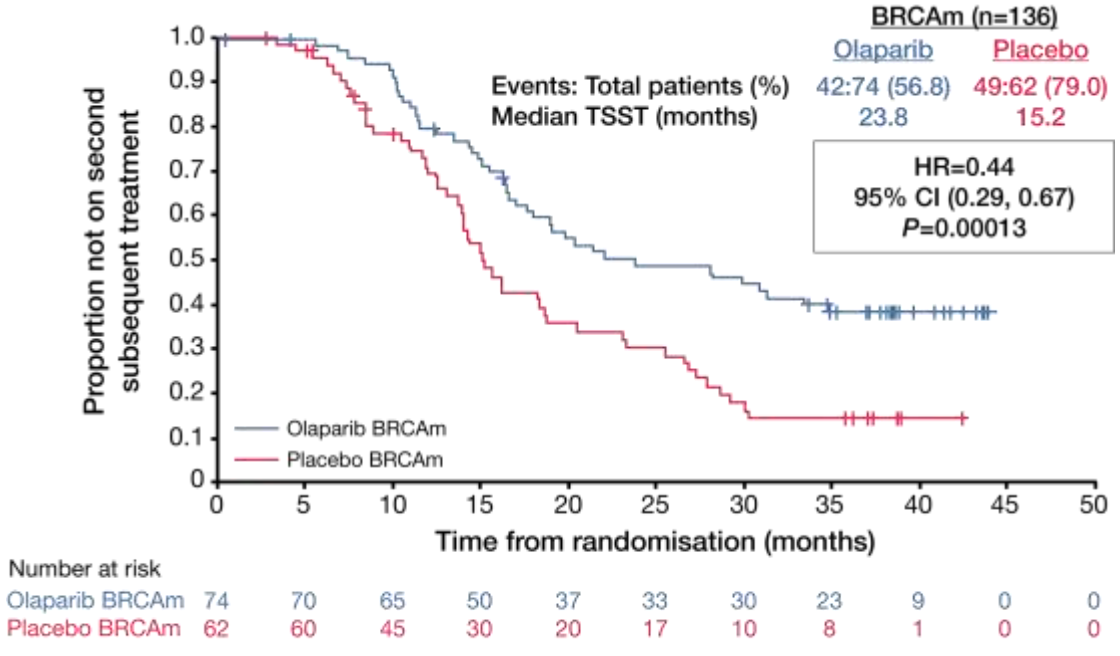


Figure 6: Kaplan-Meier curve for TFST/D in the *BRCA*m subgroup (reproduced from CS[1] Figure 6.10)



TFST, time to first subsequent treatment or death

Figure 7: Kaplan-Meier curve for TSST/D in the *BRCA*m subgroup (reproduced from CS[1] Figure 6.11)



TSST, time to second subsequent treatment or death

Quality of life

TOI and FOSI comprise subsets of questions from FACT-O. TOI was considered the primary outcome measure for HRQoL.[32] Only "best response" scores were presented, rather than aggregate

data from the whole period of measurement. Ledermann *et al*., 2014[35] reported that there was *"no significant difference in improvement rates or time to worsening of TOI, FOSI or Total FACT-O"* and concluded that HRQoL was not negatively impacted during the therapy. Any HRQoL gains associated with olaparib are likely to have been the result of avoided rounds of chemotherapy, rather than gains during maintenance therapy itself. However, the study did not record HRQoL for the duration of the follow-up period, so there is no direct evidence to support this theoretical gain.

Table 15: HRQoL best response for the *BRCA*m subgroup (adapted from CS[1] Table 6.8)

	Olaparib	**Placebo**
TOI, n (%)	**n=64**	**n=53**
Improved*	16 (25.0)	10 (18.9)
No change†	38 (59.4)	30 (56.6)
Worsened‡	7 (10.9)	10 (18.9)
Non-evaluable	3 (4.7)	3 (5.7)
FOSI, n (%)	**n=66**	**n=56**
Improved*	14 (21.2)	9 (16.1)
No change†	39 (59.1)	36 (64.3)
Worsened‡	11 (16.7)	9 (16.1)
Non-evaluable	2 (3.0)	2 (3.6)
FACT-O, n (%)	**n=63**	**n=53**
Improved*	17 (27.0)	11 (20.8)
No change†	35 (55.6)	26 (49.1)
Worsened‡	10 (15.9)	14 (26.4)
Non-evaluable	1 (1.6)	2 (3.8)

*For the patient-reported outcome measures, patients were asked to indicate, using a five-point Likert scale (not at all [0], a little bit [1], somewhat [2], quite a bit [3] and very much [4]), the severity of a given symptom or impact over the past 7 days; negatively stated questions were reversed so that higher scores indicated better well-being. *Best response of improved defined as two visit responses of 'improved' a minimum of 21 days apart without an intervening visit response of 'worsened'; †Defined as two visit responses of 'no change' or a response of 'no change' and a response of 'improved' a minimum of 21 days apart without an intervening visit response of 'worsened'. No change is defined as a change from baseline of greater than –7 (TOI), –3 (FOSI), –9 (FACT-O), but less than +7 (TOI), +3 (FOSI), +9 (FACT-O); ‡Defined as a visit of 'worsened' without a response of 'improved' or 'no change' within 21 days. Worsened is defined as a change from baseline of less than or equal to –7 (TOI), –3 (FOSI), –9 (FACT-O). Source: Ledermann et al. ESMO 2014. Poster 885PD*

Adverse events

The company presented AEs that occurred in >10% of patients, and events ≥ grade 3 that occurred in ≥3% of patients in either treatment group. It appears the selection criteria for reporting was applied to the whole population rather than the *BRCAm* subgroup, although data for both groups were presented in Table 6.9 of the CS.[1] These data are reproduced in Table 16. The footnotes to this table list grade 4 events that occurred in <3% of patients and were therefore not listed in the table.

All adverse events

The CS states that *"the most frequently occurring AEs are generally intermittent and low grade (CTCAE grade 1 or 2). Common AEs within the study did not generally require dose modifications or lead to discontinuation of treatment. The overall pattern of AEs in the BRCA mutation subgroup was generally consistent with the pattern of AEs in the overall patient population"* (CS[1] page 92). A greater proportion of people experienced AEs in the olaparib arm than the placebo arm in the whole

population (olaparib 97% versus placebo 93%), and in the *BRCAm* subgroup (olaparib 97% versus placebo 94%). The AEs that affected the most people in the whole population were nausea (71% in the olaparib arm, 36% in the placebo arm), fatigue (52% versus 39% respectively), vomiting (34% versus 14% respectively), diarrhoea (27% versus 24%) and abdominal pain (25% versus 27%). As shown in Table 16, the proportions of patients experiencing these events in each treatment group were similar in the *BRCAm* subgroup. Interestingly, abdominal pain was the only AE where the proportion of patients was similar, and even slightly higher in the placebo arm compared with the olaparib arm.

Severe adverse events ≥ grade 3

Severe AEs ≥ grade 3 affected a fairly high proportion of patients in the olaparib arm compared with the placebo arm (whole population - olaparib 40% versus placebo 22%; *BRCAm* group - olaparib 38% versus placebo 18%). The most common of these were fatigue (7% versus 3% in the whole population, 7% versus 2% in the *BRCAm* subgroup), anaemia (5% versus <1% in the whole population, 5% versus 2% in the *BRCAm* subgroup) and neutropenia (4% versus <1% in the whole population, 4% versus 2% in the *BRCAm* subgroup). Three of the neutropenia patients experienced grade 4 events.

Serious adverse events

Twenty two *BRCAm* patients reported at least one SAE during treatment or within 30 days of the end of their treatment.[1] The incidence of SAEs was higher in the olaparib arm than the placebo arm (21.6% versus 9.7%, respectively). The company states that in the whole population, *"Overall the most frequently reported SAEs were anaemia (three patients on olaparib), small bowel obstruction (two patients on olaparib and three on placebo), dyspnoea (two patients on olaparib) and gastritis (two patients on placebo)"* (CS[1] page 95).

Mortality

For the *BRCAm* subgroup, a higher proportion of patients in the placebo arm died (50% in the olaparib arm, versus 54.8% in the placebo arm). Proportionately fewer deaths during the study were due to ovarian cancer in the olaparib arm (83.8% of deaths), versus the placebo arm (88.2%). There is a lack of clarity in the CS around the causes of the remaining deaths. It is stated that 9 deaths were not attributable to ovarian cancer, but only 8 are listed in the table describing deaths in the *BRCAm* subgroup (see CS[1] Table 6.11). Of these, a haemorrhagic stroke and a case of progression with MDS were attributed in full or in part to the study treatment, and whilst the company's clarification response[9] reveals that the MDS death was in the olaparib arm, it is unclear in which arm the other death occurred. If it is assumed both occurred in the olaparib arm, this may make sense of the 4 "other" deaths described in Table 6.11 of the CS[1] as belonging to the olaparib arm, as this would total

37, the number of deaths in the olaparib arm. It is likely that the sample size in this study was too small to conclusively identify any differences in mortality between the treatment groups.

The company also presented pooled data from all olaparib monotherapy studies of the licenced dose, across a range of tumour types. This supported the findings of Study 19 in that the proportions of events in the treatment arms are similar. These results are presented in Table 17.

MDS/AML

The ERG sought clarification regarding the incidence of MDS/AML events, as these have been highlighted as potentially problematic in olaparib-treated patients.[11] MDS and AML are a common side effect of chemotherapeutic treatments, and the company state that the cumulative incidence of MDS/AML in olaparib trials (0.7%) is within the published range for this patient population (0.3 to 1.5%). However, this range is not referenced. The clarification response stated the following regarding ongoing monitoring:

"These events are closely monitored in ongoing studies. Additional pharmacovigilance activities will be undertaken to further understand the potential risk of MDS/AML as fully as possible in the context of the benefit to patients with advanced platinum sensitive relapsed ovarian cancers, including annual reports and a non interventional study. Post-marketing risk-minimization measures for haematological toxicity focus on providing information about the benefit:risk profile to prescribers and patients via the SmPC (Warnings and Precautions). Specifically: Patients should not start treatment with olaparib until they have recovered from haematological toxicity due to prior chemotherapy, and should be followed by monthly blood count monitoring during the first year of treatment. At signs of severe toxicity or blood transfusion dependence, treatment should be interrupted. If the blood parameters remain clinically abnormal after 4 weeks of dose interruption, bone marrow analysis and/or blood cytogenetics are recommended" (clarification response[9] question A9).

Other issues

The company highlighted additional safety information relating to pneumonitis, embryofoetal toxicity, pregnancy and interactions from the SmPC[11] (see CS[1] page 97).

Dose modifications and treatment discontinuation due to AEs

In the *BRCAm* group, 32.4% of olaparib patients and 8.1% of placebo patients had dose interruptions, and 21.6% of olaparib patients and 3.23% of placebo patients had dose reductions to address AEs. 8.1% of olaparib patients discontinued treatment, versus 0% of placebo patients. According to the CS,[1] results were consistent with the whole population. These results suggest that the treatment is poorly tolerated in some cases.

Table 16: Adverse events (any grade) in ≥10% of patients overall and grade ≥3 events in ≥3% of patients in either treatment group (reproduced from CS[1] Table 6.9)

AE	Overall patient population, n (%)				Patients with *BRCA* mutation, n (%)			
	All grades		Grade ≥3		All grades		Grade ≥3	
	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=136)	Placebo (n=128)	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=74)	Placebo (n=62)
Patients with any AE	132 (97)	119 (93)	55 (40)	28 (22)	72 (97)	58 (94)	28 (38)	11 (18)
Nausea	96 (71)	46 (36)	3 (2)	0	54 (73)	20 (32)	1 (1)	0
Fatigue	71 (52)	50 (39)	10 (7)	4 (3)	40 (54)	23 (37)	5 (7)	1 (2)
Vomiting	46 (34)	18 (14)	3 (2)	1 (<1)	27 (36)	5 (8)	2 (3)	0
Diarrhoea	37 (27)	31 (24)	3 (2)	3 (2)	22 (30)	12 (19)	2 (3)	1 (2)
Abdominal pain	34 (25)	34 (27)	3 (2)	4 (3)	17 (23)	18 (29)	0	2 (3)
Anaemia	29 (21)	7 (5)	7 (5)	1 (<1)	19 (26)	3 (5)	4 (5)	1 (2)
Headache	28 (21)	16 (13)	0	1 (<1)	13 (18)	10 (16)	0	1 (2)
Constipation	28 (21)	14 (11)	0	0	14 (19)	7 (11)	0	0
Decreased appetite	28 (21)	17 (13)	0	0	14 (19)	6 (10)	0	0
Dyspepsia	24 (18)	11 (9)	0	0	13 (18)	4 (6)	0	0
Cough	24 (18)	13 (10)	0	0	11 (15)	7 (11)	0	0
Upper abdominal pain	24 (18)	10 (8)	0	1 (<1)	14 (19)	4 (6)	0	0
Arthralgia	23 (17)	18 (14)	1 (<1)	0	11 (15)	10 (16)	1 (1)	0
Back pain	22 (16)	14 (11)	3 (2)	0	14 (19)	9 (15)	2 (3)	0
Dysgeusia	22 (16)	8 (6)	0	0	14 (19)	4 (6)	0	0
Nasopharyngitis	20 (15)	14 (11)	0	0	10 (14)	4 (6)	0	0
Asthenia	19 (14)	12 (9)	1 (<1)	0	12 (16)	8 (13)	1 (1)	0
Dizziness	18 (13)	9 (7)	0	0	11 (15)	3 (5)	0	0
Abdominal distension	17 (13)	11 (9)	0	0	9 (12)	6 (10)	0	0
Neutropenia	7 (5)	5 (4)	5 (4)*	1 (<1)	5 (7)	3 (5)	3 (4)†	1 (2)

*Grade 4 events not listed are: increased blood amylase (n=1, olaparib group), increased blood creatine phosphokinase (n=2, olaparib group), leucopenia (n=1, olaparib group [BRCA mutation subgroup]), pulmonary embolism (n=1, olaparib group [BRCA mutation subgroup]), small intestinal obstruction (n=2, olaparib group; n=1 placebo group [BRCA mutation subgroup]), thrombocytopenia (n=1, olaparib group [BRCA mutation subgroup]). Grade 5 events not listed are: cholestatic jaundice (n=1, olaparib group [BRCA mutation subgroup]), haemorrhagic stroke (n=1, olaparib group [BRCA mutation subgroup]). AE: adverse event. *Includes three patients with a grade 4 AE. †Includes one patient with a grade 4 AE.*

Table 17: Number of adverse events reported in *BRCA*m and overall patient populations treated with olaparib (reproduced from CS[1] Table 6.10)

AE category	Groups of patients exposed to olaparib 400 mg b.i.d. monotherapy, n(%)			
	All patients with advanced solid tumours n=735	***BRCA*m ovarian cancer n=397**	**Study 19 – all patients n=136**	**Study 19 – *BRCA*m n=74**
Any AE	718 (97.7)	387 (97.5)	132 (97.1)	72 (97.3)
Any AE causally related to study treatment	640 (87.1)	357 (89.9)	122 (89.7)	67 (90.5)
Any AE of CTCAE grade 3 or higher	334 (45.4)	189 (47.6)	56 (41.2)	29 (39.2)
Any AE with outcome = death	14 (1.9)	10 (2.5)	1 (0.7)	1 (1.4)
Any SAE (including events with outcome = death)	185 (25.2)	110 (27.7)	25 (18.4)	16 (21.6)
Any AE leading to discontinuation of study treatment	43 (5.9)	23 (5.8)	6 (4.4)	5 (6.8)

Source: EMA Lynparza assessment report[36]

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

As the relevance of the review to the decision problem could not be ascertained from the CS, the ERG conducted the following actions to ascertain whether studies were missing:

(1) The ERG conducted a focussed search of RCTs relating to olaparib (search strategy presented in Appendix 4). This did not reveal any missed studies

(2) The ERG consulted the EPAR.[23] No additional studies were identified.

4.6 Conclusions on the clinical effectiveness evidence

4.6.1 Summary of concerns regarding the clinical evidence base for olaparib

The ERG has a number of concerns relating to the data presented in the CS.[1] Whilst the CS was considered to be complete with respect to relevant clinical studies and relevant data from those

studies, (though in places only *BRCAm* subgroup data have been presented), the ERG has identified problems that threaten the validity of the study. In the opinion of the ERG, it would not be an exaggeration to suggest that the evidence base is extremely weak if judged against conventional standards of evidence-based medicine. A summary of these problems is detailed below.

Study design

There are two major problems with the study design: (i) Study 19 is a Phase II trial, and; (ii) the only data available are from an analysis of a subgroup that was defined after the study commenced.

These problems mean that the data are somewhat isolated: the study did not set out to test the hypothesis that *BRCAm* patients are a clinically valid subgroup who will gain a greater advantage from treatment than those patients not receiving treatment. There are also currently no subsequent data to confirm the findings of the subgroup analyses of the study, although a Phase III trial is ongoing (clinicaltrials.gov identifier - NCT01874353). The identification of this subgroup could be considered to have been a clinically relevant consideration, added shortly prior to the June 2010 DCO, nevertheless this remains subject to a considerable risk of bias. To compound this problem, the interaction tests that were performed were not reported in the CS[1] and appear inconclusive, meaning that it is currently unclear whether the *BRCAm* subgroup is statistically different to the whole population. As this has not been demonstrated with certainty, it is possible to argue that a difference in efficacy between the *BRCAm* subgroup and the remaining *BRCA* wild type subgroup does not exist, and that the results for the whole population should be considered the most plausible estimate of efficacy for olaparib.

Additional issues with the design and conduct of the study include:

- Concerns regarding the similarity of Study 19 to clinical practice in England in terms of how progression is defined, and when subsequent chemotherapy is initiated in relation to progression. This could affect the generalisability of the results of Study 19.
- The IVRS used in randomisation apparently mis-stratified some patients, resulting in imbalances in known prognostic factors (PR/CR), and may have impacted on unknown prognostic factors.
- Un-blinding occurred in around 20% of patients after disease progression, usually to enable patients to enter a subsequent clinical trial. This may have impacted on outcomes recorded after PFS such as TFST/D and TSST/D, as clinicians may have hastened subsequent chemotherapy for those in the placebo group, or clinical trial protocols may have dictated a different practice in terms of time to initiation of subsequent chemotherapy.

There are also a number of protocol changes which may have affected the estimates of efficacy produced from the study. These include:

- Multiple amendments to the timing of OS analyses
- The addition of *post hoc* outcomes TFST/D, TSST/D and TTD/D
- *Post hoc* changes to how *BRCA* status was determined. At study outset, no *BRCA* testing was planned. In a *post hoc* amendment, after some evidence of enhanced efficacy in *BRCA* patients was observed, testing was implemented for all patients, including not only germline but also tumour *BRCA* status.
- The *post hoc* addition of all study outcomes to the *BRCA* subgroup analysis. It is unclear which outcomes were added to the plan in the round of changes that introduced the *BRCA* subgroup in June 2010.

Patient spectrum

The ERG notes the following concerns regarding the patient spectrum within Study 19:

- The population within Study 19 was wider than the population specified within the marketing authorisation for olaparib;[11] all supporting data are subgroup data from Study 19.
- A greater proportion of patients in the olaparib arm had ECOG performance status "normal" than in the placebo arm. Results were not adjusted for this factor.
- The *BRCAm* subgroup was generally younger than the whole population, which may bias results. The direction of this potential bias is unknown.
- A greater proportion of patients in the olaparib arm had a PR to their most recent platinum-based chemotherapy compared against placebo patients; this may bias results which have not been adjusted for this factor (some outcomes were adjusted, but it is not always clear which) in an unknown direction, but possibly in favour of olaparib based on subgroup analyses presented in Figure 6.6 of the CS.

Intervention

- Patients were allowed to continue on study treatment following objective progression, which is not in line with the wording of the marketing authorisation for olaparib.[11] This may have confounded any outcome recorded beyond PFS.
- It is unclear whether the definition of disease progression that dictated treatment termination and criteria that dictated subsequent treatment were, on average, comparable to clinical practice in England. These potential biases could operate in either direction, depending on whether CA-125 was used more or less frequently than in clinical practice.

Outcomes

- PFS is a proxy for OS. Whilst its use is acceptable for regulatory purposes, as it demonstrates some benefit to patients, it is not a substitute for OS.
- The study was not powered to detect a statistically significant difference in OS. This means that an absence of an OS advantage could reflect a type II error.
- TTD/D, TFST/D and TSST/D were all *post hoc* analyses.
- TTD/D is not a measure of real-world efficacy as patients were allowed to continue treatment after progression, and is not a measure of real-world drug use for the same reason.
- Crossover of placebo patients to PARP inhibitor treatment may have resulted in the confounding of outcomes recorded after PFS, as placebo patients receive the benefit of the PARP inhibitor. Crossover may also have caused patients in the placebo arm who enrolled in subsequent PARP inhibitor trials to have received either their first or second subsequent therapy earlier than would be expected in usual clinical practice, depending on eligibility and treatment criteria of the trial.

Table 18 summarises the factors which may have affected the estimates of efficacy produced in Study 19.

Table 18: Summary of factors that may affect the estimates of efficacy produced in Study 19

Item	Issue	Likely effect in opinion of the ERG	Likely direction in opinion of the ERG
Systematic review	Systematic review irregularities	• None	None
Study design	Use of subgroup data only to support submission	• Possibility of a Type I error	May favour olaparib
	Subgroup defined after the study commenced	• Risk of data mining having occurred	May favour olaparib
	Interaction tests inconclusive	• It is not clear whether the *BRCAm* subgroup is different to the whole population	Unclear
	Lack of consistent definition of "*BRCAm*" patients – initially only those with known status, study design changed to include testing of all patients and inclusion of tumour *BRCAm* patients as well as germline patients.	• Increase sample size to gain statistically significant results • Constitutes *post hoc* analysis	Increase statistical power
	Phase II clinical trial	• Results are unconfirmed	May favour olaparib
	Unclear if subsequent treatment immediately followed progression, which does not always occur in England	• Unclear, could shorten estimates of TFST/D and TSST/D compared with clinical practice	May disadvantage olaparib
	Randomisation IVRS mis-stratified patients	• Imbalances in groups with unknown impact on efficacy	Unclear
	Un-blinding occurred in around 20% patients after progression	• Hastened TFST/D or TSST/D • Affected other outcomes post-PFS	Unclear
	Multiple changes to study protocol and analysis plan	• Risk of data mining having occurred • Risk of manipulation of outcome times to favour drug	May favour olaparib
	Protocol deviations	• Various	Unclear
Patients	ECOG performance imbalance	• Bias in unknown direction	Unclear
	BRCA subgroup younger than whole population	• May be a confounder in *BRCA* subgroup analysis	Unclear
	PR/CR imbalance between olaparib and placebo arms in whole group and *BRCA* group	• Bias in unknown direction for outcomes where no adjustment for PR/CR	Unclear, may favour olaparib for PFS in *BRCAm* subgroup
	PR/CR imbalance between *BRCA* group and whole population	• May be a confounder in *BRCAm* subgroup analysis	Unclear
Intervention	Continuation of study treatment post-progression.	• Confounding of outcomes beyond PFS, likely to cause over-estimation of efficacy	May favour olaparib

Item	Issue	Likely effect in opinion of the ERG	Likely direction in opinion of the ERG
		• Especially likely to affect TTD/D, which will not reflect real-world clinical effectiveness or drug use	
	Unclear if "progression" defined in similar way to clinical practice in England, which impacts how long treatment given for	• Unclear, could affect generalisability and efficacy	Unclear
	Unclear if subsequent treatment administered according to same criteria as in clinical practice in England	• Unclear, could affect generalisability and efficacy	Unclear
Outcomes	PFS is a proxy for OS	• Unclear if there is an OS benefit	Favours olaparib at PFS assessment point
	Study not powered to detect difference in OS	• Cannot rule out a type II error in the absence of OS advantage being demonstrated	Favours olaparib at PFS assessment point
	TFST/D, TSST/D and TTD/D outcomes defined *post hoc*	• High risk of bias/ data mining having occurred • Not all outcomes requested by NICE	May favour olaparib
Crossover	Crossover of placebo patients to PARP inhibitor therapy post-progression	• May truncate estimates of TFST/D and TSST/D in placebo arm, favouring olaparib	May favour olaparib
		• May overestimate OS and TSST/D in the placebo arm, disadvantaging olaparib	Disadvantages olaparib

4.6.2 Summary of clinical effectiveness results

Bearing in mind the critique above, the results of the trial were as follows.

The primary endpoint was met, with a HR for PFS in the whole population of 0.35 (95% c.i. 0.25 to 0.49, $p<0.01$) for olaparib versus placebo (median PFS 8.4 months versus 4.8 months, 95% c.i. NR). Within the *BRCAm* subgroup, the reported HR for PFS was lower at 0.18 (95% c.i. 0.10 to 0.31, $p<0.0001$) for olaparib versus placebo; the median PFS for olaparib was 11.2 months (95% c.i. 8.3 to "not calculable") versus 4.3 months (95% c.i. 3.0 to 5.4) for placebo. Within the *BRCA* wild type subgroup, the HR for PFS was also significant, but higher at 0.54 (95% CI 0.34 to 0.85, $p= 0.0075$) for olaparib versus placebo; the median PFS for olaparib was 7.4 months (95% c.i. 5.5 to 10.3) versus 5.5 months (95% c.i. 3.7 to 5.6) for placebo.

There was no statistically significant effect on OS in the whole population when analysed at the same time as PFS (DCO June 2010). The HR for death was 0.94 (95% c.i. 0.63 to 1.39, *p*= 0.75) for olaparib versus placebo (median OS placebo 29.7 months versus placebo 29.9 months, respectively, 95% c.i. not reported). This does, however, meet the EMA's criterion[26] of showing no detrimental effect on OS. A later analysis at 58% OS data maturity was also not statistically significant, with a HR for death of 0.88 (95% c.i. 0.64 to 1.21, *p*=0.44) for olaparib versus placebo; median survival was 29.8 months (95% c.i. 27.2 to 35.7) in the olaparib arm versus 27.8 months (95% c.i. 24.4 to 34.0) in the placebo arm. The final 85% OS maturity analysis is yet to take place. In the *BRCAm* subgroup, OS was not reported at the first DCO in June 2010. A later analysis at 52% maturity was not statistically significant with a HR for death of 0.73 (95% c.i. 0.45 to 1.17, *p*=0.19) for olaparib versus placebo; median OS was reported to be 34.9 months in the olaparib group and 31.9 months in the placebo group.

A crossover analysis was performed whereby study sites that allowed placebo patients to crossover were omitted from the analysis. This analysis produced a statistically significant difference in OS between olaparib and placebo for *BRCAm* patients, with a HR of 0.52 (95% c.i. 0.28 to 0.97, nominal *p*=0.039). Within this analysis, median survival was 34.9 months in the olaparib arm, and 26.6 months in the placebo arm. The ERG consider this to be an adequate approach to correct for crossover and as such a median survival advantage is likely for olaparib, according to this analysis. As part of the their response to clarification questions from the ERG,[9] the company also used the RPSFTM approach to adjust for placebo group crossover. [redacted] The main advantage of the RPSFTM method is that it retains patients who would otherwise be excluded using the crossover-site exclusion method, albeit at the cost of making assumptions, particularly around the commonality of the treatment effect. The ERG notes that neither of these crossover analyses included any adjustment for the continued use of the study drug in the olaparib group. Furthermore, the ERG highlights that the available Kaplan-Meier estimates of OS, including those which account for placebo group crossover, suggest that the apparent survival benefits for olaparib versus placebo diminish towards the tails of the curves. It is also noteworthy that within the ongoing Phase III trial of olaparib versus routine surveillance, OS is included only as a secondary outcome measure.

TTD/D was considered by the ERG to be a *post hoc* analysis potentially confounded by treatment continuation beyond disease progression. Within the whole population, the HR for TTD/D was 0.39 (95% CI 0.30 to 0.51) for olaparib versus placebo. The HR for TTD/D was similar at 0.36 (95% c.i.

0.24 to 0.53) for the *BRCAm* subgroup; median TTD/D within the *BRCAm* subgroup was 11.0 months in the olaparib arm versus 4.6 months in the placebo arm. It is unclear what this outcome actually demonstrates given the confounding issues.

TFST/D was considered by the ERG to be a *post hoc* analysis potentially confounded by patient switching and un-blinding of some study participants. Within the whole population, the HR for TFST/D was 0.41 (95% c.i. 0.31 to 0.54). The HR for TFST/D was 0.33 (0.22 to 0.50) for olaparib versus placebo within the *BRCAm* subgroup; median TFST/D within the *BRCAm* subgroup was 15.6 months in the olaparib arm versus 6.2 months in the placebo arm. This outcome suggests that patients receiving olaparib commenced their first subsequent therapy later than patients on placebo, but it should be borne in mind that the outcome was a *post hoc* analysis and may be confounded in either direction.

TSST/D was considered by the ERG to be a *post hoc* analysis potentially confounded by patient switching and un-blinding of some study participants. In the whole population, the HR for TSST/D was 0.54 (95% c.i. 0.41 to 0.72) for olaparib versus placebo. In the *BRCAm* subgroup, the HR for TSST/D was 0.44 (95% c.i. 0.29 to 0.67) for olaparib versus placebo; median TSST/D was 23.8 months in the olaparib arm versus 15.2 months in the placebo arm. This outcome suggests that patients receiving olaparib commenced their second subsequent therapy later than patients on placebo, but it should be borne in mind that the outcome was a *post hoc* analysis and may be confounded in either direction.

Quality of life, as measured by FACT-O, and the indexes TOI and FOSI, was not negatively impacted by therapy with olaparib compared with therapy with placebo. Putative HRQoL gains are likely to be a consequence of avoided rounds of chemotherapy, however there is no direct evidence to support this.

AEs occurred more often in the olaparib group, but were largely minor and manageable with dose reductions or interruptions. A greater proportion of patients in the olaparib arm than the placebo arm suffered from severe AEs such as fatigue, anaemia and neutropenia. SAEs occurred in 21.6% of olaparib patients versus 9.7% of placebo patients. These included anaemia, small bowel obstruction, dyspnoea and gastritis. Mortality was slightly higher in the olaparib group than the placebo group, although the study sample size was too small to conclusively identify any difference in mortality. The ERG notes that:

- Although olaparib does not seem to impact on quality of life, and may confer some OS benefit, it does have a worse AE profile than placebo, including a higher occurrence of serious and severe AEs.

- AEs led to treatment discontinuation in 32.4% of olaparib patients versus 8.1% in placebo patients, and interruption in 21.6% of olaparib patients versus 3.23% in placebo patients. 8.1% of olaparib patients discontinued treatment, versus 0% of placebo patients.
- MDS and AML have been reported in patients taking olaparib, but the incidence does not appear to be higher than normal for the population. These events are the subject of ongoing monitoring.

4.6.3 Conclusion

The evidence base for olaparib is small, and problematic for the *BRCAm* subgroup. The results from Study 19 demonstrate PFS advantages for olaparib patients in both the whole population and the *BRCAm* subgroup. OS was not improved in the whole population, nor was a statistically significant difference observed in initial estimates for the *BRCAm* subgroup. One crossover analysis, which excluded study sites allowing placebo group crossover, did suggest a survival advantage for olaparib patients.

[redacted]. Neither crossover analysis attempted to correct for patients continuing on olaparib beyond progression, which may have biased results in favour of olaparib. Benefits were seen in the *post hoc* analyses of TTD/D, TFST/D and TSST/D in both the whole population and the *BRCAm* subgroup, but results may have been confounded by continuation of therapy and treatment switching, and their *post hoc* nature may be significant. The validity of the *BRCAm* subgroup itself is questionable due to the subgroup being added to the analysis plan more than a year after the study commenced, not being well defined at this point, and interaction tests appearing inconclusive. As such, it would be difficult to conclude on the basis of current evidence that the *BRCAm* subgroup is statistically any different from the whole population, and therefore it may be more appropriate to consider the results of the whole population instead. In this case, the conclusion would be that olaparib confers a PFS advantage, but it is unclear whether it confers benefits in terms of OS. If, however, the subgroup is considered credible, it would appear that olaparib confers PFS benefits, may confer some small OS benefits at the 52% data maturity cut off, with a largely acceptable AE profile. It remains unclear whether survival benefits would be maintained over time. The results of any subgroup analysis should be confirmed in subsequent trials before the validity of the results can be confidently assessed.

5. COST-EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analysis presented within the CS.[1] Additional analyses undertaken by the ERG are also presented within this chapter.

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

5.1.1 Description of company's systematic review of cost-effectiveness evidence

The company undertook a systematic review of published economic studies and economic evaluations in ovarian cancer in order to (1) identify economic models developed to assess the cost-effectiveness of treatments for ovarian cancer, (2) identify costing data that could be used to populate the economic model and (3) identify data on the economic burden of ovarian cancer.

The company searched the following electronic literature databases using the Embase.com and PubMed search interfaces:

- MEDLINE;
- MEDLINE In-Process;
- EMBASE
- The Cochrane Library (including the National Health Service Economic Evaluation Database [NHS EED])
- EconLit.

In addition, the company searched the websites of a number of health technology assessment (HTA) agencies in order to retrieve additional studies which may have been missed by the electronic searches. These included:

- The Canadian Agency for Technology and Drugs in Health (CADTH)
- The Haute Autorité de Santé (HAS)
- The Institute for Quality and Efficiency in Healthcare (IQWiG)
- The National Institute for Health and Care Excellence (NICE)
- The Norwegian Medicines Agency (NOMA)
- The Pharmaceutical Benefits Advisory Committee (PBAC)
- The pan-Canadian Oncology Drug Review (pCODR)
- The Pharmacology and Therapeutics Advisory Committee (PTAC) of the Pharmaceutical Management Agency (PHARMAC)
- The Scottish Medicines Consortium (SMC)
- The Dental and Pharmaceutical Benefits Agency of Sweden (TLV)

A detailed set of inclusion/exclusion criteria are presented in Section 10.10.2 of the CS.[1] Studies were included in the review if they related to patients with ovarian cancer and if they were studies which described economic models or the economic burden associated with ovarian cancer. Included studies were restricted to those in which the title and abstract was available in English, which related to humans, and which were published in the last 10 years. Study selection was undertaken according to the inclusion/exclusion criteria, firstly by title and/or abstract and secondly based on the full text of the publication. According to the CS[1] study selection was undertaken by a single reviewer, with auditing of inclusion/exclusion decisions by a second reviewer. Disagreements were resolved through discussion between the two reviewers.

Nine cost-effectiveness analyses of pharmacological interventions for advanced ovarian cancer met the inclusion criteria for the company's review. According to the CS[1] (Table A17) three of these studies were undertaken in the UK,[37-39] although the ERG notes that the manufacturer's submission for NICE TA284 (bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer)[40] is not included in the table of included studies but is mentioned in the text of the CS (see CS[1] page 104). Only five studies[37-39,41,42] included in the company's review (or 6 studies, including NICE TA284[40]) describe cost-utility analyses in which the outcome assessed relates to the incremental cost per QALY gained.

Only one of the included studies, Secord *et al*[43] reports a health economic comparison of olaparib versus routine surveillance in patients with PSR high-grade serous ovarian cancer after a partial or complete response to a platinum-containing regimen. Secord *et al* compared three options in terms of the incremental cost per PFLYS: Strategy 1: Observe (routine surveillance); Strategy 2: Olaparib maintenance therapy (without *BRCA* mutation testing), and; Strategy 3: Olaparib maintenance therapy (with prior *BRCA* mutation testing, including maintenance treatment for *BRCA* mutation carriers). Within this study, the authors used a modified Markov model to estimate the costs and health outcomes associated with each strategy using data from Study 19.[14] The authors reported that global olaparib without *BRCA* mutation testing (Strategy 2) was the most effective strategy, followed by *BRCA* mutation testing plus olaparib for mutation carriers (Strategy 3) and routine surveillance (Strategy 1). The ICER for *BRCA* mutation testing plus olaparib treatment for *BRCA* mutation carriers versus routine surveillance was reported to be $193,442 PFLYS. The ICER for global olaparib versus *BRCA* mutation testing plus olaparib treatment for *BRCA* mutation carriers was reported to be $234,128 per PFLYS.[43]

The CS[1] highlights five weaknesses associated with the analysis reported by Secord *et al:*[43]

(1) Health outcomes are measured in terms of PFLYS rather than QALYs.

(2) The assumed cost-effectiveness thresholds of $50,000 and $100,000 per PFLYS were based on historical estimates of the willingness to pay per LYG which has been generalised to PFLYS without justification.
(3) The analysis assumes that the PFS benefits for olaparib versus placebo would not translate into any benefits in terms of OS. The CS[1] argues that this is not consistent with the findings of Study 19.
(4) The time horizon of the economic analysis is limited to 12 months; the CS argues that this will not adequately reflect downstream effects of treatment in terms of delayed morbidity and mortality.
(5) The analysis includes the costs of platinum-based chemotherapies following disease progression but does not include the consequent survival benefits of these treatments.

5.1.2 ERG critique of company's systematic review of cost-effectiveness evidence

The databases for economic studies and HTA agency websites for economic evaluations for ovarian cancer were relevant and clearly reported in Section 7.1 of the CS[1] (pages 102-104). With respect to the search strategies, the keywords relating to the ovarian cancer population were combined with an economic evaluation filter (Appendix 10 of the CS,[1] page 236). All strategies were provided and the filters used were referenced appropriately. Since language and date limits to cover the last 10 years were applied in the company's searches, it is unclear whether any non-English publications or studies published before 2003 may have been missed. The search strategies are fully reported and transparent. The ERG re-ran the company's cost-effectiveness search strategy in PubMed (see CS[1] Table A13, page 239) on 11th February 2015 for studies published since the company's search in November 2014. Forty six records were retrieved; none of these studies related to economic evaluations of olaparib for ovarian cancer. The search strategies for identifying economic studies and evaluations in Section 7.1 of the CS[1] were also used to identify resource use and costs relating to ovarian cancer in the UK (see Section 5.2.4.6). The ERG considers that the strategies used are appropriate for the systematic review of resource use.

The ERG agrees with the company that the economic analysis reported by Secord *et al*[43] falls short of the requirements of the NICE Reference Case[44] and is of limited value for informing this appraisal. The ERG considers the company's decision to develop a *de novo* model to be appropriate.

5.2 Description of the company's model

5.2.1 Health economic evaluation scope

As part of their submission to NICE,[1] the company submitted an executable health economic model to assess the cost-effectiveness of olaparib versus routine surveillance in patients with ovarian cancer. The scope of the company's health economic analysis is summarised in Table 19.

Table 19: Scope of the company's health economic analysis

Population	Women with *BRCA1/2* mutated (germline and/or somatic), PSR high-grade serous ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy
Intervention	Olaparib (Lynparza™) 400mg twice-daily capsules, including prior *BRCA* mutation testing.
Comparator	Routine surveillance ("watch and wait")
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	15 years (intended to reflect patients' remaining lifetime)
Discount rate	3.5% per year

BRCA - Breast cancer susceptibility gene; PSR – platinum-sensitive relapsed; QALY – quality-adjusted life year; PSS – personal social services

The population considered within the company's health economic analysis relates to women with *BRCA1/2m* (germline and/or somatic), PSR high-grade serous ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy. This population is based on the *BRCAm* subgroup within Study 19 and reflects the marketing authorisation for olaparib issued by the EMA.[11] The intervention is defined as olaparib 400mg b.i.d. Whilst the population relates specifically to *BRCAm* patients, the costs of *BRCA* mutation testing are excluded from the company's base case analysis. Discontinuation of olaparib is modelled largely according to the experience of patients within Study 19, thereby reflecting treatment up to progression, although the ERG notes that some patients in both randomised groups continued to receive the allocated drug beyond RECIST progression; this is not in line with recommendations on the use of olaparib treatment issued by the EMA[11] (see Section 5.3). The comparator included in the company's analysis is routine surveillance, otherwise referred to as "watch and wait." The analysis adopts an NHS and PSS perspective over a 15-year time horizon. The CS suggests that the analysis is intended to reflect a lifetime horizon. All costs and health outcomes are discounted at a rate of 3.5% per year.

The CS[1] highlights that *BRCA* mutation testing is a prerequisite for olaparib treatment in patients with ovarian cancer and that such testing may result in additional costs and benefits beyond the recipients of olaparib. In particular, women without disease who are *BRCA1/2* mutation carriers have an increased lifetime risk of developing breast and ovarian cancer. The CS argues that the additional benefits of *BRCA* mutation testing can be observed in relatives of the index case *BRCAm* ovarian cancer patient, who can be offered testing, with those testing positive for the same mutation having the option of undergoing surveillance or risk-reducing surgery, such as mastectomy or oophorectomy.[1] In order to capture the potential additional QALY benefits and costs associated with *BRCA* mutation testing, the results from the company's *de novo* cost-effectiveness analysis of olaparib maintenance treatment versus routine surveillance were combined with the results of a separate cost-

utility analysis of genetic testing for individuals with a family history of breast cancer, developed as part of NICE CG164.[8]

The company's health economic analysis is thus comprised of two evaluations:

- The base case economic evaluation of olaparib maintenance treatment versus routine surveillance in patients with *BRCAm* PSR ovarian cancer. This analysis excludes the costs of *BRCA* mutation testing and considers costs and benefits relating to the index *BRCAm* ovarian cancer patient only.
- A broader economic evaluation that also accounts for: (a) the costs of *BRCA* mutation testing in PSR ovarian cancer patients, and; (b) the costs and benefits of expanding *BRCA* mutation testing to family members of relapsed *BRCAm* ovarian cancer patients undergoing *BRCA* mutation testing as a prerequisite in consideration of olaparib as a potential treatment option. This analysis considers costs and benefits relating to the index *BRCAm* ovarian cancer patient and family members. This latter analysis is not presented as part of the base case analysis within the CS[1] and is thus treated as a secondary analysis within this ERG report.

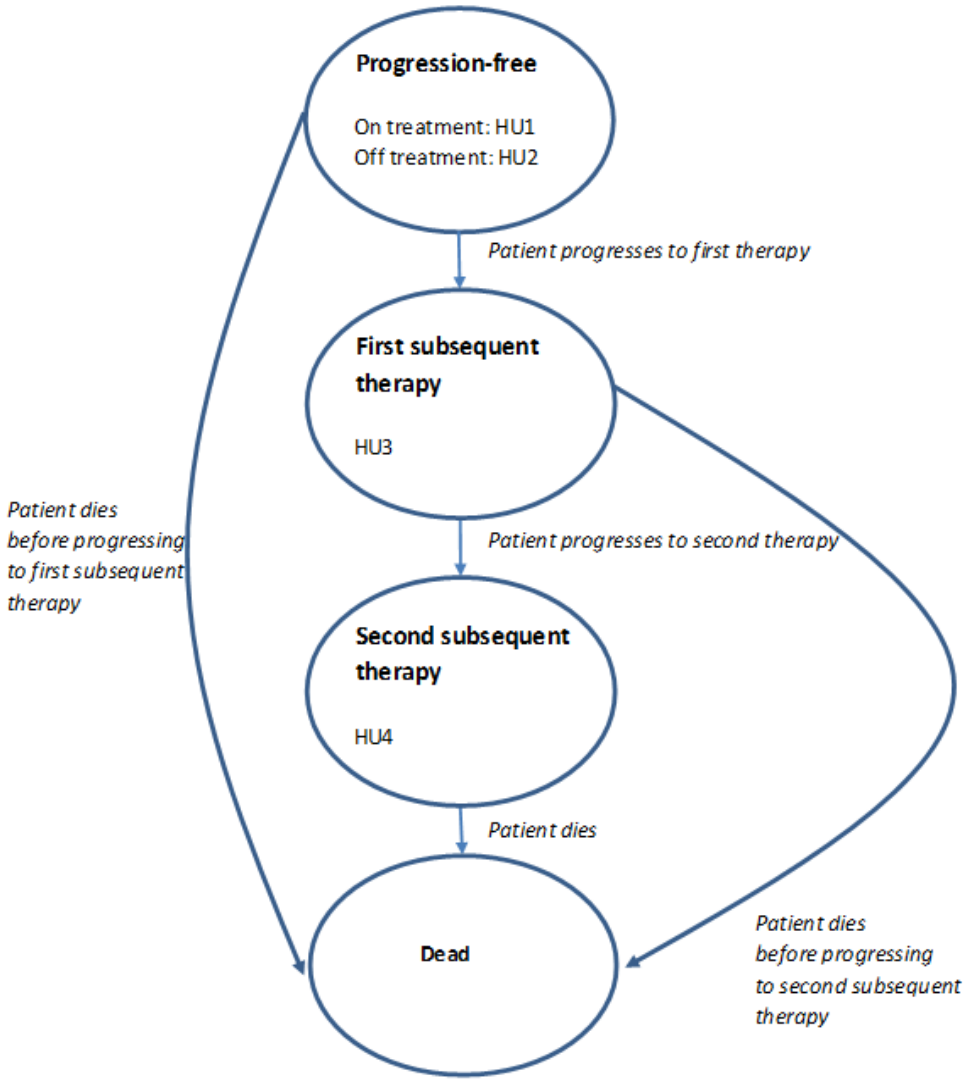
5.2.2 Description of the company's health economic model structure and logic

The company's health economic analysis takes the form of a semi-Markov model whereby sojourn time in each health state is dependent on the time since entry into that state. Tunnel states are used to model health state occupancy over time. The structure of the company's model is shown in Figure 8. The health states included in the model are defined in terms of whether the patient is "progression-free" (receiving maintenance treatment or discontinued) and whether they have progressed to first subsequent therapy or second subsequent chemotherapy. The model includes five health states: (i) progression-free (on maintenance treatment); (ii) progression-free (discontinued maintenance treatment); (iii) first subsequent chemotherapy (on treatment or discontinued); (iv) second subsequent chemotherapy (on treatment or discontinued), and; (v) dead. The trajectory of patients through the model is determined largely by parametric survival curves fitted to four time-to-event (TTE) outcomes derived from Study 19:[27]

- Time from randomisation to treatment discontinuation or death (TTE outcome 1)
- Time from randomisation to first subsequent therapy or death (TTE outcome 2)
- Time from first subsequent therapy to second subsequent therapy or death (TTE outcome 3)
- Time from second subsequent therapy to death (TTE outcome 4).

The trajectory of patients through the health states is also influenced by the probability that a patient leaving the progression-free and first subsequent therapy health states dies rather than progresses to the next state.

Figure 8: Company's model structure (drawn by the ERG)



HSUV – health state utility value

All patients enter the model in the "progression-free (on treatment)" state. It should be noted from the outset that whilst this state is referred to as "progression-free", occupancy within this health state is determined by the patient having not progressed to subsequent chemotherapy, rather than the patient being free from documented radiological tumour progression based on RECIST criteria.[45] The probability of being progression-free at time *t* is determined by a parametric survival curve fitted to time-to-event data on the time from randomisation to first subsequent therapy or death (TFST/D) in the *BRCAm* subgroup within Study 19.[27] The proportion of patients in the progression-free state at time *t* is then subdivided into those who are currently receiving maintenance treatment and those who have discontinued maintenance treatment; this is modelled using a parametric survival curve fitted to time-to-event data on the time from randomisation to treatment discontinuation or death (TTD/D) outcome in the *BRCAm* subgroup within Study 19.[27] The difference between these two modelled curves reflects the proportion of patients who have discontinued maintenance therapy but have not yet

started first subsequent chemotherapy. Upon leaving the progression-free state, patients may either die or progress to the first subsequent line of chemotherapy. The hazard of dying after progression is assumed to be dependent on prior maintenance treatment received (olaparib or placebo) and is assumed to be directly proportional to the broader hazard of progressing or dying; that is, a fixed proportion of first subsequent therapy events are assumed to be deaths. These proportions are assumed to differ between the olaparib group and the routine surveillance group, based on data for the *BRCAm* subgroup in Study 19.[27] Those patients who survive the first subsequent therapy event progress to the first subsequent therapy state. The probability of remaining in the first subsequent therapy state during any given cycle is determined by a parametric survival curve fitted to time-to-event data relating to the time from first subsequent therapy to second subsequent therapy or death within Study 19.[27] The same curve, i.e. that of the olaparib group only, is applied to both the olaparib and routine surveillance groups. Upon leaving the first subsequent therapy state, patients may either die or progress to the second subsequent therapy. The hazard of dying after progression from the first subsequent therapy state is assumed to be independent of prior maintenance therapy and is again assumed to be directly proportional to the broader hazard of progressing or dying; that is, a fixed proportion of second subsequent therapy events are assumed to be deaths and this proportion is assumed to be the same in both treatment groups. This probability is based on pooled data for both treatment groups in the *BRCAm* subgroup within Study 19.[27] Those patients who survive the second subsequent therapy event progress to the second subsequent therapy state. The probability of remaining in the second subsequent therapy state is determined by a parametric curve fitted to time-to-event data relating to the time from second subsequent therapy to death, again based on data collected within Study 19.[27] The same parametric curve, i.e. that for the olaparib group, is applied to both the modelled olaparib and routine surveillance groups. All transition probabilities are calculated on a monthly basis using the following formula:

$$TP(t,u) = 1 - \frac{S(t)}{S(t-u)} \qquad \text{[i]}$$

where *TP(t,u)* is the transition probability at time *t* for cycle length *u*; *S(t)* is the survival at time *t*; *S(t-u)* is the survival in the previous cycle.

A half-cycle correction is applied to adjust for the timing of events.

The mean number of LYGs for each treatment group is calculated as the sum of the mean sojourn time in the progression-free, first subsequent therapy and second subsequent therapy health states. Different health utilities are applied to each of the four living health states; the highest utility value is assigned to the progression-free (on treatment) state and the lowest utility value is assigned to the second subsequent chemotherapy state.

The model includes the costs of olaparib maintenance therapy, the costs associated with first subsequent therapies for those patients who progress from the progression-free state and survive, the costs associated with second subsequent therapies for those patients who progress from the first subsequent therapy state and survive, the costs associated with managing AEs, follow-up costs and end-of-life costs. The costs of *BRCA* mutation testing are included within a sensitivity analysis.

Olaparib costs are applied to those patients who are receiving maintenance therapy, as determined by the TTD/D curve. The cost of maintenance therapy does not include an administration cost as olaparib is an oral therapy.

First subsequent chemotherapy costs include drug acquisition and administration costs associated with 10 platinum and 5 non-platinum based therapies. The platinum-based regimens include (i) carboplatin, (ii) carboplatin and gemcitabine, (iii) carboplatin and doxorubicin, (iv) carboplatin and cyclophosphamide, (v) carboplatin and docetaxel, (vi) cisplatin and cyclophosphamide, (vii) cisplatin and paclitaxel, (viii) carboplatin and gemcitabine hydrochloride, (ix) cisplatin, cyclophosphamide and docetaxel and (x) carboplatin and paclitaxel. The non-platinum regimens include (i) doxorubicin, (ii) topotecan, (iii) paclitaxel, (iv) etoposide, and (v) gemcitabine. The proportion of patients receiving each regimen was based on usage within the *BRCA* subgroup within Study 19;[27] utilisation of each regimen is assumed to be the same for first- and subsequent-line chemotherapies.

The costs of first subsequent chemotherapy are calculated as follows. Upon entry into the first subsequent therapy state, the use of chemotherapy is partitioned according to whether the patient has progressed and commenced their first line of subsequent chemotherapy within 6-months of model entry (platinum-resistant) or not (platinum-sensitive). With respect to the platinum-sensitive population progressing to first subsequent therapy, the model calculates the number of patients who are alive, who entered the first subsequent therapy state greater than or equal to 6 months post-model entry and who have been in the first subsequent therapy tunnel states for less than the maximum treatment duration of each given regimen (6 months for all regimens except carboplatin plus doxorubicin which is assumed to be given for 4 months). The cost of each first subsequent platinum-based regimen (drug acquisition and administration) is then applied to those patients who are still eligible for treatment in the given model cycle, weighted according to the proportionate use of each regimen within Study 19.[27] With respect to the platinum-resistant population, the model tracks those patients who are still alive who entered the first subsequent therapy state within 6 months of model entry and who have been in the first subsequent therapy tunnel states for less than the maximum treatment duration for each given regimen (6 months for all regimens). The cost of each first subsequent non-platinum-based regimen is then applied to those patients who are still eligible for treatment, weighted according to the proportionate use of each regimen within Study 19.

The costs of second subsequent chemotherapy are calculated as follows. With respect to the platinum-sensitive population, the model calculates the number of patients entering the second subsequent therapy state from a minimum of 18-months post-model entry and estimates the proportion of these who are still platinum-sensitive according to the time at which they progress and the risk of dying rather than progressing. The model calculates the number of patients who have been in the second subsequent therapy state for less than or equal to the maximum treatment duration for each chemotherapy regimen (6 months for all regimens excluding carboplatin plus doxorubicin which is assumed to be given for 4 months). The cost of each second subsequent platinum-based regimen is then applied to those patients who are still eligible for treatment, weighted according to the proportionate use of each regimen within Study 19.[27] With respect to the platinum-resistant population, the model tracks those patients who are still alive and who entered the second subsequent therapy state within 6 months of entry into the first subsequent therapy state and who have been in the second subsequent therapy tunnel states for less than the maximum treatment duration for each given regimen (6 months for all regimens). The cost of each second subsequent non-platinum-based regimen is then applied to those patients who are still eligible for treatment, weighted according to the proportionate use of each regimen within Study 19.[27]

Costs are included for CTCEA ≥ grade 3 AEs that occurred in ≥2% of the *BRCAm* subgroup in Study 19.[27] AEs include anaemia, neutropaenia, leucopaenia, diarrhoea, vomiting abdominal pain, fatigue, pneumonia and back pain. Serious AEs including MSD/AML were not included. The costs associated with managing AEs are applied only during the first model cycle.

Follow-up costs include those associated with clinical consultations, computerised tomography (CT) scans and blood tests (olaparib group only); these costs are applied to patients in the progression-free state. For patients who have progressed to first and subsequent therapies, only the costs of consultations are included.

The model assumes that 51% patients incur end of life care costs. This once-only cost is applied retrospectively upon the event of death.

Key model assumptions

The CS[1] (pages 131-132) highlights a number of key assumptions within the company's health economic analysis:

(1) The use of PARP inhibitors following disease progression in the placebo arm of Study 19 may have caused an imbalance in the efficacy of subsequent therapies between the randomised treatment groups. The company's model assumes that this imbalance can be removed by setting the efficacy of next-in-line therapies to be the same between treatment

groups.[1] The ERG notes that this assumption involves assuming that (a) the time-to-event curve for time from first subsequent therapy to second subsequent therapy or death, (b) the probability that a second subsequent therapy event is death, and (c) the time-to-event curve for time from second subsequent therapy to death, are the same for both the olaparib and routine surveillance groups.

(2) There is no positive or negative residual effect of maintenance treatment on the efficacy of subsequent treatment following maintenance treatment.

(3) AEs resulting from drug treatment are assumed to be resolved upon treatment discontinuation, and the costs associated with managing AEs are assumed to occur in the first monthly cycle. This assumption was made on the basis that the major cost component of managing an AE would be acute care, which would likely occur only once for an individual patient.[1] The CS[1] states that this approach to modelling AEs is consistent with approaches used in previous economic evaluations in ovarian cancer.

(4) The use of subsequent treatment following the discontinuation of maintenance therapy is assumed to reflect the onset of symptomatic (rather than radiological) disease progression.

(5) The cohort that occupied the first subsequent therapy and second subsequent therapy states of the model was assumed to receive a fixed regimen treatment lasting a maximum of six cycles, and received follow-up care that was consistent with what is offered to a patient with progressed disease. This is justified on the basis that a course of chemotherapy (platinum- or non-platinum based) typically lasts six cycles.

(6) Treatment decisions following the discontinuation of olaparib in the first subsequent therapy and second subsequent therapy states of the model are based on established definitions of platinum-sensitivity (>6 months recurrence-free patients receive platinum-based compounds).[1]

(7) Patients in a given particular health state are assumed to have the same probability of transiting between states, irrespective of their previous history.

The ERG notes the following additional assumptions which are not explicitly highlighted within the CS:

(8) As a consequence of the implemented model structure, patients can receive only two lines of subsequent chemotherapy following symptomatic disease progression. The ERG notes that more than 36% patients in each treatment group within the *BRCAm* subgroup in Study 19 received three or more subsequent lines of chemotherapy (see CS[1] Figure 6.8).

(9) All patients who progress to the next line of therapy are assumed to receive active chemotherapy. Supportive care alone (without cytotoxic therapy) is not included as a treatment option for patients with progressed disease.

(10) The "progression-free (on maintenance treatment)" health state is assumed to be associated with a higher health utility score than the "progression-free (discontinued maintenance treatment)" health state.[1] Whilst routine surveillance does not involve the use of active treatment, a progression-free "off treatment" phase is modelled for both treatment groups.

(11) A fixed proportion of first subsequent therapy events and a fixed proportion of second subsequent therapy events are assumed to be deaths; the hazard of death is therefore assumed to be directly proportional to the hazard of progressing to the next therapy or dying.

These assumptions are discussed in further detail in Section 5.3.

Wider economic evaluation of the costs and benefits of BRCA mutation testing and olaparib versus routine surveillance

Subsequent to the presentation of the base case analysis, the CS presents a further analysis which attempts to capture the additional costs and health benefits associated with *BRCA* mutation testing for relatives of the index case *BRCAm* PSR ovarian cancer patient (see CS[1] page 186). These additional costs and QALY gains were not estimated within the company's model itself; rather, estimates of incremental costs and QALYs for relatives undergoing *BRCA* mutation testing were taken from a separate model-based cost-utility analysis of genetic testing for individuals with a family history of breast cancer, developed as part of NICE CG164.[8] In the CS, these costs and health outcomes were estimated for a sample of five family pedigrees (diagrams showing genetic relationships between members of a family that are used to analyse patterns of inheritance of a specific genetic trait such as the *BRCA1/2* mutation) each including one ovarian cancer patient who was assumed to be a proxy for the index case within each pedigree. The pedigrees were provided by clinical experts at the UK Institute of Cancer Research (see Appendix 5). A revised ICER for olaparib versus routine surveillance was then calculated by combining the results from NICE CG164[8] with the results of the company's base case analysis (see Table 20). The company calculated a range of ICERs for each pedigree, as well as an average (mean) ICER based on the combined results across the five pedigrees.

Table 20: Calculations of cost-effectiveness of olaparib maintenance treatment for *BRCA*-mutated PSR ovarian cancer and *BRCA* mutation testing for unaffected relatives

Beneficiary	**Without testing**		**With *BRCA* testing**		**Incremental costs and QALYs**	
	Total lifetime costs	**Total lifetime QALYs**	**Total lifetime costs**	**Total lifetime QALYs**		
Index case: olaparib (vs routine surveillance)	-	-	-	-	ΔCosts	ΔQALYs
Relative 1	Costs (NT_1)	QALYs (NT_1)	Costs (T_1)	QALYs (T_1)	$\Delta Costs_1$	$\Delta QALYs_1$
Relative 2	Costs (NT_2)	QALYs (NT_2)	Costs (T_2)	QALYs (T_2)	$\Delta Costs_2$	$\Delta QALYs_2$
Relative 3	Costs (NT_3)	QALYs (NT_3)	Costs (T_3)	QALYs (T_3)	$\Delta Costs_3$	$\Delta QALYs_3$
Relative 4	Costs (NT_4)	QALYs (NT_4)	Costs (T_4)	QALYs (T_4)	$\Delta Costs_4$	$\Delta QALYs_4$
ICER per QALY gained	**Total incremental costs (index case + relatives) / Total incremental QALYs (index case + relatives)**					

NT - no testing; T - BRCA mutation testing; QALY – quality-adjusted life year

5.2.4 Evidence sources used to inform the company's model parameters

5.2.4.1 Summary of evidence sources

Table 21 summarises the evidence sources used to inform the company's model parameters. The derivation of the company's model parameter values using these sources is described in further detail in the following sections.

Table 21: Summary of evidence sources used to inform the company's model parameters

Parameter group	Source and comments
Patient characteristics	
Start age	*BRCAm* subgroup within Study 19.[24]
Patient weight (kg)	*BRCA*m subgroup within Study 19[24] - weighted mean based on olaparib and placebo groups
Glomerular filtration rate	Source unclear from CS[1]
Body surface area	Source unclear from CS[1]
Percent of cohort with complete OR to previous chemotherapy	*BRCAm* subgroup within Study 19[24]
Percent of cohort with TTP >12 months	
Percent of cohort with Jewish ethnicity	
Transition probabilities	
Time from randomisation to treatment discontinuation or death	*BRCAm* subgroup within Study 19[27] Patient characteristics (percent of cohort with complete OR to previous chemotherapy, percent of cohort with TTP >12 months and percent of cohort with Jewish ethnicity) were included as adjustment factors for time-to-event outcomes. Time from first subsequent therapy to second subsequent treatment or death, time from second subsequent therapy to death and the probability of transiting from first-subsequent therapy to death were assumed to be the same for both the olaparib and routine surveillance groups.
Time from randomisation to first subsequent therapy or death	
Time from first subsequent therapy to second subsequent therapy or death	
Time from second subsequent therapy to death	
Probability that first subsequent therapy event is death	
Probability that second subsequent therapy event is death	
Health-related quality of life	
Progression-free (on maintenance therapy)	Mapping of FACT-O to EQ-5D using algorithm reported by Longworth *et al*[46,47]
Progression-free (discontinued maintenance therapy)	
First subsequent therapy	Monk *et al*[48] (OVA-301 trial) as reported within the manufacturer's submission for NICE TA222[38]
Second subsequent therapy	
Adverse event frequency	
AE rates (anaemia, neutropaenia, leucopaenia, diarrhoea, vomiting abdominal pain, fatigue, pneumonia and back pain)	*BRCAm* subgroup within Study 19[24]
Resource use	
Utilisation of alternative platinum and non-platinum chemotherapy regimens	*BRCAm* subgroup within Study 19.[27] Only those chemotherapy regimens that were reported in greater than 3% of the total *BRCA* mutation subgroup and were classified as licensed anticancer treatments were included.[1]
Dose and frequency of subsequent chemotherapy regimens	Yorkshire Cancer Network. Gynaecology Network Group[49]
Mean doses of subsequent chemotherapy regimens	Various sources (unspecified in the CS[1]) including company's systematic literature review of economic studies in ovarian cancer.
Unit costs	
Olaparib (28 day pack - 448 x 50mg capsules)	CS[1]
Olaparib monitoring (blood tests)	NHS Reference Costs 2012/13[25]
Chemotherapy administration (infusional and oral)	
AE costs	
Follow-up (consultations, blood tests and CT scans)	
End of life costs	Cost taken from Guest *et al.*[50] Proportion of

Parameter group	Source and comments
	patients incurring end of life costs taken from Gao *et al.*[51]
***BRCA* mutation testing parameters**	
Prevalence of *BRCA*m in PSR ovarian cancer patients	Ovarian Cancer Action 2014[52]
Proportion of subjects previously identified	Astra Zeneca Horizon 2013[53]
*BRCA*m test laboratory cost	UK Genetic Testing Network[54]
Genetic counselling cost	Curtis *et al* 2013[55]
Costs and benefits of detecting *BRCA* mutation carriers	NICE CG164[8]

BRCA - Breast cancer susceptibility gene; EQ-5D – Euroqol 5-Dimensions; Functional Assessment of Cancer Therapy – Ovarian; CT – computerised tomography; TTP – time to progression

5.2.4.2 Patient characteristics

The model includes parameters describing patient characteristics relating to age, patient weight, glomerular filtration rate (GFR), body surface area, the percent of cohort with complete OR to previous chemotherapy, the percent of cohort with TTP >12 months and the percent of cohort with Jewish ethnicity. A mean start age of 56.70 years and a mean body weight of 73.3kg were assumed within the model, based on the *BRCAm* subgroup within Study 19.[24] The model assumes a mean GFR of 60 and a mean body surface area of 1.70m^2; the sources for these parameter estimates are not reported within the CS.[1] The proportion of patients with complete OR to previous chemotherapy (0.51), the proportion of patients with TTP >12 months (0.60) and the proportion of patients with Jewish ethnicity (0.21) were based on the *BRCAm* subgroup within Study 19.[24]

5.2.4.3 Transition probability parameters

Transitions through the company's model health states are based on survival curves fitted to time-to-event data for each treatment group, together with estimates of the proportion of progression events that are deaths. Data relating to four time-to-event outcomes are used in the model:

- Time from randomisation to treatment discontinuation or death – TTD/D (TTE outcome 1)
- Time from randomisation to first subsequent therapy or death – TFST/D (TTE outcome 2)
- Time from first subsequent therapy to second subsequent treatment or death (TTE outcome 3)
- Time from second subsequent therapy to death (TTE outcome 4).

The time-to-event data for the outcomes of time from first subsequent therapy to second subsequent treatment or death and time from second subsequent therapy to death (TTE outcomes 3 and 4) are conditioned on prior events, therefore the number of patients at risk decreases for events taking place at chronologically later points along the modelled patient pathway.

The CS[1] states that the general approach followed for curve-fitting and model discrimination was based on NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[56] External

information (including expert judgement) was not used to inform the model discrimination process. All survival analyses undertaken by the company include adjustments for TTP on the penultimate platinum-based chemotherapy, Jewish ethnicity and full versus partial platinum-sensitivity as covariates; this is not explained or justified further in the CS[1] but was likely undertaken to adjust for potential confounding due to imbalances in these covariates in the *BRCAm* subgroup. Other potential confounders, such as patient age and performance status (see Table 6), were not included as covariates in the survival models. The survivor functions and associated parameters for each of the four time-to-event outcomes used in the company's base case analysis are summarised in Table 22.

Table 22: Summary of survivor function parameters used in the company's model

Outcome	Survivor function	Time to event distribution parameters	
TTE outcome 1: Time from randomisation to treatment discontinuation or death	Log logistic (treatment-adjusted model)*	Scale	3.3702
		Shape	1.6709
		Treatment	0.9020
		TTP on penultimate platinum	0.1757
		Jewish ethnicity	0.0867
		Fully versus partially platinum sensitive	0.4531
TTE outcome 2: Time from randomisation to first subsequent therapy or death	Log normal (treatment-adjusted model)	Scale	1.4832
		Shape	0.9566
		Treatment	0.9206
		TTP on penultimate platinum	0.4681
		Jewish ethnicity	-0.0883
		Fully versus partially platinum sensitive	0.5940
TTE outcome 3: Time from first subsequent therapy to second subsequent treatment or death	Weibull (independent hazards model)*	Scale	9.7936
		Shape	1.3848
		Treatment	0
		TTP on penultimate platinum	0.0644
		Jewish ethnicity	-0.3379
		Fully versus partially platinum sensitive	-0.2932
TTE outcome 4: Time from second subsequent therapy to death	Weibull (independent hazards model)*	Scale	15.3694
		Shape	1.82985
		Treatment	0
		TTP on penultimate platinum	0.2532
		Jewish ethnicity	0.1733
		Fully versus partially platinum sensitive	-0.1343

TTE – time-to-event; TTP – time to progression

** These distribution parameters were sourced from the company's model as they were not reported within the CS[1]*

TTE outcome 1: Time from randomisation to treatment discontinuation or death (TTD/D)

The analysis of time from randomisation to treatment discontinuation or death was based on the full *BRCAm* dataset within Study 19 (olaparib N=74: placebo N=62). The company fitted log logistic, log normal, generalised gamma, Gompertz, exponential and Weibull survivor functions to the available trial data. The CS[1] states that visual inspection of the log-log plot of cumulative survival versus time indicated that the proportional hazards assumption could be considered valid (see Figure 9), hence all model-fitting involved treatment-adjusted models which included treatment as a covariate. The fitting

of independent hazards models for each individual treatment group was not considered within the company's analysis of this outcome. A graphical plot of the log logistic distribution against the empirical Kaplan-Meier survival data is presented in the CS (see Figure 10).[1] The equivalent survivor functions for the log normal, Gompertz, exponential, generalised gamma and Weibull distributions were not presented graphically within the CS. The treatment-adjusted log logistic model was selected by the company for use in the base case health economic analysis. The selection criteria used to inform the process of model discrimination appear to have been based on an examination of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics, both of which were lowest for the log logistic model (AIC= 815.54, BIC=833.02, see Table 23).

Figure 9: TTE outcome 1 - Time from randomisation to treatment discontinuation or death - log-log plot of cumulative survival versus time (reproduced from CS[1] Figure 7.6)

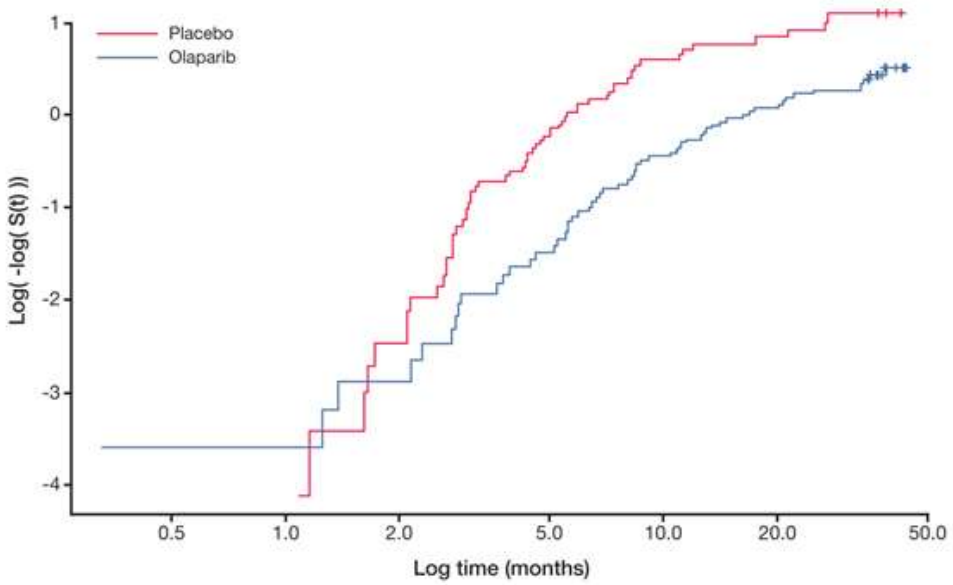
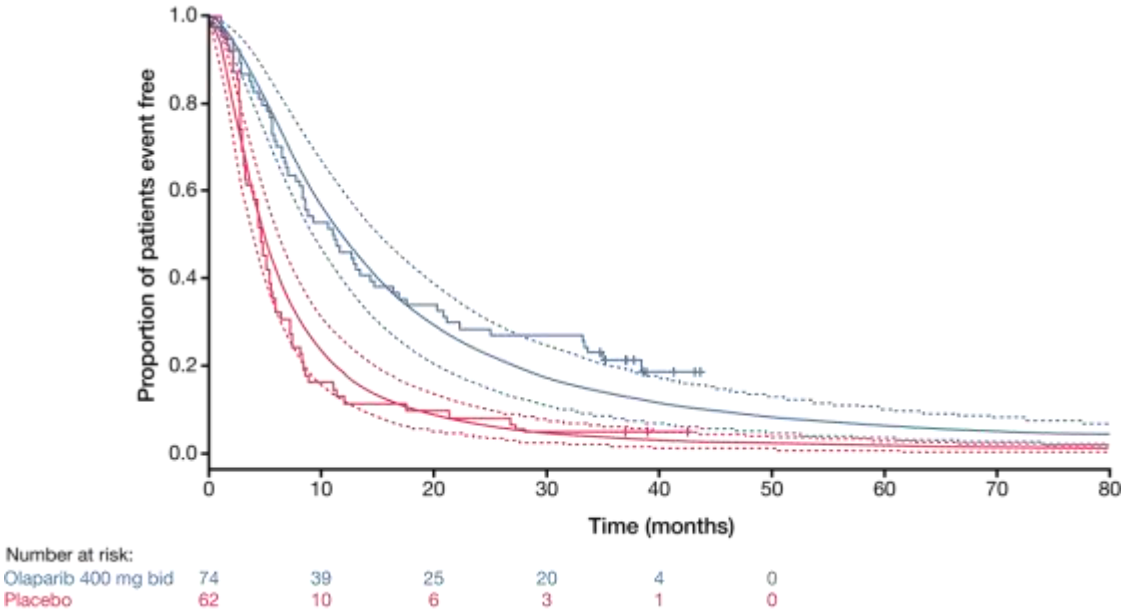


Figure 10: TTE outcome 1 - Time from randomisation to treatment discontinuation or death – treatment-adjusted log logistic model (reproduced from CS[1] Figure 7.7)



Dashed lines indicate confidence interval

Table 23: TTE outcome 1 - Time from randomisation to treatment discontinuation or death – AIC and BIC goodness of fit statistics (reproduced from CS[1] Table 7.5)

Model	AIC	BIC
Log logistic	**815.54**	**833.02**
Log normal	820.55	838.02
Generalised gamma	822.47	842.86
Gompertz	830.11	847.59
Exponential	834.84	849.40
Weibull	836.61	854.08

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

TTE outcome 2: Time from randomisation to first subsequent therapy or death (TFST/D)

The analysis of time from randomisation to first subsequent therapy or death was based on the full *BRCAm* dataset within Study 19 (olaparib N=74: placebo N=62). The company fitted log logistic, log normal, generalised gamma, Gompertz, exponential and Weibull survivor functions to the available trial data. The CS[1] states that the visual inspection of the log-log plot of cumulative survival versus time indicated that the proportional hazards assumption could be considered valid (see Figure 11), hence all model-fitting involved treatment-adjusted models which included treatment as a covariate. The fitting of independent hazards models for each individual treatment group was not considered within the company's analysis of this outcome. Graphical plots of the log normal and generalised gamma distributions against the empirical Kaplan-Meier survival data are presented in the CS[1] (see Figure 12 and CS[1] Figures 7.4 and 7.5). The equivalent survivor functions for the log logistic, Gompertz, exponential and Weibull distributions were not presented graphically. The treatment-

adjusted log normal distribution was selected for use in the base case health economic model as this survival model was associated with the lowest BIC statistic (BIC=771.78, see Table 24). The CS notes however that the generalised gamma distribution was associated with the lowest AIC statistic (AIC=753.78); this alternative survivor function is considered within the company's scenario analysis (see CS[1] Table 7.34).

Figure 11: TTE outcome 2 - Time from randomisation to first subsequent therapy or death - log-log plot of cumulative survival versus time (reproduced from CS[1] Figure 7.3)

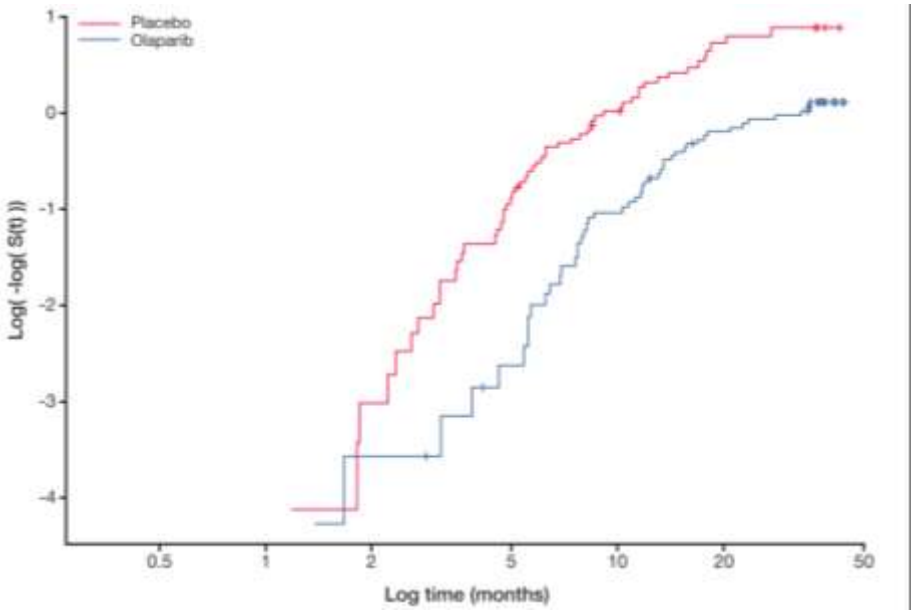
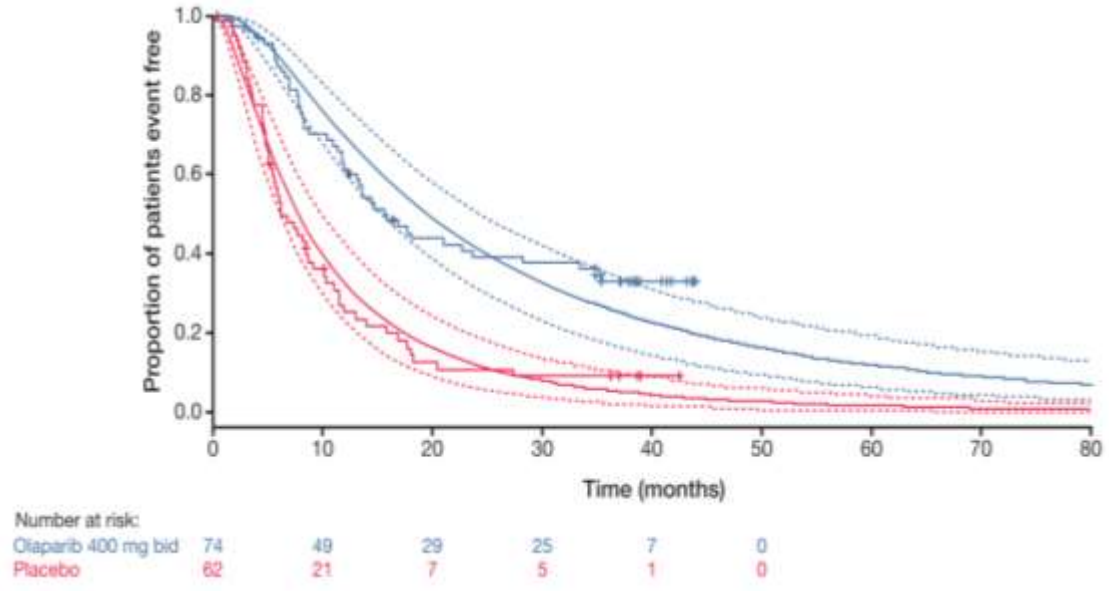


Figure 12: TTE outcome 2 - Time from randomisation to first subsequent therapy or death – treatment-adjusted log normal model (reproduced from CS[1] Figure 7.4)



Dashed lines indicate confidence interval

Table 24: TTE outcome 2 - Time from randomisation to first subsequent therapy or death – AIC and BIC goodness of fit statistics (reproduced from CS[1] Table 7.2)

Model	AIC	BIC
Generalised gamma	**753.78**	774.16
Log normal	754.30	**771.78**
Log logistic	756.21	773.68
Weibull	770.42	787.90
Exponential	772.70	787.26
Gompertz	773.51	790.98

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

Within the company's health economic model, the outcome of time to first subsequent therapy or death curve is used to estimate the probability of transiting from the progression-free state (either whilst on treatment or following discontinuation) to either first subsequent therapy or death. The probability of dying in those who leave the progression-free state, i.e. the proportion of first subsequent therapy events that are deaths, was based on data for the *BRCAm* subgroup within Study 19[27] (see Table 25). The proportion of first subsequent events that were deaths was estimated to be 10.87% in the olaparib group and 3.70% in the placebo group. Within the health economic model, these probabilities are assumed to be constant with respect to time, that is, the hazard of death in patients leaving the first subsequent therapy state is assumed to be directly proportional to the broader hazard of progression or death. The CS[1] does not report any evidence to support this assumption and its appropriateness is unclear.

Table 25: TTE outcome 2 - Number of first subsequent events that were deaths in the *BRCA*m subgroup within Study 19 (adapted from CS[1] Table 7.4)

Transition to	Olaparib N (%)	Placebo N (%)
Death	5 (10.87%)	2 (3.70%)
First subsequent treatment	41 (89.13%)	52 (96.30%)

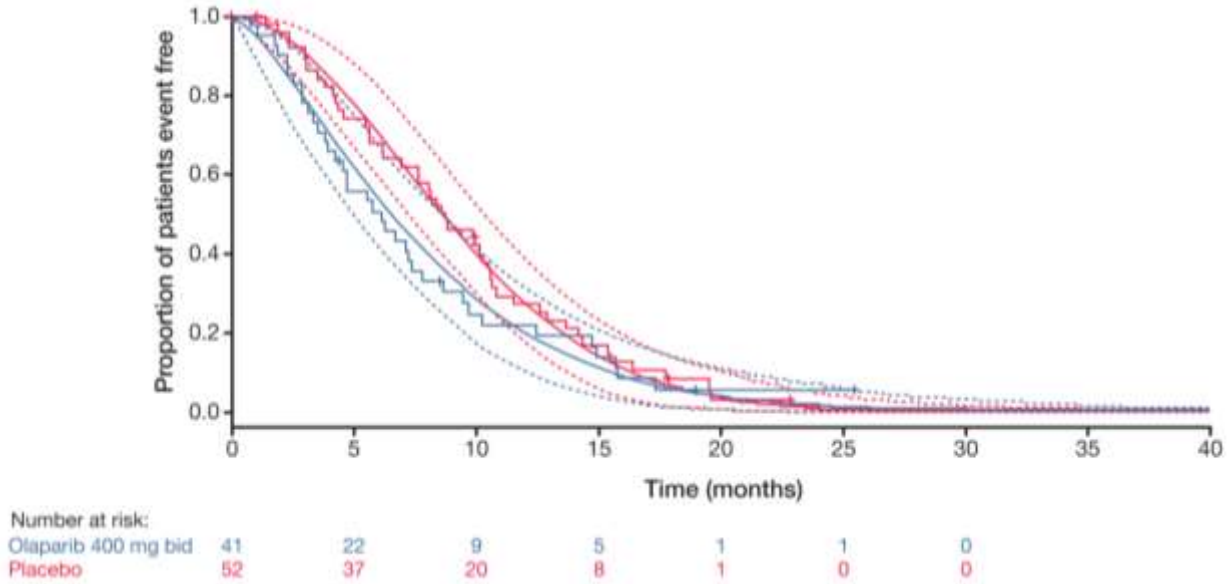
TTE outcome 3: Time from first subsequent therapy to second subsequent treatment or death

The analysis of time from first subsequent therapy to second subsequent therapy or death appears to have been based on those patients included within the Study 19 *BRCAm* subgroup that experienced a first subsequent therapy event and survived. The number of patients at risk within this analysis is not mentioned in the main text of the CS but is reported in the Kaplan-Meier curves presented within Figure 7.8 of the CS[1] (olaparib N=41: placebo N=52). The CS states that since this event does not represent a randomised comparison, treatment-adjusted models were not considered to be appropriate. All curve-fitting for this time-to-event outcome was undertaken using separate models for each treatment group without the inclusion of a treatment covariate. Log logistic, log normal, generalised gamma, Gompertz, exponential and Weibull models were fitted to the available data for each individual treatment group. A graphical plot of the Weibull survivor function against the empirical

Kaplan-Meier survival curves is presented in the CS (see Figure 13 and CS[1] Figure 7.8). The equivalent survivor functions for the log logistic, log normal, Gompertz, exponential and generalised gamma distributions were not presented graphically within the CS.[1] The CS notes that for the placebo group, the Weibull distribution was associated with the lowest AIC and BIC statistics (AIC=295.24, BIC=304.00) whilst for the olaparib group, the log normal distribution was associated with the lowest AIC and BIC statistics (AIC=229.56, BIC=238.13, see Table 26). However, the CS notes that all six distributions provide a reasonable fit to the data based on the AIC and BIC statistics.[1] The Weibull distribution was selected for use in the base case analysis. The justification for selecting the Weibull distribution for both treatment groups, rather than one of the alternative candidate survivor functions, is not entirely clear from the text. The CS states that the log normal and generalised gamma distributions are considered in the sensitivity analysis, however the ERG notes that cost-effectiveness estimates using these alternative survivor functions are not actually presented.

It is important to note that the same time from first to second subsequent therapy or death curve is applied to both treatment groups in the model, based on data for the olaparib group only. The curve relating to the placebo group is not used in the base case model. Consequently, the justification for selecting the Weibull model is unclear.

Figure 13: TTE outcome 3 - Time from first subsequent therapy to second subsequent therapy or death using independent Weibull models (reproduced from CS[1] Figure 7.8)



Dashed lines indicate confidence interval

Table 26: TTE outcome 3 - Time from first subsequent therapy to second subsequent therapy or death – AIC and BIC goodness of fit statistics (adapted from CS[1] Table 7.6)

Olaparib		
Model	**AIC**	**BIC**
Log normal	**229.56**	**238.13**
Log logistic	230.77	239.34
Generalised gamma	231.54	241.82
Weibull	231.64	240.21
Exponential	235.05	241.90
Gompertz	235.29	243.86
Placebo		
Model	**AIC**	**BIC**
Weibull	**295.24**	**304.00**
Generalised gamma	297.19	308.90
Log logistic	298.90	308.66
Log normal	299.20	308.95
Gompertz	300.41	310.17
Exponential	315.11	322.91

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

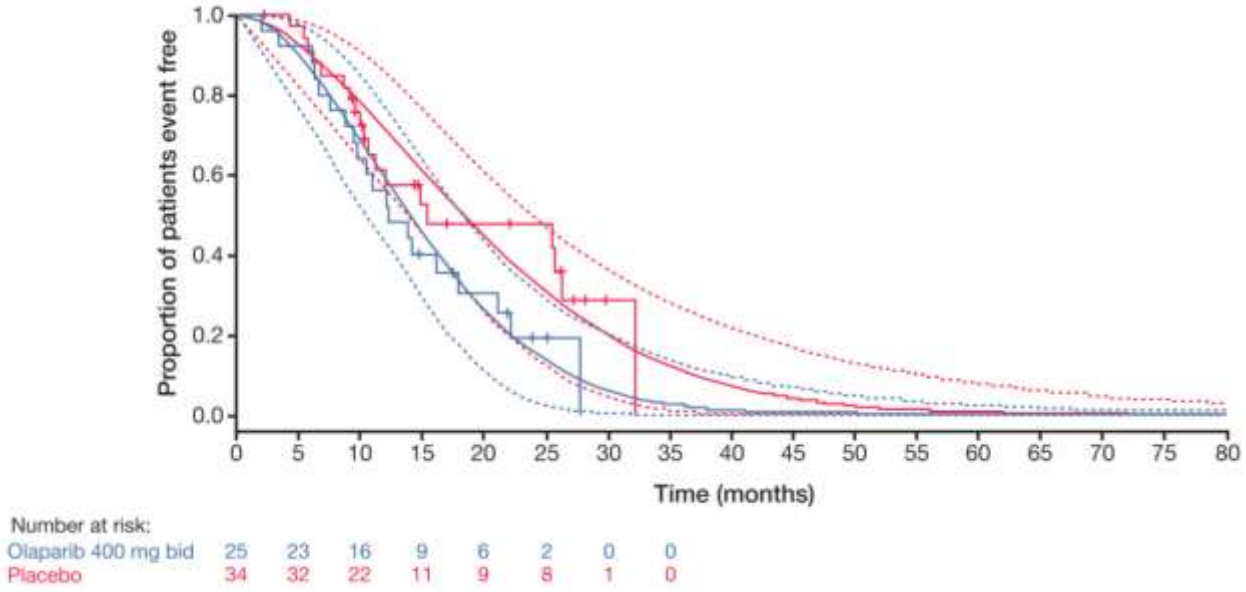
The time from first subsequent therapy to second subsequent therapy or death curve is used in the company's model to estimate the probability of transiting from the first subsequent therapy state to either second subsequent therapy or death. The probability of dying in those who leave the first subsequent therapy state was based on data for the *BRCAm* subgroup within Study 19.[27] Within the text of the CS,[1] the number of second subsequent therapy events that were deaths across both treatment groups is reported to be 32/91 (35.2%). The CS states that the same probability of death is assumed in both groups as the number of events in each treatment group was similar (17 deaths in the olaparib group and 15 deaths in the placebo group). However, examining the number of patients at risk according to the Kaplan-Meier curve (see Figure 13) shows that the number of patients at risk is greater in the placebo group (41 olaparib patients versus 52 placebo patients) hence the observed probability of death from first subsequent therapy is not similar between the two groups (the probability that a second subsequent event is death is 0.41 for olaparib and 0.29 for placebo). Within the health economic model, this probability of transiting from first subsequent therapy to death is assumed to be constant with respect to time, that is, the hazard of death is assumed to be directly proportional to the broader hazard of progression or death. The CS[1] does not report any evidence to support this assumption.

TTE outcome 4: Time from second subsequent therapy to death

The analysis of time from second subsequent therapy to death appears to have been based on those patients included within the *BRCAm* subgroup within Study 19 who reached the second subsequent therapy event and survived. The number of patients at risk within this analysis is not detailed in the

text of the CS but is reported in the Kaplan-Meier curves presented within the CS (see CS[1] Figure 7.9, olaparib N=25: placebo N=34). Again, the CS states that since this event does not represent a randomised comparison, treatment-adjusted models were not used. All curve-fitting for this time-to-event outcome was thus undertaken using separate models for each treatment group without the inclusion of a treatment covariate. Log logistic, log normal, generalised gamma, Gompertz, exponential and Weibull models were fitted to the available data for each individual treatment group. A graphical plot of the Weibull distribution against the empirical Kaplan-Meier data is presented in the CS (see Figure 14 and CS[1] Figure 7.9). The equivalent survivor functions for the log logistic, log normal, Gompertz, exponential and generalised gamma distributions were not presented graphically. The CS[1] states that for the olaparib group, the generalised gamma distribution was associated with the lowest AIC and BIC statistics (AIC=154.00, BIC=161.31). This is not true as the BIC statistic for the Weibull is slightly lower than that of the generalised gamma distribution (Weibull AIC=161.09) However, the CS notes that the generalised gamma distribution provided a poor fit to the empirical survival data. Instead, the Weibull distribution was selected for use in the base case analysis on the basis of its BIC statistic and visual inspection. For the placebo group, the CS states that the generalised gamma distribution was associated with the best goodness of fit statistics (AIC=160.53, BIC=169.69, see Table 27).[1] This is not true as the BIC statistic is lowest for the log normal distribution (log normal BIC=168.56). The CS also states that the generalised gamma distribution fitted the data well visually. The CS states that for the sake of consistency between the two treatment groups, the Weibull distribution was also selected for the placebo group. It is important to note however that the same time from second subsequent therapy to death curve is applied to both treatment groups in the model, based on data for the olaparib group only. The placebo group data for this outcome are not used in the health economic model.

Figure 14: TTE outcome 4 - Time from second subsequent therapy to death – independent Weibull models (reproduced from CS[1] Figure 7.9)



Dashed lines indicate confidence interval

Table 27: TTE outcome 4 - Time from second subsequent therapy to death – AIC and BIC goodness of fit statistics (adapted from CS[1] Table 7.7)

Olaparib		
Model	**AIC**	**BIC**
Generalised gamma	**154.00**	161.31
Weibull	154.99	**161.09**
Log logistic	155.94	162.04
Log normal	156.45	162.55
Gompertz	157.02	163.12
Exponential	161.10	165.97
Placebo		
Model	**AIC**	**BIC**
Generalised gamma	**160.53**	169.69
Log normal	160.93	**168.56**
Log logistic	162.14	169.77
Weibull	164.50	172.13
Gompertz	167.26	174.89
Exponential	169.23	175.33

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

5.2.4.4 Health-related quality of life

The model includes health utility scores associated with the four living health states (progression-free [on maintenance treatment], progression-free [discontinued maintenance treatment], first subsequent therapy and second subsequent therapy). As noted in Chapter 4, Study 19 did not include a preference-based measure of HRQoL. Health utilities for the progression-free (on maintenance

treatment) and progression-free (discontinued maintenance treatment) health states were estimated by mapping from the FACT-O data collected in Study 19[27] to the EQ-5D by applying a published algorithm for cross-walking from the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire to the EQ-5D.[46] Utility estimates for the first and second subsequent therapy states were based on estimates reported within the EVO-301 trial of trabectedin plus PLDH versus PLDH alone in patients with advanced relapsed epithelial ovarian cancer.[38,48] HRQoL decrements associated with AEs are not explicitly included in the company's base case model. The utility values assumed within the company's model are presented in Table 28; their derivation is described in further detail below.

Table 28: Utility values employed within the company's model

Health state	Utility value	Source
Progression-free (on maintenance therapy)	0.77	Mapping analysis[1,47]
Progression-free (discontinued maintenance therapy)	0.71	
First subsequent therapy	0.72	OVA-301 trial (Monk *et al*[48]) as reported within from manufacturer's submission for TA222[38]
Second subsequent therapy	0.65	

Utility scores for progression-free states (mapping analysis)

As discussed in Section 4.2.1.4, Study 19 included the measurement of quality of life using three measures: FACT-O, FACT/NCCN FOSI and the TOI. Data on these outcomes were collected within Study 19 every 28 days until disease progression. The company estimated utility scores for the progression-free health states in the model via a mapping analysis from the FACT-O data collected in Study 19[27] to the EQ-5D. Full details of this mapping analysis are detailed in a further technical report[47] which is cited in the CS.

The company undertook searches to identify potential mapping algorithms by searching a free online database of published peer-reviewed mapping algorithms provided by the Health Economics Research Centre (HERC) at the University of Oxford[57] and through a separate systematic review of the impact of advanced ovarian cancer on HRQoL. The company's systematic review did not identify any studies which reported algorithms that would allow for the mapping of FACT-O to health utility. The company's searches did however identify three published studies that mapped from the FACT-G to the EQ-5D (Longworth *et al*[46], Cheung *et al*[58] and Dobrez *et al*,[59] see Table 29). Two of the studies, Longworth *et al*[46] and Cheung *et al*,[58] explored a variety of alternative statistical regression models including ordinary least squares (OLS), Tobit, response mapping, polynomial splines and mixture models. The algorithm reported by Dobrez *et al*[59] only used an OLS model to map from the FACT-G questionnaire to the EQ-5D.

Table 29: Summary of mapping studies considered by the company

Author	From	To	Disease	Statistical models considered
Longworth *et al*[46]	FACT-G	EQ-5D	Cancer	OLS; 2-part; Tobit; response mapping; polynomial spline, limited dependent variable mixture model
Cheung *et al*[58]	FACT-G	EQ-5D	Cancer	OLS; 2-part; Tobit; response mapping; polynomial spline, limited dependent variable mixture model
Dobrez *et al*[59]	FACT-G	EQ-5D	Cancer	OLS

FACT-G - Functional Assessment of Cancer Therapy – General; EQ-5D – Euroqol 5-Dimensions; OLS – ordinary least squares

The selection of potential mapping algorithms was based on a consideration of whether the characteristics of the estimation sample for the mapping algorithm were similar to, or at least representative of, the target sample of patients within Study 19 and goodness of fit statistics (accuracy of predicted mean and standard error, mean absolute error, shrinkage, reproducibility of the model across different severity states).[47] A comparison of the baseline characteristics of the estimation samples and the target population is presented in Table 30.

Table 30: Comparison of characteristics of alternative estimation datasets considered by the company (adapted from mapping technical report[47])

Characteristic	Sample populations for algorithms			Target population (Study 19)
	Cheung *et al*[58]	Dobrez *et al*[59]	Pickard *et al*[60]* (used in Longworth *et al*[46])	
General				
Sample size	558	717	530	136
Age	49.3	57 (17-99)	59.3 (11.8)	56.7 (10.45)
Gender, female (%)	62.9	47.0	51.0	100.0
Currently undergoing chemotherapy (%)	54.7	NR	NR	0.00†
Tumour site				
Brain	NA	NA	NA	NA
Breast	37.1	17.5	NR	NA
Head & neck (including nasopharyngeal cancer)	18.6	11.4	NR	NA
Colorectal	10.9	NR	NR	NA
Lung	6.1	NR	NR	NA
Gynaecological	6.1	NR	NA	NA
Lymphoma	4.1	NR	NR	NA
Prostate	3.1	13.2	NR	NA
Hodgkin's lymphoma	NA	2.6	NA	NA
Non-Hodgkin's lymphoma	NA	10.3	NA	NA
Non-small cell lung cancer	NA	10.2	NA	NA
Small cell lung cancer	NA	2.4	NA	NA
Ovarian	NA	NA	NR	87.5
Fallopian tube	NA	NA	NR	2.2
Primary peritoneal	NA	NA	NA	10.3
Unknown primary	NA	0.8	NA	NA
Others known	14	20.1	NA	NA
ECOG status (%)				
0	32.8	29.1	23.4	78.7
1	40.3	26.4	48.4	19.1
2	23.5	32.5	23.5	0.7
3	3.4	11	4.7	0
unknown	NR	1	NR	1.5

NA – not applicable; NR – not reported; ECOG - Eastern Co-operative Oncology Group
** Longworth et al state that participants in the survey by Pickard et al had one of 11 cancers at stage 3 or 4 and had undergone at least two cycles of chemotherapy for non-cyclical treatments, and had received treatment for more than 1 month.*
† Study 19 enrolled patients who had PSROC and had received at least two previous rounds of chemotherapy

The OLS algorithm for mapping from the FACT-G to the EQ-5D reported by Longworth *et al*[46] was selected for use in the company's analysis. The technical report submitted alongside the CS[47] states that this choice was made on the basis that (1) the profile of patients enrolled to the survey used to generate the OLS algorithm by Longworth *et al* were generally more comparable to Study 19 than the surveys used in Cheung *et al* and Dobrez *et al*, and (2) the OLS model was considered to have a

stronger goodness of fit profile than the Tobit, Dobrez and Cheung algorithms. Using the OLS algorithm, it was possible to estimate utility values for 247 of 264 patients included in the ITT population of Study 19. An average of 6.67 utility values were available per patient enrolled in the trial.

Single factor regression analyses were undertaken to explore associations between patient characteristics and predicted health utility (see Table 31). Within this analysis, only *BRCA* mutation status and discontinuation of olaparib treatment were statistically significant predictors of EQ-5D utility ($p<0.05$).

Table 31: ITT group single-factor regression models: OLS-generated utility values ~ factor (fixed-effects coefficients) (reproduced from CS[1] Table 7.10)

Variable	Coefficient	Standard error	*p*-value
Time since randomisation	–0.0000409	0.0000386	0.2900
BRCA status (positive vs not positive)	–0.0321	0.0162	0.0489
Randomisation group (placebo vs olaparib)	–0.0138	0.0163	0.3973
AEs (grade 1 or 2 vs no grade 1 or 2)*	–0.0188	0.0103	0.0685
AEs (grade 3 or 4 vs no grade 3 or 4)*	–0.0204	0.0161	0.2065
AEs (categorical) AE 1–2 (reference)			
AE 3–4	–0.0234	0.0485	0.6290
AE both	–0.0178	0.0169	0.2920
No AE	0.0193	0.0104	0.0630
Ongoing treatment vs treatment discontinuation	0.0559	0.0168	0.0001
Radiological progression vs no radiological progression	–0.0228	0.0123	0.0645

**The association between utilities and AEs was mapped by identifying all FACT-O questionnaires collected during an AE episode. As the FACT-O questionnaire requires the respondent to value their health over the last 7 days, any FACT-O questionnaires collected within 7 days of an AE were assumed to be associated with the event.*

The utility values used in the company's health economic model were estimated using multivariate mixed-effects regression models applied to patient-level data from Study 19.[27] The multivariate regression models were used to predict average health state utility values with parametric adjustments for clinically relevant co-factors. These multivariate mixed-effects models included random factors to account for within-patient correlations for repeated measures.[1] Three regression models were fitted to the data from Study 19:

1. A stepwise regression model fitted to data from the ITT population of Study 19. Factors included in the stepwise selection routine were *BRCA* mutation status and treatment discontinuation. This model was selected for use in the base case analysis as it provided the strongest overall fit to the data.

2. A mixed-effects regression model fitted to data from the ITT population within Study 19. Factors included in the mixed effects regression included *BRCA* status, treatment discontinuation, and AEs. This model is considered in the company's sensitivity analysis.
3. A mixed-effects regression model fitted to data from the *BRCA* subgroup within Study 19. Factors included in mixed effects regression included treatment discontinuation and AEs. This model is considered in the company's sensitivity analysis.

The fixed-effects coefficients of the regression models used to predict OLS utility for these three models are presented in Table 32.

Table 32: Fixed-effects coefficients of the regression models used to predict OLS utility in the company's health economic model (reproduced from CS[1] Table 7.11)

Coefficient	Stepwise regression model* (base-case analysis)			ITT population regression* (sensitivity analysis)			*BRCA*-only population regression (sensitivity analysis)†		
	Coeff.	**SE**	***p*-value**	**Coeff.**	**SE**	***p*-value**	**Coeff.**	**SE**	***p*-value**
Intercept	0.745	0.020	<0.01	0.743	0.020	<0.01	0.722	0.025	<0.01
BRCA status:									
Mutation not positive	–	–	–	–			–	–	–
Mutation positive	–0.032	0.016	0.051	–0.032	0.016	0.05			
Adverse event:									
Grade 1–2				–			–		
Grade 3–4	–	–	–	–0.023	0.048	0.640	0.030	0.058	0.582
Both grade				–0.020	0.017	0.232	–0.036	0.025	0.140
No AE				0.0193	0.010	0.063	0.032	0.016	0.042
Treatment discontinuation:									
Discontinued treatment	–	–		–			–		
Ongoing treatment	0.056	0.017	<0.01	0.056	0.017	<0.01	0.042	0.022	0.060
Number of observations	1,428			1,428			741		
Equation	Utility = 0.745 + (*BRCA*=Y) x (–0.032) + (ongoing treatment = Y) x 0.056			Utility = 0.743 + (*BRCA*=Y) x (–0.032) + (AE 3–4) x (–0.023) + (both AEs) x (–0.020) + (no AEs) x 0.0193 + (ongoing treatment = Y) x 0.056			Utility = 0.722 + (AE 3–4) x (–0.030) + (both AEs) x (–0.036) + (no AEs) x 0.032 + (ongoing treatment = Y) x 0.042		
AIC	–2659.373			–2620.337			–1351.491		
BIC	–2611.997			–2557.219			–1310.08		
R^2	0.554			0.544			0.566		
RMSE	0.0694			0.0695			0.0724		

Coeff. – coefficient; ITT – intention-to-treat; BRCA - Breast cancer susceptibility gene; SE – standard error; AE – adverse event; AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; RMSE – root mean squared error

**Within-patient correlation modelled using an autocorrelation moving-average structure;*

†Within-patient correlation modelled using an autocorrelation structure

The utility scores applied in the base case analysis and sensitivity analyses using these three models are summarised in Table 33. The utility scores predicted by the mapping analysis are similar across all three mixed-effects models; the utility estimates for the progression-free on treatment state range from 0.75 to 0.77, whilst the utility estimates for the progression-free discontinued treatment state range from 0.71 to 0.72. The ERG notes that the parameter estimates presented in Tables 7.13 and 7.14 of the CS[1] are inconsistent and do not fully reflect the values applied within the company's model. The values applied in the model itself are summarised in Table 33.

Table 33: Progression-free utility values applied in base case and sensitivity analyses

Model	**Health state**			
	Olaparib		**Routine surveillance**	
	Progression-free (on maintenance treatment)	**Progression-free (discontinued maintenance treatment)**	**Progression-free (on maintenance treatment)**	**Progression-free (discontinued maintenance treatment)**
Stepwise regression model (base case analysis)	0.769	0.713	0.769	0.713
ITT population regression (sensitivity analysis)	0.760*	0.708	0.764*	0.708
BRCA-only population regression (sensitivity analysis	0.750†	0.717	0.759†	0.717
Unadjusted mean EQ-5D	0.768	0.708	0.768	0.708

ITT – intention to treat; BRCA - Breast cancer susceptibility gene; EQ-5D – Euroqol 5-Dimensions
** Within CS[1] Table 7.14, utilities for olaparib and routine surveillance reported to be 0.764 and 0.760, respectively*
†Within CS[1] Table 7.14, utilities for olaparib and routine surveillance reported to be 0.759 and 0.750, respectively

Utility scores for subsequent therapy states

As Study 19 included the collection of HRQoL data only up to the point of disease progression, it was not possible to use the mapping analysis to inform the health utility values for the remaining health states in the model (first subsequent therapy and second subsequent therapy). The CS[1] notes that only 13 questionnaires were recorded at the time of starting a first subsequent therapy within Study 19. Consequently, the company undertook a systematic review to identify alternative estimates of HRQoL associated with first and second subsequent therapy. MEDLINE; MEDLINE In-Process and EMBASE were searched. In addition, utility data reported within published economic model reports included in the systematic review of existing cost-effectiveness studies and within RCTs included in the clinical systematic review were also included in the review. Hand-searching of included studies was undertaken to identify studies that were missed by the electronic searches. Studies were included if they reported on ovarian cancer health utilities; where possible, searches were restricted to publications with a title and abstract available in English, undertaken in humans, and published in the last 10 years.

The searches identified 10 studies which reported health utility values. The CS notes that none of these specifically related to patients with *BRCA* mutations. Only one study was identified which related specifically to patients with platinum-sensitive ovarian cancer;[48] this study was the OVA-301 trial of trabectedin plus PLDH versus PLDH alone in patients with advanced relapsed epithelial ovarian cancer. The values used in the company's model were taken from the manufacturer's submission from NICE TA222.[38] Within this submission, the manufacturer reported EQ-5D utilities of 0.718 for stable disease and 0.649 for progressive disease. These utilities do not directly correspond to the health states used in the company's model which applies differential HRQoL values according to line of subsequent therapy rather than the presence or absence of disease progression. Thus, the company's model makes the implicit assumptions that patients in the first subsequent therapy state have a level of HRQoL which is comparable to those with stable disease and that patients in the second subsequent therapy state have a level of HRQoL which is comparable to those with progressive disease. This assumption is not discussed within the CS.

5.2.4.5 Adverse event frequency

The company's model includes grade 3 or higher AEs that occurred in ≥2% (i.e. >1 patient) of the *BRCAm* subgroup in Study 19 (see Table 34). AE management costs are applied only in first monthly cycle. The company's base case model assumes that AEs have no additional impact on patients' HRQoL.

Table 34: List of adverse events (CTCAE grade >3) included in the company's model

AE	Olaparib, % (n)	Routine surveillance, % (n)
Anaemia	5.4 (4)	1.6 (1)
Neutropenia	4.1 (3)	1.6 (1)
Leucopenia	2.7 (2)	0 (0)
Diarrhoea	2.7 (2)	1.6 (1)
Vomiting	2.7 (2)	0 (0)
Abdominal pain	0 (0)	3.2 (2)
Fatigue	6.8 (5)	1.6 (1)
Pneumonia	2.7 (2)	0 (0)
Back pain	2.7 (2)	0 (0)

5.2.4.6 Resource use parameters

The company's economic evaluation searches (see Section 5.1) were also designed to identify published studies describing resource use (see CS[1] Section 7.5.3). The CS state that three studies[37-39] were found to be relevant to UK clinical practice and that only data reported within these studies were used. The ERG notes that the company's model also includes resource use and cost estimates derived from a number of other sources.[12,27,25,49-51,61] These are detailed in the following sections.

Resource use associated with follow-up

Follow-up costs applied in the model are summarised in Table 35. For the progression-free health state, resource use associated with follow-up was based on NICE TA285[39] (bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer). Prior to commencing subsequent chemotherapy, the model assumes that patients will undergo one outpatient visit each month and one CT scan every two months. For patients receiving olaparib, an additional monthly blood test is assumed. The CS states that resource use estimates from other sources identified in the systematic literature review were examined within the sensitivity analyses; the ERG notes that these analyses are not actually presented within the CS.[1] It was assumed that there are no additional administration costs associated with treatment with olaparib, with the CS stating that olaparib would be prescribed at the time of a regular scheduled follow-up consultation. The resource use estimates associated with the first and second subsequent therapy states were based on the manufacturer's submission within NICE TA285.[39] The company's model assumes that patients in these states will undergo one outpatient visit every three months. The costs of blood tests and CT scans are not included in these states. It should be noted that the resource use estimates reported in the manufacturer's submission for NICE TA285,[39] which are applied to the first and second subsequent therapy states in the company's model, relate to a state of "progressed disease" and do not reflect differential resource use associated with a progression-free interval whilst on chemotherapy.

Table 35: Monthly follow-up resource use

Follow-up resource component	Company's base case[1]	NICE TA285[39] (base case)	NICE TA284[40]	Fisher *et al* 2013[37]
Progression-free state				
Outpatient visit (consultant oncologist)	1.00	1.00	0.33	1.00
CT scan	0.50	0.50	0.00	0.50
Blood test*	1.00	n/a	n/a	n/a
First and second subsequent therapy states				
Outpatient visit (consultant oncologist)	0.33	0.33	1.00	n/a†
CT scan	0.00	0.00	0.50	n/a†
Blood test	0.00	n/a	n/a	n/a

CT – computerised tomography
**included only for olaparib patients*
†*relevant costs assumed to be palliative care only*

Chemotherapy resource use

Chemotherapy treatments included in the company's model were those that were (a) reported in greater than 3% of the total *BRCAm* subgroup within Study 19 (n=136), and (b) classified as licensed anticancer treatments (i.e. investigational treatments were excluded). According to the CS,[1] 15 out of total of 108 unique chemotherapy regimens administered during the period following disease

progression in Study 19 met these restrictions and were included in the company's model. The ERG notes that within the company's model, the utilisation of carboplatin and paclitaxel is actually zero, hence only fourteen regimens are included. The chemotherapy regimens used in the company's model are summarised in Table 36.

Table 36: Chemotherapy regimens included in the company's model (reproduced from CS[1] Table 7.24)

Regimen	Drug	Dose per administration	Administrations per cycle	Schedule	Frequency of cycle	Utilisation
Platinum-based chemotherapy regimens						
Carboplatin	Carboplatin	3 vials	1	Day 1	Repeated every 21–28 days for up to 6 cycles	29%
Carboplatin and gemcitabine	Carboplatin	3 vials	1	Carboplatin: Day 1 Gemcitabine: Days 1 and 8 Day 1	Repeated every 21 days for up to 6 cycles Repeated every 28 days for up to 6 cycles	24%
	Gemcitabine	1 vial	2			
Carboplatin and doxorubicin	Carboplatin	3 vials	1	Carboplatin: Day 1 Doxorubicin: Day 1	Repeated every 21 days for up to 6 cycles	15%
	Doxorubicin	7 vials	1			
Carboplatin and cyclophosphamide	Carboplatin	3 vials	1	Carboplatin: Day 1 Cyclophosphamide: Continuous until disease progression	Repeated every 21–28 days for up to 6 cycles	7%
	Cyclophosphamide	50 mg	28			
Carboplatin and docetaxel	Carboplatin	3 vials	1	Carboplatin: Day 1 Docetaxel: Day 1	Repeated every 21 days for up to 6 cycles	7%
	Docetaxel	2 vials	1			
Cisplatin and cyclophosphamide	Cisplatin	3 vials	1	Cisplatin: Day 1 Cyclophosphamide: Continuous until disease progression	Repeated every 21 days for up to 6 cycles	6%
	Cyclophosphamide	50 mg	28			
Cisplatin and paclitaxel	Cisplatin	3 vials	1	Cisplatin: Day 1 Paclitaxel: Day 1	Repeated every 21 days for up to six cycles Repeated every 21 days for up to six cycles	5%
	Paclitaxel	3 vials	1			
Carboplatin and	Carboplatin	3 vials	1	Carboplatin:	Repeated every 21 days for up to	4%

Regimen	Drug	Dose per administration	Administrations per cycle	Schedule	Frequency of cycle	Utilisation
gemcitabine hydrochloride	Gemcitabine hydrochloride	1 vial	2	Day 1 Gemcitabine: Days 1 and 8	six cycles Repeated every 21 days for up to six cycles	
Cisplatin and cyclophosphamide and docetaxel	Cisplatin	3 vials	1	Carboplatin: Day 1 Gemcitabine: Days 1 and 8	Repeated every 21 days for up to six cycles	3%
	Cyclophosphamide	50 mg	28			
	Docetaxel	2 vials	1			
Carboplatin and paclitaxel	Carboplatin	4 vials	1	Carboplatin: Day 1 Paclitaxel: Day 1	Repeated every 21 days for up to six cycles	0%
	Paclitaxel	3 vials	1			
Non-platinum-based chemotherapy regimens						
Doxorubicin	Doxorubicin	7 vials	1	Day 1	Repeated every 21–28 days for up to four cycles	38%
Topotecan	Topotecan	1 vial	5	Days 1–5 inclusive	Repeated every 21 days for up to six cycles	24%
Paclitaxel	Paclitaxel	3 vials	1	Day 1	Repeated every 21 days for up to six cycles	20%
Etoposide	Etoposide	100 mg	14	Days 1–14 inclusive	Repeated every 21 days for up to six cycles	11%
Gemcitabine	Gemcitabine	1 vial	2	Gemcitabine: Days 1 and 8	Repeated every 21 days for up to six cycles	7%

For each regimen, the company estimated chemotherapy treatment doses based on a review of the relevant SmPC for each product and guidelines reported by Yorkshire Cancer Network Gynaecology Network Group.[49] The average number of cycles of chemotherapy administered to patients with ovarian cancer over the course of a single-treatment programme was estimated from various sources including studies identified as part of the company's systematic review of economic evaluation studies in ovarian cancer. Details relating to the sources for the dosage and frequency of the treatment regimens were not provided within the CS. In the company's model, the single therapy regimens of carboplatin, paclitaxel, and topotecan were administered as one-off treatment regimens, rather than as an alternative weekly programme of treatment administration whereby the full dose is administered over repeated visits. The CS states that patients with advanced ovarian cancer who have undergone several previous courses of chemotherapy (reflecting the patients in Study 19) would not be eligible for weekly treatment.[1]

5.2.4.7 Unit costs

Cost of olaparib maintenance therapy

The cost of olaparib treatment was calculated based on the UK list price of £3,950 per pack, with each pack containing 448 50-mg capsules (equivalent to 28 days treatment, 16 capsules per day). The model applies a mean dosage of 675.9mg per day, based on the experience of patients within *BRCAm* subgroup within Study 19.[1] This corresponds to a monthly cost of olaparib of £3,627.78 per month (see Table 37).

Table 37: Cost of olaparib assumed within the company's model

Item	Cost
Cost per pack	£3,950
Units per pack	448
Mg per capsule	50
Cost per mg	£0.18
Mean daily dose (mg)	675.9
Days per month	30.4375
Cost per month	£3,627.78

Follow-up costs

The unit costs associated with follow-up (blood tests, outpatient visits and CT scans) used in the company's model were taken from NHS Reference Costs 2012/13 (see Table 38).

Table 38: Follow-up costs used in the company's model

Item	Unit cost	Source
Outpatient visit (consultant oncologist)	£127	NHS Reference Costs 2012/13.[25] Consultant-led outpatient attendance – non-admitted face to face, follow-up. Code: WF01A 503, gynaecological oncology
CT scan	£90	NHS Reference Costs 2012/13.[25] Diagnostic imaging; CT scan, one area, no contrast. 19 years and over. Code: RA08A
Blood test	£3	NHS Reference Costs 2012/13.[25] Haematology, directly accessed pathology services. Code: DAPS05

CT – computerised tomography

Adverse event costs

The costs of managing AEs were based on NHS Reference Costs 2012/13[25] and assumptions (see Table 39). Fatigue and back pain were assumed not to require medical care.

Table 39: Adverse event costs used in the company's model

AE	Unit cost, £ (2012–13)	Source
Anaemia	£792.16	NHS Reference Costs 2012/13.[25] Total HRG costs, iron deficiency anaemia with CC, currency codes: SA04G-SA04L (weighted by activity)
Neutropenia	£179.00	NHS Reference Costs 2012/13.[25] Total HRG costs, neutropenia drugs, band 1, currency code: XD25Z
Leucopaenia	£179.00	NHS Reference Costs 2012/13.[25] Total HRG costs, neutropenia drugs, band 1, currency code: XD25Z
Diarrhoea	£1,332.52	NHS Reference Costs 2012/13.[25] Total HRG costs, fluid and electrolyte disorders, with interventions, with CC, currency codes: KC05G-KC05N (weighted by activity)
Vomiting	£1,015.63	NHS Reference Costs 2012/13.[25] Total HRG costs, feeding difficulties and vomiting, with CC, currency codes: PA28A-PA28B (weighted by activity)
Abdominal pain	£699.00	NHS Reference Costs 2012/13.[25] Total HRG costs, abdominal pain, currency code: PA29Z
Fatigue	£0.00	Assumption of no medical care
Pneumonia	£1,846.44	NHS Reference Costs 2012/13.[25] Total HRG costs, lobar, atypical or viral pneumonia, with CC, currency codes: DZ11D-DZ11J (weighted by activity)
Back pain	£0.00	Assumption of no medical care

CC - complications and comorbidities; HRG - healthcare resource group

Chemotherapy costs

Chemotherapy costs in the company's model include those associated with drug acquisition and administration. Unit costs for generic chemotherapy drugs were obtained from the NHS Commercial Medicines Unit (CMU) through the Electronic Marketing Information Tool (eMit) and from the BNF[12] for those products which were unavailable from the CMU (see Table 40). Chemotherapy administration costs applied within the company's model are summarised in Table 41.

Table 40: Cost of subsequent chemotherapy applied in the first and subsequent therapy states in the company's model (adapted from CS[1] 7.23)

Chemotherapy	Available formulations	Pack size	Unit cost per pack	Cost per mg	Source
Carboplatin*	5 mL (50 mg) 15 mL (150 mg) 45 mL (450 mg) 60 mL (600 mg)	1 vial	£3.51 £7.71 £19.07 £28.89	£0.07 £0.05 £0.04 £0.05	NHS CMU[61]
Gemcitabine	200 mg 1000 mg 2000 mg	1 vial	£3.37 £10.55 £21.64	£0.02 £0.01 £0.01	NHS CMU[61]
Doxorubicin	10 mg 50 mg	1 vial	£18.72 £100.12	£1.87 £2.00	BNF[12]
Topotecan	1 mg 4 mg	1 vial	£19.84 £33.06	£19.84 £8.27	NHS CMU[61]
Paclitaxel†	5 mL (30 mg) 16.7 mL (100.2 mg) 25 mL (150 mg) 50 mL (300 mg)	1 vial	£3.21 £7.54 £12.23 £22.78	£0.11 £0.08 £0.08 £0.08	NHS CMU[61]
Cyclophosphamide	50 mg/tablet	100 tablets	£82.00	£0.01	BNF[12]
Docetaxel‡	1 mL (20 mg) 4 mL (80 mg) 7 mL (140 mg) 8 mL (160 mg)	1 vial	£12.87 £33.41 £77.54 £29.78	£0.64 £0.42 £0.55 £0.19	NHS CMU[61]
Cisplatin	10 mL (10 mg) 50 mL (50 mg) 100 mL (100 mg)	1 vial	£3.55 £11.21 £16.69	£0.35 £0.22 £0.17	NHS CMU[61]
Etoposide§	50 mg/capsule 100 mg/capsule	20 capsules 10 capsules	£99.82 £87.23	£0.10 £0.09	BNF[12]

BNF – British National Formulary; CMU – Commercial Medicines Unit
**Based on 10 mg of carboplatin per mL of solution*
†Based on 6 mg of paclitaxel per mL of solution
‡Based on 10 mg of docetaxel per mL of solution for 2-, 8- and 16-mL formulations. Based on 20 mg/mL of docetaxel per mL of solution for the 1-, 4- and 7-mL formulations
§Based on capsule formulation of Vepesid®

Table 41: Chemotherapy administration costs used in the company's model

Resource	Unit cost	Source
i.v. infusion first administration	£155	NHS Reference Costs 2012/13[25] Chemotherapy, Deliver simple parenteral chemotherapy at first attendance, outpatient, Code: SB12Z
i.v. infusion subsequent administration	£255	NHS Reference Costs 2012/13[25] Chemotherapy, Deliver subsequent elements of a chemotherapy cycle, outpatient, Code: SB15Z
Oral chemotherapy administration	£156	NHS Reference Costs 2012/13[25] Chemotherapy, Deliver exclusively oral chemotherapy, outpatient, Code: SB11Z

The CS[1] states that the cost of treatment was based on the least expensive vial size or tablet strength available in the UK as this provided a conservative estimate of the cost of chemotherapy in the model. The costs of administration depend on the number of days in the administration schedule for each cycle. The costs per cycle of the chemotherapies used in the model are presented in Table 42.

Table 42: Per-cycle cost of subsequent chemotherapies (adapted from CS[1] Table 7.25)

Regimen	Drug	Dose per administration	Administrations per cycle	Acquisition cost per cycle	Total administration cost	Total cost per cycle
Carboplatin	Carboplatin	3 vials	1	£19.07	£255.00	£274.07
Carboplatin and gemcitabine	Carboplatin	3 vials	1	£62.35	£410.00	£472.35
	Gemcitabine	1 vial	2			
Doxorubicin	Doxorubicin	7 vials	1	£131.04	£255.00	£386.04
Carboplatin and doxorubicin	Carboplatin	3 vials	1	£150.11	£255.00	£405.11
	Doxorubicin	7 vials	1			
Topotecan	Topotecan	1 vial	5	£165.30	£875.00	£1,040.30
Paclitaxel	Paclitaxel	3 vials	1	£22.62	£255.00	£277.62
Carboplatin and cyclophosphamide	Carboplatin	3 vials	1	£42.03	£255.00	£297.03
	Cyclophosphamide	50 mg	28			
Carboplatin and docetaxel	Carboplatin	3 vials	1	£48.85	£255.00	£303.85
	Docetaxel	2 vials	1			
Cisplatin and cyclophosphamide	Cisplatin	3 vials	1	£56.34	£255.00	£311.34
	Cyclophosphamide	50 mg	28			
Etoposide	Etoposide	100 mg	14	£122.12	£156.00	£278.12
Cisplatin and paclitaxel	Cisplatin	3 vials	1	£56.00	£255.00	£311.00
	Paclitaxel	3 vials	1			
Carboplatin and gemcitabine hydrochloride	Carboplatin	3 vials	1	£62.35	£410.00	£472.35
	Gemcitabine hydrochloride	1 vial	2			
Cisplatin and cyclophosphamide and docetaxel	Cisplatin	3 vials	1	£86.12	£255.00	£341.12
	Cyclophosphamide	50 mg	28			
	Docetaxel	2 vials	1			
Gemcitabine	Gemcitabine	1 vial	2	£43.28	£410.00	£453.28
Carboplatin and paclitaxel	Carboplatin	4 vials	1	£60.76	£255.00	£315.76
	Paclitaxel	3 vials	1			

End-of-life costs

The costs of end-of-life care were applied as a once-only cost in the model applied at the point of death. This cost was based on studies reported by Gao *et al*[51] and Guest *et al.*[50] The CS[1] states that Gao *et al* estimate that 51% of end-of-life care in England is administered in a health service setting. A study reported by Guest *et al* estimated the end-of-life costs for patients with ovarian cancer, based on 21 ovarian cancer patients, to be £7,342 (inflated from 2000/01 to 2012/13 prices) for an average time period of 399 days. The total end-of-life care cost applied at death in the model was £3,765 per patient.

5.2.4.8 *BRCA* mutation testing costs

The costs of *BRCA* mutation testing are included in the company's sensitivity analyses but are excluded from the base case analysis. The resource use and costs associated with *BRCA* mutation testing was estimated using the following formula:

Number tested to reach population

$$= \frac{\text{Cohort size} - (\text{proportion previously identified} * \text{cohort size})}{\text{Prevalence of } \textit{BRCA} \text{ mutation}}$$

Table 43: Resource use and costs associated with *BRCA* mutation testing

Attribute	Value	Source
Cohort size	1,000	Model default setting
Prevalence of *BRCA*m in PSR ovarian cancer patients	20%	Ovarian Cancer Action 2014[52]
Proportion of subjects previously identified, %	20%	Astra Zeneca Horizon 2013[53]
*BRCA*m test laboratory cost	£600.00	UK Genetic Testing Network[54]
Genetic counselling cost (two sessions)	£126.00	Based on rate/hour of patient contact for band 7 counsellor in primary medical care[55]

Based on the data presented in Table 43, the number tested to reach a cohort size of 1,000 was calculated in the model as 4,000 (i.e. = (1000 *x* (1-0.20)) / 0.20). This value was then multiplied by the cost of testing to estimate the total cost of *BRCA* mutation testing in the cohort. The CS[1] states that the laboratory costs of *BRCA* mutation testing ranged from £350 to £1,040 in centres across England and Wales that currently provide the testing service; the model uses a laboratory cost of £600 for *BRCA* mutation testing. The economic section of the CS does not clearly specify whether the estimated costs of *BRCA* mutation testing reflect germline and/or somatic testing.

5.2.4.9 Costs and benefits of *BRCA* mutation testing in unaffected relatives

As noted in Section 5.2, the potential costs and benefits associated with *BRCA* mutation testing of unaffected relatives were not estimated directly in the model but were instead taken from a supplementary report of a model-based analysis of *BRCA* mutation testing undertaken alongside the development of NICE CG164.[8,53] The CS states that the objective of the economic model in NICE CG164 was to assess the cost-effectiveness of *BRCA* mutation testing compared with no testing in individuals with a family history of breast or ovarian cancer for a range of different carrier probabilities (the probabilities of carrying the same genetic mutation) ranging from 5–40% and ages (from 20 years to >70 years).

Separate analyses were presented for three populations in NICE CG164.[8] The company considered results from Population 2 (people unaffected by cancer with an affected relative available to test) to be applicable to first- and second-degree relatives of women with *BRCAm* PSR ovarian cancer, stating that, in the CG164 model, genetic testing is offered to individuals in this population only if a positive result is obtained as a result of genetic testing in their affected relative. The results for Population 1 (people affected by breast/ovarian cancer) and Population 3 (people unaffected by cancer without an affected relative available to test) were not considered to be applicable to the decision problem.

The company assumed that any first-degree relatives (parents, children or siblings) will have a 50% probability of carrying the same mutation and any second-degree relatives (grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings) will have a 25% probability of carrying the same mutation. However, since the NICE CG164 model report did not present analyses for these carrier probabilities, the results for individuals with carrier probabilities of 40% and 20% were applied for first-degree relatives and second-degree relatives, respectively.

Overview of CG164 model structure and methods

The model developed as part of NICE CG164 takes the form of an initial decision tree for *BRCA* mutation testing (Stage 1, see Figure 15) and a subsequent semi-Markov model to reflect the natural progression of disease following risk-reducing surgery decisions, made as a result of genetic testing or in its absence (Stage 2, see Figure 16).[8] Within Stage 2, both cancer-related deaths and all-cause mortality were included. Transitions between health states were modelled using annual cycles over a 50-year time horizon. The model assumed that unaffected relatives would start in a state of no cancer from which they could enter a state of new breast cancer or new ovarian cancer. The model also assumed that breast and ovarian cancers would not be detected in the same cycle. Surviving patients were assumed to enter a state of existing cancer and remained in this state until the development of a new cancer or death. The existing cancer states were divided into five sub-states, defined by the time

since incidence of the most recently developed cancer, in order to estimate costs, HRQoL and survival rates specific to time since diagnosis.[8]

The model adopted a UK NHS perspective with health outcomes expressed in terms of QALYs. Costs and health outcomes were discounted at a rate of 3.5% per annum. Clinical model input parameters were obtained from the published literature and the expert opinion of the NICE Guideline Development Group (GDG). Clinical data inputs included uptake and accuracy of *BRCA* mutation testing, uptake of risk-reducing surgery and risk-reduction rates, and non-disease specific and cancer-related mortality. Annual cancer incidence according to *BRCA* mutation status and carrier probability was estimated using the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA). Utility values relating to the breast and ovarian cancer states and the impact of risk-reducing surgery and *BRCA* mutation testing were based on literature and assumptions. Resource use and cost inputs included the costs of *BRCA* mutation testing (laboratory costs plus genetic counselling), risk-reducing surgery, surveillance (magnetic resonance imaging [MRI] or mammography), cancer treatment and end-of-life care.

Figure 15: Stage 1 decision tree model schematic for Population 2 (reproduced from NICE CG164 cost-effectiveness review[8])

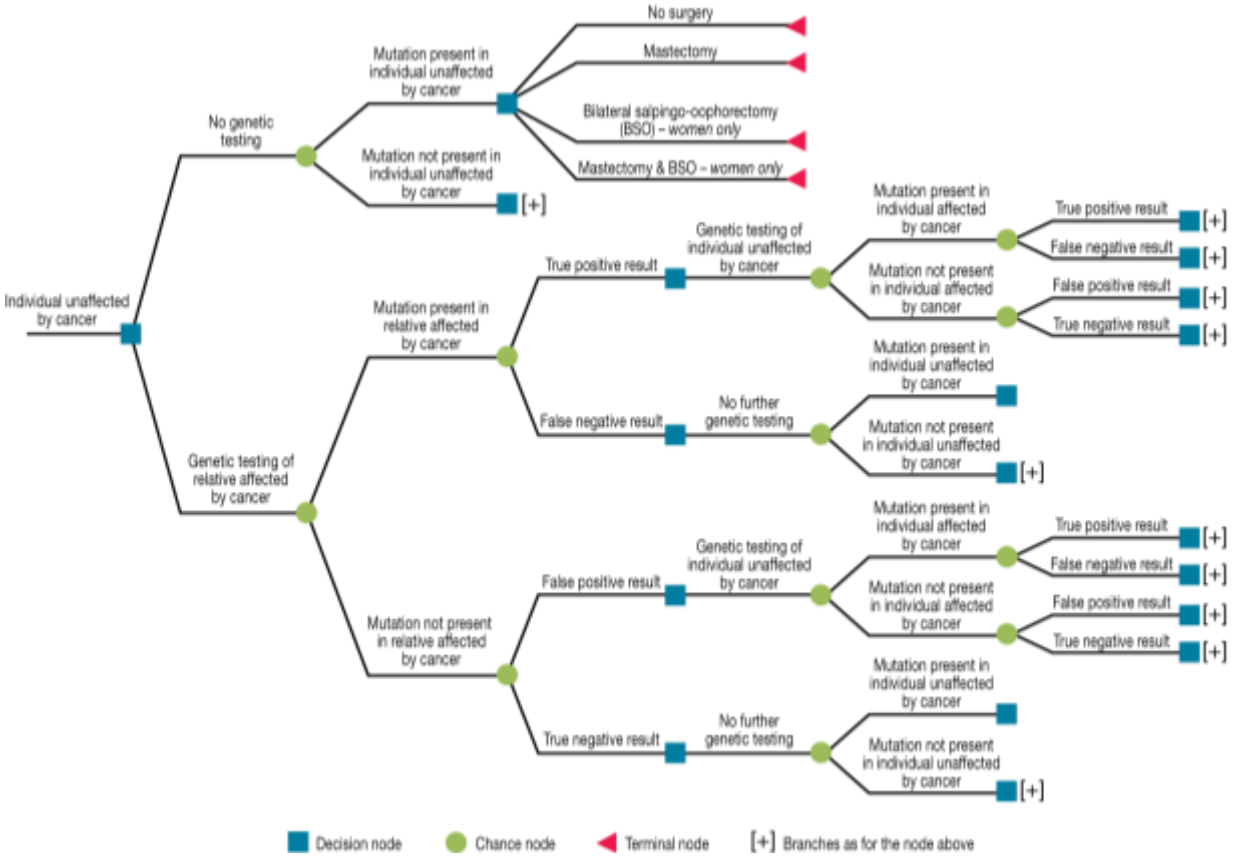
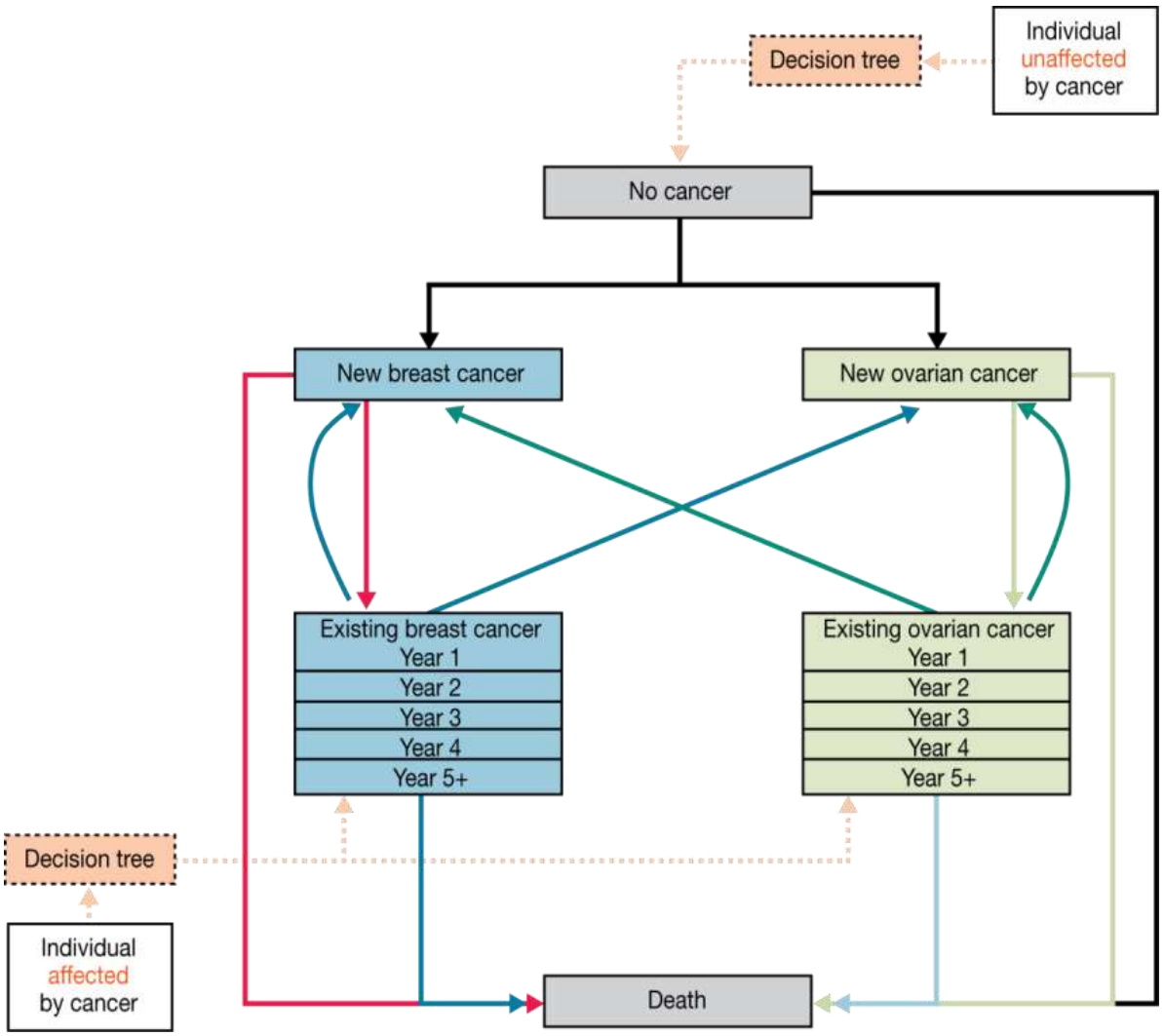


Figure 16: Stage 2 semi-Markov model schematic (reproduced from NICE CG164 cost-effectiveness review[62])



Results from NICE CG164 cost-effectiveness analysis for Population 2

Table 44 summarises the costs and QALY estimates reported for Population 2 within NICE CG164;[8] these estimates are used within the company's secondary analysis of the cost-effectiveness of olaparib in conjunction with the wider costs and benefits of *BRCA* mutation testing for relatives.

Table 44: Results for Population 2 (adapted from NICE CG164 cost-effectiveness review[8])

Carrier probability	Outcome/patient	No testing	*BRCA* mutation testing	Difference
Individuals aged 20–29 years				
20%	Total costs	£11,518	£12,719	£1,200
	Total QALYs	19.63	19.72	0.0932
40%	Total costs	£18,447	£19,137	£690
	Total QALYs	18.67	18.81	0.1357
Individuals aged 30–39 years				
20%	Total costs	£15,357	£16,437	£1,080
	Total QALYs	18.22	18.33	0.1158
40%	Total costs	£23,827	£24,432	£605
	Total QALYs	16.99	17.15	0.1546
Individuals aged 40–49 years				
20%	Total costs	£17,698	£18,781	£1,083
	Total QALYs	16.40	16.50	0.1084
40%	Total costs	£26,930	£27,587	£657
	Total QALYs	15.16	15.29	0.1389
Individuals aged 50–59 years				
20%	Total costs	£16,376	£17,599	£1,222
	Total QALYs	14.31	14.38	0.0759
40%	Total costs	£24,209	£25,082	£873
	Total QALYs	13.41	13.51	0.0963
Individuals aged 60–69 years				
20%	Total costs	£13,777	£15,159	£1,382
	Total QALYs	11.67	11.71	0.0437
40%	Total costs	£19,785	£20,889	£1,104
	Total QALYs	11.15	11.21	0.0550
Individuals aged >70 years				
20%	Total costs	£10,638	£12,211	£1,575
	Total QALYs	8.38	8.39	0.0181
40%	Total costs	£14,783	£16,161	£1,378
	Total QALYs	8.14	8.16	0.0236

BRCA - Breast cancer susceptibility gene; QALY – quality-adjusted life year

Company's assumptions regarding the family pedigrees included in the company's analysis

Within the company's secondary analysis, the estimated costs and benefits of *BRCAm* testing from NICE CG164[8] were combined with five family pedigrees to estimate costs and QALY gains of *BRCA* mutation testing for family members of the index case PSR ovarian cancer patient. These analyses incorporated a number of assumptions:

- The index case in each pedigree was assumed to have PSR ovarian cancer.
- If the age of the index case in a pedigree was not available, it was assumed that they were aged 57 years, based on the average age of *BRCAm* patients enrolled within Study 19.
- It was assumed that index case in each pedigree developed PSR ovarian cancer 2 years following initial diagnosis of ovarian cancer if they were still alive. At this point in time, they would be considered for *BRCA* mutation testing in consideration of olaparib as a subsequent treatment option following completion of chemotherapy.

- Only first-degree (mother, daughters and sisters of the index case) and second-degree (granddaughter, niece, half-sister) female relatives were included for analysis. Second-degree relatives older than the index case were excluded from the analysis.
- Within each family pedigree, only female relatives unaffected by breast or ovarian cancer who were eligible for *BRCA* mutation testing were included. Female relatives affected by breast or ovarian cancer, and any of their children, were excluded.
- Unaffected male relatives who may have been eligible for *BRCA* mutation testing were excluded.
- Any unaffected relatives denoted as unknown gender in the pedigree were excluded.
- The analysis included only relatives eligible for testing who were 20 years of age or older.
- If the ages of any unaffected relatives within a pedigree were not available, it was assumed that there was a 30-year age difference between generations (e.g. mother and daughter).
- Unaffected relatives of unknown age within a pedigree were assumed to be the same age as a sibling with known age.

5.2.5 Methods for economic evaluation

The results of the company's health economic analysis of olaparib versus routine surveillance are presented in terms of the incremental cost per QALY gained. The base case results are based on point estimates of parameters; the ICER based on the expectation of the mean is also presented within the text of the CS. Uncertainty surrounding the incremental costs and health outcomes associated with olaparib were evaluated using probabilistic sensitivity analysis (PSA), one-way sensitivity analysis and scenario analysis.

Within the company's PSA, probability distributions were assigned to uncertain parameters (see Table 45). Uncertainty was propagated through the model over 5,000 iterations using Monte Carlo sampling and represented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

Table 45: Distributions used in company's PSA (adapted from CS[1] Table 7.27)

Parameter group	Parameters	Distribution assigned
Patient characteristics	Proportion of patients with complete OR, partial platinum sensitivity and Jewish ancestry	Beta
	Weight, body surface area and GFR	Normal
Clinical events (time-to-event outcomes, death probabilities and AE probabilities)	Survival distributions for PF, FST, SST and time on treatment	Multivariate normal with correlation between shape and scale parameters
	Proportion of events leading to death	Beta
	Proportion of patients with AEs	Beta
HRQoL	Regression equation for utility value assigned to PF state	Multivariate normal
	Utility values assigned to FST and SST states	Beta
Resources and costs	Case mix of platinum- and non-platinum-based chemotherapy	Dirichlet
	Resource use at PF, FST and SST states	Gamma
	AE costs	Gamma

OR – objective response; GFR - glomerular filtration rate; PF – progression-free; FST – first subsequent therapy; SST – second subsequent therapy; AE – adverse event; HRQoL – health-related quality of life

In the company's one-way sensitivity analysis, the input values for key parameters in the model were varied between ± 20% of the expected value used in the deterministic base case. The CS[1] states that utilities, clinical data and costs were included in the one-way sensitivity analysis. ICERs associated with changes in the 10 most influential parameters were presented using a tornado diagram.

In the company's scenarios analyses, alternative assumptions were made regarding the choice of time-to-event survivor functions and the utility values for the progression-free health state. In addition, further scenarios are presented assuming time horizons of 3-, 5- and 10-years respectively. An additional scenario analysis which includes the cost of *BRCA* mutation testing is also presented.

5.2.6 Cost-effectiveness results presented by the company

5.2.6.1 Central estimates of cost-effectiveness

The central estimates of cost-effectiveness for olaparib versus routine surveillance are summarised in Table 46. As noted in Section 5.2.5.1, the company's base case results are based on point estimates of parameters. The estimates of cost-effectiveness based on the expectation of the mean (i.e. the PSA) presented within Table 46 were derived from the company's model directly (note – LYGs are not reported as these are not recorded within the company's PSA sub-routine).

Table 46: Central estimates of cost-effectiveness presented within the CS

Central estimates of cost-effectiveness (point estimates of parameters)							
Option	LYGs	QALYs	Costs	LYGs	Inc. QALYs	Inc. costs	ICER
Olaparib	3.55	2.58	£82,041	1.17	0.89	72,143	**81,063**
Routine surveillance	2.38	1.69	£9,898	-	-	-	-
Central estimates of cost-effectiveness (expectation of the mean)							
Option	LYGs*	QALYs	Costs	LYGs*	Inc. QALYs	Inc. costs	ICER
Olaparib	-	2.60	£82,048	-	0.90	£72,232	**£79,953**
Routine surveillance	-	1.70	£9,816	-	-	-	

Inc. – incremental; LYG – life year gained; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio
**life years gained are not recorded within the company's PSA sub-routine*

Based on the probabilistic analysis of the model, olaparib is expected to produce an additional 0.90 QALYs at an additional cost of £72,232 compared against routine surveillance. The ICER for olaparib versus routine surveillance is therefore expected to be £79,953 per QALY gained. The results based on point estimates of parameters are similar, with olaparib yielding an ICER of £81,063 per QALY gained compared against routine surveillance.

Table 47 presents a breakdown of costs and QALYs for olaparib and routine surveillance based on values reported within the company's model (deterministic, discounted and half-cycle corrected).

Table 47: Breakdown of costs and QALYs for olaparib and routine surveillance

Component	**Olaparib**	**Routine surveillance**	**Difference (olaparib vs routine surveillance)**
QALYs			
Progression-free on treatment	1.24	0.54	0.70
Progression-free discontinued treatment	0.52	0.21	0.31
First subsequent therapy	0.39	0.44	-0.05
Second subsequent therapy	0.44	0.50	-0.06
Total QALYs gained	2.58	2.69	0.89
Costs			
Maintenance therapy (olaparib)	£70,152.48	£0.00	£70,152.48
AEs	£168.20	£59.23	£108.98
First subsequent therapy	£1,459.07	£1,887.95	-£428.88
Second subsequent therapy	£1,423.16	£1,669.23	-£246.07
Follow-up	£5,498.29	£2,761.14	£2,737.15
End-of-life	£3,339.40	£3,520.07	-£180.67
Total costs	£82,040.60	£9,897.60	£72,142.99

QALY – quality-adjusted life year

The results presented in Table 47 suggest that the majority of the incremental QALY gains for olaparib versus routine surveillance are generated within the "progression-free" states (1.01 additional

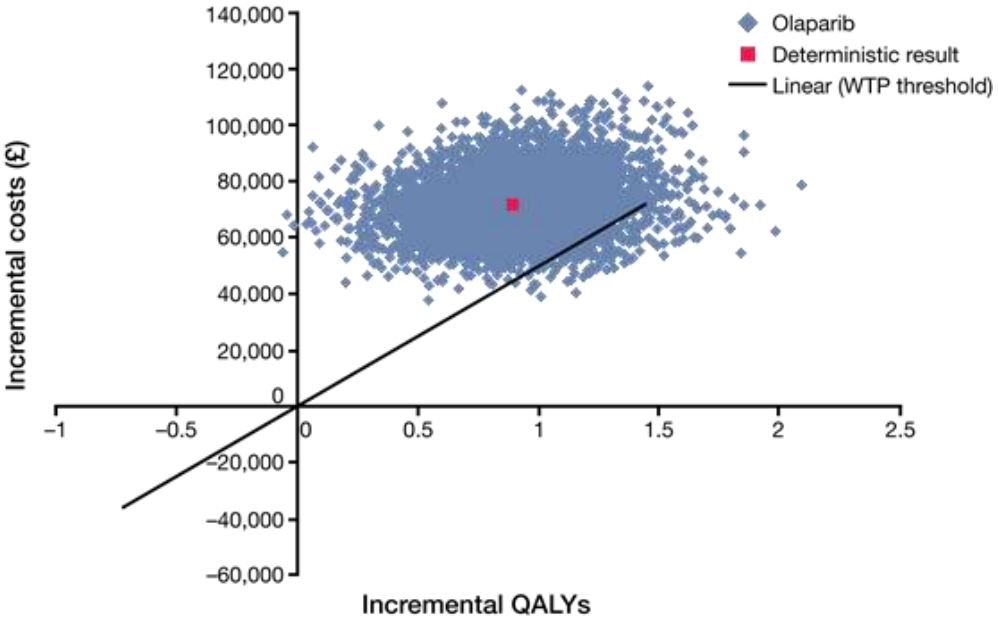
QALYs for olaparib versus surveillance). QALY gains generated in the first and subsequent therapy states are greater for routine surveillance than olaparib, however the difference between the groups is comparatively small. Table 47 also clearly indicates that most of the difference in costs between the two groups is a consequence of the additional drug costs associated with olaparib.

5.2.6.2 Company's uncertainty analysis results

Company's probabilistic sensitivity analysis results

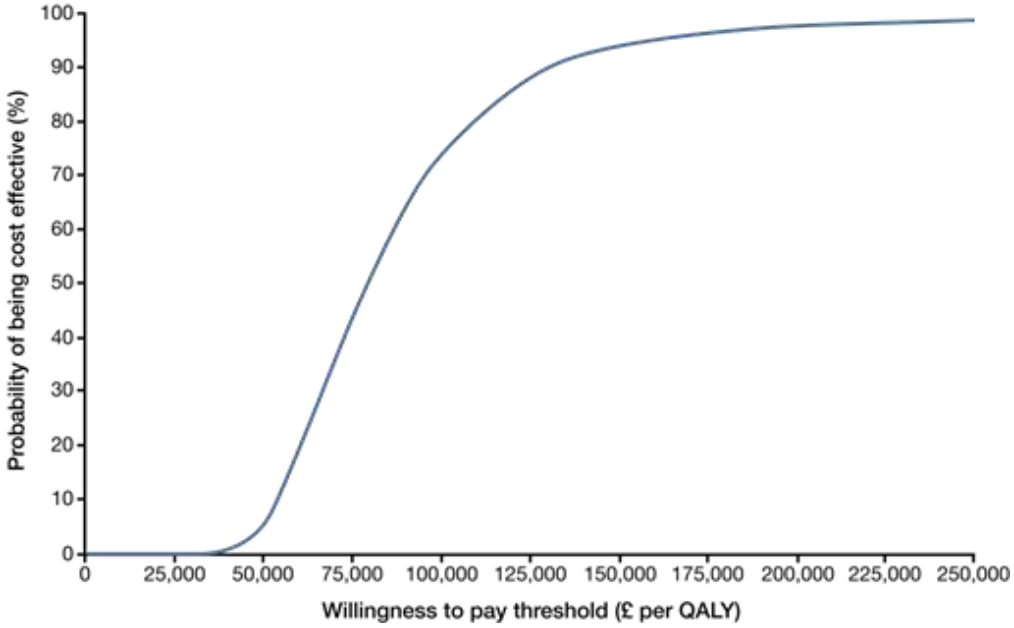
The results of the company's PSA are presented in Figures 17 and 18. Assuming a willingness-to-pay threshold of £20,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately zero. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately zero. Assuming a willingness to pay threshold of £50,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately 0.05.

Figure 17: Cost-effectiveness plane for olaparib versus routine surveillance (reproduced from CS[1] Figure 7.14)



WTP – willingness to pay

Figure 18: Cost-effectiveness acceptability curve for olaparib versus routine surveillance (reproduced from CS[1] Figure 7.15)

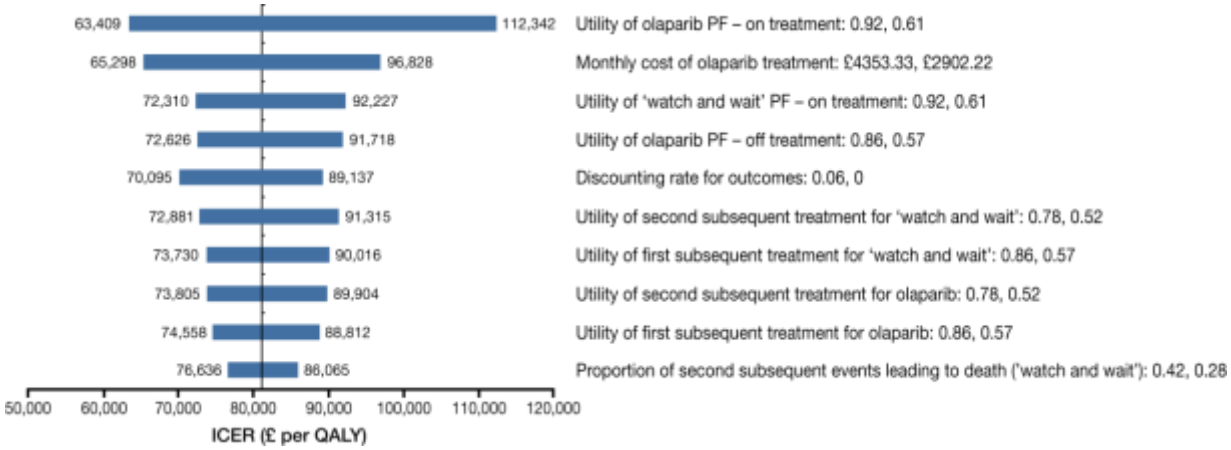


QALY – quality-adjusted life year

Company's one-way sensitivity analysis results

Figure 19 presents the results of the company's one-way sensitivity analysis. This analysis suggests that the utility values for patients receiving olaparib and routine surveillance, the monthly cost of olaparib treatment, the discount rate for health outcomes and the proportion of second subsequent events which are deaths are the most influential parameters within the model. The lowest ICER reported within the company's one-way sensitivity analysis is £63,409 per QALY gained (utility for olaparib, progression-free [on maintenance therapy] state =0.92); the highest ICER reported within the company's one-way sensitivity analysis is £112,342 per QALY gained (utility for olaparib, progression-free [on maintenance therapy] state =0.61).

Figure 19: One-way sensitivity analysis results (+/-20% deterministic mean, reproduced from CS[1] Figure 7.13)



PF – progression-free; ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year

Company's scenario analysis results

The results of the company's scenario analysis are summarised in Table 48.

Table 48: Company's scenario analysis results (adapted from CS[1] Table 7.34)

Scenario	Olaparib		Routine surveillance		Incremental		
	QALYs	Costs	QALYs	Costs	Incremental QALYs	Incremental costs	ICER
Base case	2.58	£82,041	1.69	£9,898	0.89	£72,143	£81,063
TFST/D – PARPi adjusted, generalised gamma	2.65	£82,166	1.86	£10,320	0.79	£71,846	£91,172
TFST/D – trial-based, log normal	2.58	£82,041	1.94	£10,212	0.64	£71,829	£112,260
TFST/D – trial-based, generalised gamma	2.65	£82,166	2.11	£10,631	0.54	£71,535	£132,026
BRCA mutation population regression analysis	2.56	£82,041	1.69	£9,898	0.87	£72,143	£82,997
ITT population regression	2.56	£82,041	1.69	£9,898	0.88	£72,143	£82,325
Mean EQ-5D *BRCA* subpopulation	2.58	£82,041	1.69	£9,898	0.89	£72,143	£81,316
Costs of *BRCA* mutation testing included	2.58	£84,945	1.69	£9,898	0.89	£75,047	£84,326
Time horizon = 3 years	1.77	£62,520	1.46	£8,348	0.3	£54,172	£177,889
Time horizon = 5 years	2.22	£72,035	1.64	£9,582	0.58	£62,453	£107,061
Time horizon = 10 years	2.52	£79,666	1.69	£9,876	0.83	£69,790	£83,735

PARPi - Poly(ADP-ribose) polymerase inhibitor; BRCA – Breast cancer susceptibility gene; EQ-5D – Euroqol 5-Dimensions

The company's scenario analysis suggests that the choice of survivor function for the first subsequent event has the propensity to substantially increase the ICER for olaparib versus routine surveillance. The use of the trial-based generalised gamma distribution increases the base case ICER from £81,063 per QALY gained to £112,260 per QALY gained. The choice of regression equation used in the mapping from the FACT-O to the EQ-5D does not substantially impact upon the ICER for olaparib versus routine surveillance; using alternative equations produces a range of ICERs from £81,063 per QALY gained to £82,997 per QALY gained. Including the cost of *BRCA* mutation testing increases the costs of olaparib by approximately £2,900, thereby leading to an ICER for olaparib versus routine surveillance of £84,326 per QALY gained. The use of a shorter time horizon increases the ICER for olaparib substantially. It should be noted that all of the ICERs presented in the company's scenario analyses are higher than the ICER produced using the company's base case scenario.

Company's analysis of the cost-effectiveness of olaparib which includes the wider costs and benefits of BRCA mutation testing for unaffected relatives

Table 49 summarises the results of the company's secondary analysis of the cost-effectiveness of olaparib plus the wider costs and benefits of *BRCAm* testing for unaffected relatives versus routine surveillance (without *BRCAm* testing for relatives). Within this analysis, the results for each family pedigree are equally weighted.

Table 49: Results of the company's secondary analysis of the cost-effectiveness of olaparib which includes the costs and benefits of *BRCA* mutation testing for unaffected relatives (adapted from CS[1] Table 7.43)

Pedigree	Unaffected relatives		Index case: Olaparib (vs 'watch and wait') *BRCA* mutation test costs excluded		Combined results (index case plus unaffected relatives)		
	Inc. costs	Inc. QALYs	Inc. costs	Inc. QALYs	Inc. costs	Inc. QALYs	Incremental cost per QALY gained
Pedigree 1	£79,847	1.26	£72,143	0.89	£78,306	1.19	£65,901
Pedigree 2	£79,113	1.55	£72,143	0.89	£77,719	1.42	£54,756
Pedigree 3	£79,484	1.49	£72,143	0.89	£78,016	1.37	£57,056
Pedigree 4	£79,482	1.24	£72,143	0.89	£78,014	1.17	£66,729
Pedigree 5	£78,977	1.31	£72,143	0.89	£77,610	1.23	£63,238
Average ICER across all 5 pedigrees							**£61,159**

Inc. – incremental; BRCA – Breast cancer susceptibility gene; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

The results of the company's secondary analysis suggest that taking into account the wider benefits and costs of *BRCA* mutation testing improves the ICER for olaparib versus routine surveillance. Across the five individual pedigrees, the ICER for olaparib versus routine surveillance ranges from £54,756 per QALY gained to £66,729 per QALY gained. Based on these five pedigrees, the company

presents an average deterministic ICER for olaparib versus routine surveillance of £61,159 per QALY gained.

5.3 Critical appraisal of the company's health economic analysis

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

The ERG employed 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:

- The use of published economic evaluation and health economic modelling checklists[63,64] to critically appraise the company's model and analysis.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- A partial re-build of the deterministic version of the company's model to assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any errors in the implementation of the model.
- Examination of correspondence between the description of the model reported within the CS[1] and the executable model.
- Replication of the base case results, PSA, 1-way sensitivity analysis and scenario analysis presented within the CS.[1]
- Checking of parameter values used in the company's model against the original data sources.
- The use of expert clinical input to judge the clinical credibility of the company's economic evaluation and assumptions underlying the company's model.

5.3.2 Adherence of the company's health economic analysis to the NICE Reference Case

Table 50 summarises the extent to which the company's health economic analysis adheres to the NICE Reference Case.[44]

Table 50: Adherence of the company's health economic analysis to the NICE Reference Case

Element of HTA	Reference Case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's economic analysis is generally in line with the final NICE scope. It is noteworthy that the outcomes data used in the model do not include OS or PFS.
Comparator(s)	As listed in the scope developed by NICE	The company's model includes routine surveillance ("watch and wait") as the comparator.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The base case analysis includes direct health effects on patients and costs borne by the NHS and PSS. The wider impact of expanding *BRCA* mutation testing to unaffected relatives is included in the company's secondary analysis. The model includes functionality to consider societal costs although these are not presented within the CS.
Perspective on costs	NHS and PSS	
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The model estimates the incremental cost per QALY gained for olaparib versus routine surveillance.
Time horizon	Long enough to reflect all important differences between the technologies being compared	A 15-year time horizon is assumed, which is intended to reflect the patients' remaining lifetime. Approximately 1.6% patients in the olaparib group are still alive at this timepoint. The model does not include the functionality to consider longer time horizons.
Synthesis of evidence on health effects	Based on systematic review	All outcomes data used in the model are based on analyses of data from the *BRCAm* subgroup within Study 19.[27] This was the only study identified within the company's systematic review of clinical effectiveness evidence.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Health outcomes are measured and valued in terms of QALYs. Health utility scores for the progression-free states are based on a mapping of FACT-O data collected in Study 19 to the EQ-5D based on an algorithm reported by Longworth *et al*.[46] Health utilities for the first- and second-subsequent chemotherapy states are taken from OVA-301 trial.[38,48] All utilities were valued using the UK tariff.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity weightings are applied.
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	Costs are valued from an NHS and PSS perspective.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5% per annum.

The company's health economic analysis is generally in line with the NICE Reference Case[44] and the final NICE scope.[10] As discussed in Section 5.2, the company's model adopts a 15-year time horizon. However, 1.6% patients in the olaparib group are still alive at this timepoint. The model does not include functionality to consider longer time horizons. It is very unlikely however that the adoption of a longer time horizon would have a marked impact upon the company's ICER for olaparib versus routine surveillance. It is noteworthy that whilst specified in the final NICE scope,[10] the company's base case analysis does not include the costs of *BRCA* mutation testing; this is discussed further in Section 5.3.3.

5.3.3 Summary of main issues identified through critical appraisal of the company's model

The main issues identified through the critical appraisal of the company's health economic analysis and the model upon which this is based are summarised in Box 2.

Box 2: Summary of main issues identified through the critical appraisal of the company's model

(1) Model errors and other issues surrounding model implementation
(2) Potential bias in the *BRCAm* subgroup within Study 19
(3) Concerns regarding company's model structure and use of outcomes data from Study 19
(4) Potential confounding of end points used in the company's model
(5) Concerns regarding the methods and presentation of modelling of time-to-event outcomes
(6) Discordance between model predictions and observed data
(7) Issues surrounding HRQoL within the company's model
(8) Omission of the cost of *BRCA* mutation testing from the company's base case analysis
(9) Issues surrounding the company's secondary analysis of the cost-effectiveness of olaparib including the wider costs and benefits of *BRCA* mutation testing for unaffected relatives
(10) Limited use of sensitivity analysis

(1) Model errors and other issues surrounding model implementation

The ERG partially rebuilt the company's model in order to assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any errors in the implementation of the model. The semi-Markov trace for the olaparib and routine surveillance groups was fully redeveloped using time-to-event data contained within the "Survival data" worksheet of the company's model. A comparison of intermediate model outputs from the company's model and the ERG rebuilt model is presented in Table 51. The ERG rebuilt model produced estimates of 2.58 discounted QALYs for olaparib and 1.69 discounted QALYs for routine surveillance; these are the same as those generated from the deterministic version of the company's model. The ERG is satisfied

that the QALY estimates produced by the company's model have been implemented as detailed in the CS without unintended programming errors. In addition, the ERG's estimates of the costs of olaparib, the management of AEs, and follow-up costs are all very similar to those generated from the company's model.

Table 51: Comparison of outcomes from the company's model and the ERG double-programmed model

Outcome	ERG rebuilt model		Company's model	
	Olaparib	Routine surveillance	Olaparib	Routine surveillance
Mean LYG*	3.54	2.38	3.55	2.38
Mean QALYs*	2.58	1.69	2.58	1.69
Olaparib costs†	£76,513	-	£76,477	-
AE costs†	£168	£59	£168	£59
Routine PFS follow-up costs†	£5,260	£2,199	£5,260	£2,199
Additional PFS follow-up costs†	£63	-	£63	N/a
FST follow-up costs†	£294	£320	£297	£324
SST follow-up costs†	£379	£415	£383	£419
End-of-life costs†	£3,714	£3,762	£3,714	£3,762

LYG – life year gained; QALY – quality-adjusted life year; AE – adverse event; PFS – progression-free survival; FST – first subsequent therapy; SST – second subsequent therapy
** Discounted and half-cycle corrected*
† Undiscounted, not half-cycle corrected

Owing to considerable complexity in its implementation (see clarification response[9] question B12), the ERG was unable to fully rebuild the first and second subsequent chemotherapy cost components of the company's model. This is because the company's model estimates the costs of platinum- and non-platinum-based chemotherapy for patients who are platinum-sensitive and platinum-resistant, but does not track platinum sensitivity/resistance directly; instead this is calculated according to the number of patients who progress to the next line of therapy within a certain timeframe. This is particularly problematic in the second subsequent therapy cost calculations, whereby patients may have remained platinum-sensitive following both maintenance therapy and the first subsequent line of chemotherapy, become platinum-resistant after the first line of chemotherapy, or become resistant after maintenance therapy. The resulting calculations in the company's model, which take account both of platinum sensitivity and differential chemotherapy durations, are convoluted and involve multiple =OFFSET() functions which are particularly difficult to verify. The ERG considers that tracking platinum-sensitivity could have been more easily implemented using a patient-level simulation approach. It was however possible to amend the company's model to explore the likelihood that programming errors may be present by simplifying it such that all subsequent chemotherapies bear the same cost and are used for the same duration. Applying a crude mean cost of £371 for each therapy and assuming that all therapies are used for 6-months within the company's model yields undiscounted costs of £1,598 and £1,742 for olaparib and routine surveillance,

respectively (see Table 52). The ERG rebuilt model produces almost identical first subsequent chemotherapy costs in each group. The corresponding estimates of second subsequent chemotherapy costs were also very similar between the company's model and the ERG rebuilt model. As such, the ERG is broadly satisfied that the cost components of the company's model have been implemented as detailed in the CS without unintended programming errors.

Table 52: Comparison of crude first and second subsequent therapy costs from the company's model and the ERG-double-programmed model

Outcome	ERG rebuilt model		Company's model		Notes
	Olaparib	Routine surveillance	Olaparib	Routine surveillance	
First subsequent chemotherapy costs	£1,598	£1,742	£1,598	£1,741	Undiscounted, not half-cycle corrected, crude mean cost of £371 per cycle, all regimens set=6 cycles
Second subsequent chemotherapy costs	£1,223	£1,334	£1,223	£1,334	

FST – first subsequent therapy; SST – second subsequent therapy

Replication of the company's analysis

The ERG was able to reproduce the company's deterministic base case, 1-way sensitivity analysis and scenario analysis results. The ERG was also able to re-run the company's PSA; this analysis produced similar results to those reported by the company (re-run probabilistic base case ICER = £79,437 per QALY gained).

Issues surrounding data inputs to the company's model

Two apparent errors were identified in the input parameters applied within the company's model:

1. *Risk of death.* Within the worksheet "Parameter data store", the model contains calculations of the proportion of first subsequent therapy events which were deaths. Cell C191 suggests that 2/52 (3.85%) first subsequent therapy events in the placebo group were deaths. However, according to Table 7.4 of the CS,[1] the denominator should be 54, thereby suggesting a slightly lower probability of 3.70%. Correcting this error marginally increases the company's deterministic ICER from £81,063 per QALY gained to £81,184 per QALY gained.
2. *Frequency of follow-up visits for routine surveillance*. The CS[1] states *"Current UK follow up of patients on 'watch and wait' would be anticipated to be 3-monthly follow-up appointments, with blood tests to monitor the same parameters. It is therefore anticipated that an additional two appointments and blood tests will be required per quarter for patients on olaparib."* However, the model actually assumes that patients on routine surveillance in the progression-free state undergo monthly appointments (see Table 35). Rectifying this error marginally increases the ICER from £81,063 per QALY gained to £82,201 per QALY gained.

(2) Potential bias in the BRCA subgroup within Study 19

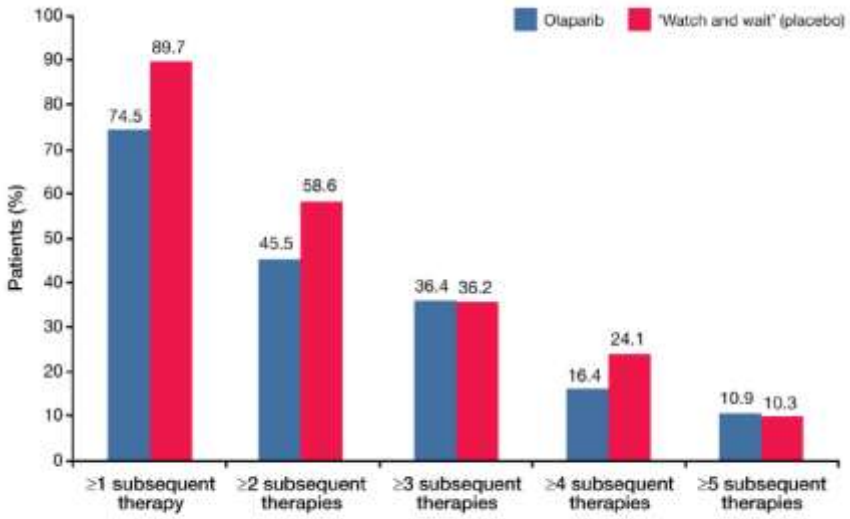
The ERG highlight that whilst the *BRCAm* subgroup was specified before the DCO point for PFS, it was not specified before the study commenced. The validity of the subgroup itself is unknown due to the point at which the subgroup was defined and a lack of conclusive statistical tests for interactions. These concerns are discussed in detail in Section 4.2.1.6.

(3) Concerns regarding company's model structure and use of outcomes data from Study 19

The ERG has concerns regarding the conceptual structure of the model submitted by the company and the use of the available evidence within that structure. Specifically, these concerns relate to (i) questionable structural assumptions regarding the treatment pathway, (ii) the exclusion of key clinical outcome data relating to PFS from the company's model, and (iii) the company's approach to modelling mortality based on constant proportional risks and state-specific risks.

With respect to the modelled treatment pathway, the company's model assumes that all patients who survive the first subsequent therapy event (i.e. the "progression-free" period) go on to receive a first subsequent course of active chemotherapy and subsequently, all patients who survive the second subsequent therapy event go on to receive a second course of chemotherapy. This is problematic in that all patients who enter the first subsequent therapy and second subsequent therapy states are assumed to receive active chemotherapy. Clinical advisors to the ERG suggest that this may not be clinically realistic as for some patients with advanced disease, chemotherapy is expected to be of limited benefit; these patients, and even some who are sufficiently fit to receive chemotherapy, may instead opt to receive best supportive care. Furthermore, the structure of the company's model limits the number of subsequent lines of chemotherapy available to a maximum of two; data from the *BRCAm* subgroup within Study 19 reported within the CS[1] indicate that more than 36% patients went on to receive three or more subsequent lines of therapy (see Figure 20), with some patients receiving five or more subsequent lines of therapy. The costs associated with these further treatments are not included in the company's model.

Figure 20: Use of subsequent lines of chemotherapy in the *BRCA*-mutated subgroup within Study 19 (reproduced from CS[1] Figure 6.8)



Number of patients eligible to receive a subsequent therapy at data cut-off: olaparib 74.3% (55/74) vs placebo 93.5% (58/62).
Source: Data on file: Study 19 CSR, Table 11.2.6.6.c

More importantly, the ERG has concerns regarding the use of outcomes data included in the company's model and the range of clinical evidence which has been excluded from it. The company's model is based on the time to first and subsequent therapy and survival within those states, with olaparib conferring a clinical benefit in delaying the time to subsequent therapy, and as a consequence, delaying time to death.

As noted in Section 5.2, the interval of time spent within the "progression-free" state within the model does not specifically relate to the outcome of PFS within the trial. Rather, this state is defined by the time interval from randomisation to either death or commencement of first subsequent chemotherapy (TFST/D). PFS, which is defined as time from the date of randomisation to objective tumour progression or death,[1] and which was used as the primary end point in Study 19, is not used in the model. The ERG requested clarification regarding the company's choice of end points within their model (see clarification request[9] question B1). In response, the company stated that TTD/D and TFST/D were considered more clinically and economically meaningful endpoints than PFS for three reasons:

(i) Within Study 19, TFST/D was evaluated at a later cut-off (November 2012) than PFS (June 2010) hence PFS data were relatively immature for the olaparib arm compared with placebo.

(ii) In clinical practice, a number of factors in addition to RECIST progression will be taken into account before the discontinuation of maintenance therapy and the reintroduction of chemotherapy.

(iii) Patients in Study 19 were required to discontinue the study drug on evidence of RECIST progression. However, the study protocol permitted patients to continue to receive study drug

beyond progression provided the investigator considered the patient was still benefiting from treatment and did not meet any other discontinuation criteria (as discussed in Chapter 4). The company argues that TTD/D therefore provides a more accurate estimate of treatment exposure and associated costs in the economic model than an extrapolation of RECIST progression.[9]

The ERG notes that clinically, the outcome of TFST/D reflects the RECIST progression-free interval, a further period in which the patient's disease has progressed but the patient has not yet elected to receive further chemotherapy, as well as a competing risk of death. This is not an entirely objective outcome measure and may be influenced by subjective decisions regarding future chemotherapy use, eligibility for treatment (e.g. fitness and capacity to benefit) as well as loss of blinding within Study 19, see Section 4.2.1.5). The ERG also notes that the continued use of olaparib beyond progression of the underlying disease, as described in the company's third point above, is not in line with the EMA's recommendations on the use of olaparib.[11] As noted previously, within Study 19, TFST/D and TSST/D were *post hoc* exploratory outcomes which were added as exploratory analyses at the time of the interim OS analysis (*BRCAm* 52% maturity).[23] Whilst the ERG acknowledges that patients with ovarian cancer may typically wait for symptoms to manifest before commencing further chemotherapy, the ERG remains concerned by the complete exclusion of the primary end point of Study 19 from the company's model.

The ERG also has concerns that the OS data collected within Study 19 are not directly included in the company's model. The CS[1] argues that these data are immature (48% censoring in the *BRCAm* subgroup) and notes that these data are confounded by 23% patients in the placebo group crossing over to receive a PARP inhibitor. The clarification response from the company further argues that *"direct modelling of overall survival outcomes from Study 19 would have produced a biased estimate of the cost effectiveness of olaparib"* (see clarification response[9] question B2). Instead, the company's model applies conditional risks of death at three points in the modelled pathway (see Table 53). Mortality data are therefore captured in the model as conditional events for patients reaching different health states (rather than by fitting curves to the Kaplan-Meier data for OS). Assumptions about equivalence in risks are used in an attempt to remove the potential confounding impact of treatment switching in the placebo group of Study 19; this is discussed further below.

Table 53: Mortality risks in the company's model

Mortality risk in model	Description of risk	Application of mortality risk	Assumptions
Point 1	Probability that first subsequent therapy event is death	Applied to a fixed proportion of patients on leaving the progression-free state	Treatment-specific
Point 2	Probability that second subsequent therapy event is death	Applied to a fixed proportion of patients on leaving the first subsequent therapy state	Assumed to be the same for both groups, based on pooled data for both groups
Point 3	Probability of transiting from second subsequent therapy to death	Applied as time-to-event curve for all patients in second subsequent therapy state	Assumed to be the same for both groups, based on olaparib group

The first two points at which death is included, that is, the probability that a first subsequent therapy event is death and the probability that a second subsequent therapy event is death, both involve an implicit assumption that a fixed proportion of events occurring in patients leaving the progression-free state and the first subsequent therapy state, respectively, are deaths. This does not imply a fixed hazard of death, but rather implies than the hazard rate for death is directly proportional to the overall hazard of progressing or dying. The CS does not present any evidence regarding the nature of the hazard of death in these patients hence the validity of this assumption is entirely unclear. The third point at which patients may die within the company's model, that is, once patients have entered the second subsequent therapy state, is based only on data for the olaparib group. The ERG believes that this approach may produce estimates of OS in each group which are inferior, or rather, more biased, than estimates of OS produced by adjusting for placebo group crossover and directly fitting parametric curves to the adjusted Kaplan-Meier data for each treatment group (discussed later within this section).

Within the CS,[1] the company makes the argument that the four state model, with states defined as progression-free (on treatment or discontinued), first subsequent therapy, second subsequent and dead, provides a better representation of the expected benefits of maintenance treatments for advanced cancer in terms of both delaying disease progression and the transition to subsequent lines of chemotherapy (see CS[1] page 110). However, the ERG would argue that the best model is that which both represents clinical reality and which makes the best use of the evidence available. The ERG does not believe that ignoring the available data on PFS, compounding multiple assumptions regarding the mortality risk associated with specific health states within and between treatment groups, and limiting the treatment pathway to only two lines of chemotherapy, satisfies both of these criteria.

(4) Potential confounding of end points used in the company's model

(a) Potential confounding due to crossover in the placebo group

The CS recognises that patients crossing over from placebo to receive a subsequent PARP inhibitor may have resulted in confounding in the observed trial results from Study 19 (see CS[1] page 131). The company's model attempts to deal with this potential confounding by assuming that the time from first subsequent therapy to second subsequent therapy or death, the probability that a second subsequent therapy event is death and the time from second subsequent therapy to death, are the same for both treatment groups.

The CS includes details of an analysis of OS which attempts to account for confounding by excluding study sites which allowed post-progression crossover in the placebo group (previously discussed in Section 4.2.1.6). This analysis produced a statistically significant difference in OS between olaparib and placebo for *BRCAm* patients, with a HR of 0.52 (95% c.i. 0.28 to 0.97, nominal p=0.039). However, the company's model does not allow for the direct modelling of OS hence the results of this analysis are not actually used. The CS[1] (page 185) also mentions, but does not include, the use of more sophisticated statistical approaches for adjusting survival time estimates in the presence of treatment switching. A range of methods exist for handling treatment switching, for example, RPSFTM, Iterative Parameter Estimation (IPE), the 2-stage Weibull approach and the IPCW method.[33] As discussed in Section 4.2.1.6, the company's response to clarification[9] (question A2), includes an additional analysis of OS using the RPSFTM method.[9] The company's RPSFTM analysis generated three outcomes [redacted] (see Table 54), all of which generated a numerical improvement in the HR for OS compared with the full *BRCAm* subgroup, [redacted] The adjusted HR is dependent on both proportion of switchers and the length of the time period the switchers stay on active treatment.[9]

Table 54: Summary of RPSFTM analysis (reproduced from clarification response[9] Table A2.1)

[redacted]

As discussed in Section 4.2.1.6, the main advantage of the RPSFTM approach is that it retains patients who would otherwise be excluded using the crossover-site exclusion method, albeit at the cost of making assumptions, particularly around the commonality of the treatment effect.

Figures 21 and 22 present the crossover site-excluded and RPSFTM-adjusted Kaplan-Meier curves for olaparib and placebo, respectively.

Figure 21: Kaplan-Meier plot of overall survival in *BRCA*-mutated patients in Study 19 – Excluding sites with crossover (reproduced from company's clarification response[9])

Figure 22: RPSFTM-adjusted Kaplan-Meier curves for *BRCA*-mutated subgroup within Study 19 (reproduced from company's clarification response[9]) CONFIDENTIAL

Figure 21 suggests that for the crossover-site excluded Kaplan-Meier curves, the hazard of death in the placebo group appears to be slowing towards the tail of the curve, with little difference in the probability of survival between the treatment groups by around month 36 (although the ERG notes that the number of patients at risk is small by this timepoint). [redacted] It is important to note however that Kaplan-Meier estimates are most uncertain in the tails of the curves.

Neither the crossover-site excluded estimates of OS nor the RPSFTM-adjusted estimates of OS have been applied in the company's health economic analysis. Consequently, the extent to which the company's assumptions regarding equivalence between treatment groups in terms of time from first subsequent therapy to second subsequent therapy or death, the probability that a second subsequent therapy event is death and the time from second subsequent therapy to death, appropriately adjusts for confounding due to placebo group crossover is unclear and has not been formally examined within the CS.

(b) Potential confounding due to continued use of olaparib beyond disease progression

As noted in Chapter 4, patients were allowed to continue to receive olaparib beyond disease progression. In response to a request for clarification by the ERG (see clarification response[9] question A3), the company stated that [redacted] discontinued treatment more than 2 weeks following RECIST disease progression. Of these, [redacted] remained on

treatment for a significant amount of time (>2 months) after documented RECIST disease progression.[9] The ERG notes that the continued use of olaparib beyond disease progression does not reflect the EMA's recommendations on the use of olaparib, which state that treatment should be continued until progression of the underlying disease.[11] This may have resulted in some bias in the time-to-event outcomes and mortality hazards for the olaparib group, as well as for those outcomes for the routine surveillance group which are assumed to be equivalent between the treatment groups. No attempt to correct for this continuation of treatment was reported in the CS.

(5) Concerns regarding the methods for modelling of time-to-event outcomes

The CS[1] includes several pages detailing the process of fitting parametric curves to observed time-to-event data (see CS[1] pages 116 to 126). A summary of the data used within these analyses, the methods for fitting curves and the goodness of fit statistics, as produced by the ERG, is detailed in Table 55.

Table 55: Summary of company's survival modelling approach

	TTE event 1 - Time from randomisation to treatment discontinuation or death		**TTE event 2 - Time from randomisation to first subsequent therapy or death**		**TTE event 3 - Time from first subsequent therapy to second subsequent therapy or death***		**TTE event 4 - Time from subsequent therapy to death***	
Group	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
N at risk in analysis	74	62	74	62	41	52	25	34
Model type	Treatment-adjusted		Treatment-adjusted		Individual hazards	Individual hazards	Individual hazards	Individual hazards
ERG's view of validity of proportional hazards assumption	Questionable due to intersection of curves		Questionable due to intersection of curves		N/a	N/a	N/a	N/a
Survivor functions presented visually in the CS[1]	Generalised gamma and log logistic only		Generalised gamma and log normal only		Weibull only	Weibull only	Weibull only	Weibull only
Lowest AIC of candidate curves	815.54 (log logistic)		753.78 (generalised gamma)		229.56 (log normal)	295.24 (Weibull)	154.00 (generalised gamma)	160.53 (generalised gamma)
Lowest BIC of candidate curves	833.02 (log logistic)		771.78 (log normal)		238.13 (log normal)	304.00 (Weibull)	161.09 (Weibull)	168.56 (log normal)
Highest AIC of candidate curves	836.61 (Weibull)		773.51 (Gompertz)		235.05 (exponential)	315.11 (exponential)	161.10 (exponential)	169.23 (exponential)
Highest BIC of candidate curves	854.08 (Weibull)		790.98 (Gompertz)		243.86 (Gompertz)	322.91 (exponential)	165.97 (exponential)	175.33 (exponential)
Selected curve	Log logistic		Log normal		Weibull	Weibull	Weibull	Weibull
Subjective visual model fit (by the ERG)	Reasonable for placebo group, poor estimation of tail for olaparib group		Reasonable for placebo group, poor estimation of tail for olaparib group		Reasonable	Reasonable	Reasonable	Reasonable

TTE – time-to-event; AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

** Same time-to-event curve applied to both treatment groups*

According to the CS,[1] the process for fitting parametric survival curves to patient-level data was based on NICE DSU TSD 14.[56] However, the ERG considers that the guidance suggested within the TSD has only been partially adhered to. The ERG has concerns relating to: (a) a lack of clarity regarding adjustments for covariates; (b) use of external data and expert clinical judgement; (c) unclear model discrimination criteria; (d) limited presentation of graphical plots of alternative candidate curves; (e) the potentially inappropriate use of proportional hazards assumptions, and; (f) missing sensitivity analyses around alternative candidate survivor functions.

(a) Lack of clarity regarding adjustments for covariates

The CS includes the covariates of TTP on the penultimate platinum-based chemotherapy, Jewish ethnicity and full versus partial platinum-sensitivity. This is not well described within the CS but was presumably undertaken to adjust for potential imbalances between the treatment groups. It is unclear why other covariates (e.g. age and ECOG performance status), which may also be imbalanced, were not included in the analysis. It is unclear how covariates have been included in the extrapolated Kaplan-Meier curves within the CS. Ideally, separate curves should be presented for each covariate subgroup, although the ERG recognises that this would be limited by the small sample size within the *BRCAm* subgroup within Study 19.

(b) Use of external data and expert clinical judgement

The company's curve-fitting process does not appear to have included the consideration of any external data or expert subjective judgement on the plausibility of the extrapolated curves. Instead, model discrimination appears to have been based only on a consideration of visual inspection of how well the curves fit the observed data and goodness of fit according to AIC and BIC statistics.

(c) Unclear model discrimination criteria

For the analysis of time from second subsequent therapy to death, the CS[1] misrepresents which curve has the lowest BIC, whilst for the outcomes of time from first subsequent therapy to second subsequent therapy and time from second subsequent therapy to death, the justification for the choice of curve is unclear.

(d) Limited presentation of graphical plots of alternative candidate curves

With the exception of time to first subsequent therapy or death, in which two parametric survivor functions were presented (log normal and generalised gamma), only the curve for the selected model for each outcome is presented graphically within the CS.[1] Consequently, the ERG was unable to verify from the CS whether other candidate curves may have provided equally, or potentially more, plausible model fits than those selected by the company. It is important to note that the use of AIC/BIC statistics and visual inspection focusses only the observed period. Where there is little

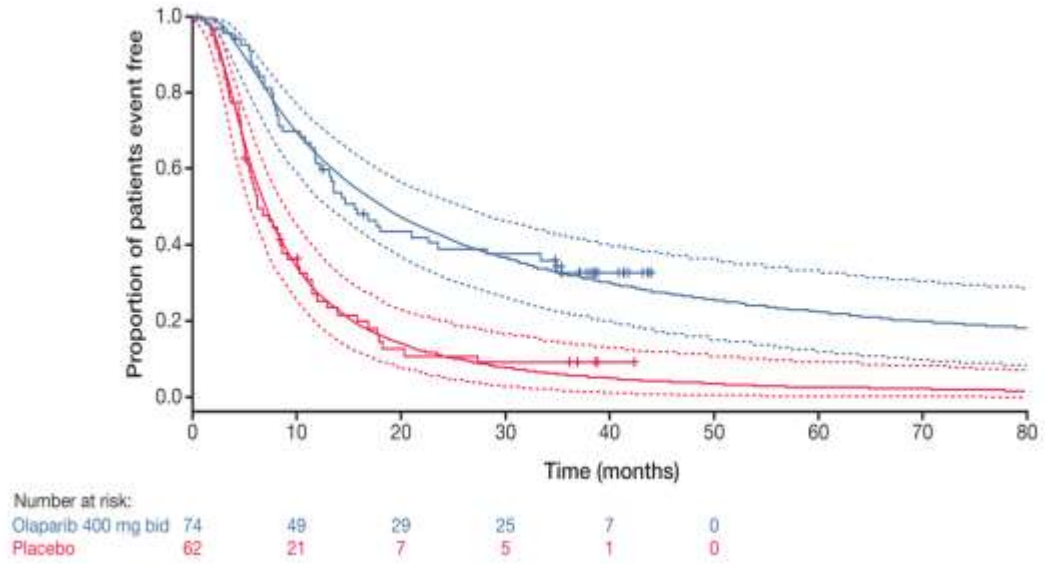
difference between the curves in terms of how well they fit the data for the observed period, the plausibility of the tail of the distribution becomes the more important factor in discriminating between candidate curves. Without access to visual plots of all candidate curves, either including or excluding an assumption of proportional hazards between treatment groups, it is not possible determine whether any of the company's decisions regarding the most appropriate parametric curve are reasonable.

(e) Potentially inappropriate use of proportional hazards assumptions

The ERG has concerns regarding the use of parametric models which include treatment covariates (the proportional hazards assumption). An assumption of proportional hazards is made for the analysis of time-to-event outcomes of time from randomisation to treatment discontinuation or death (TTD/D) and for time from randomisation to first subsequent therapy or death (TFST/D). However, the log-log survival plots for each of these outcomes (see Figures 9 and 11) demonstrate that the curves for each treatment group cross, and the lines within the log-log survival plot for the outcome of TTD/D do not appear to be constant with respect to time. This indicates that the proportional hazards assumption may not be appropriate. The ERG would suggest that where there is doubt regarding the appropriateness of the proportional hazards assumption, and where patient-level data are available, it is preferable to fit independent parametric models to each treatment group thereby making fewer restrictive assumptions within the analysis.[56] In particular, the ERG notes that visually the outcomes of TTD/D and TFST/D do not appear to provide a good visual fit to the observed data. It is possible that a better model fit may have been achieved by avoiding the proportional hazards assumption altogether.

As part of their clarification response (see clarification response[9] question B5), the company presented a re-analysis of the model by fitting the generalised gamma distribution to each treatment group for the outcome of TFST/D (see Figure 23). This analysis resulted in an ICER for olaparib versus routine surveillance of £50,014 per QALY gained. The company notes however that within this analysis, the model predicts that 11% olaparib patients will be alive and progression-free at 15-years. This was considered less clinically plausible than the company's base case. No other re-analyses of the health economic model using alternative candidate survivor functions were presented within the company's clarification response.[9]

Figure 23: TTE outcome 2 - Time from randomisation to first subsequent therapy or death – independent hazards generalised gamma models



Dashed lines indicate confidence interval

(f) Missing sensitivity analyses around alternative candidate survivor functions

Whilst the CS[1] purports to have undertaken sensitivity analysis around the choice of parametric survivor functions, this analysis is restricted only to the outcome of TFST/D. The CS does not include any sensitivity analyses exploring the use of alternative parametric curves for the outcomes of TTD/D, time from first subsequent therapy to second subsequent therapy or death, or time from second subsequent therapy to death. It is thus unclear from the CS whether alternative parametric models, together with the avoidance of assumptions regarding proportional hazards, would provide very different estimates of cost-effectiveness for olaparib.

In response to a request for clarification (see clarification response[9] question B4), the company provided graphical plots of log normal, generalised gamma, log logistic, Weibull, exponential and Gompertz survivor functions for the outcomes of TTD/D and TFST/D (see Appendix 6). The ERG notes that each of these plots assumes proportional hazards and a re-analysis of the company's health economic model using these alternative functions has not been presented.

(6) Discordance between model predictions and observed data

The CS includes a comparison of median model-predicted end points and median observed end points from the *BRCAm* subgroup within Study 19 (see Table 56). This comparison is not ideal as it is based on medians rather than means, therefore the comparison does not reflect the ability of the model to predict the shape of the time-to-event data. Nevertheless, this comparison indicates some discrepancy

between what is being predicted by the company's model and what was observed within the trial. All comparisons suggest that the model predictions are over-estimating the observed trial results, however the degree of over-estimation is consistently greater in the olaparib group.

Table 56: Company's model results compared with observed clinical data from *BRCA*-mutated subgroup within Study 19 (adapted from CS[1] Table 7.28)

Outcome	Olaparib			Routine surveillance		
	Study 19, median (months)	Model, median (months)	Difference (predicted-observed)	Study 19, median (months)	Model, median (months)	Difference (predicted-observed)
Time to treatment discontinuation or death	11.0	12.0	1.0	4.6	5.0	0.4
Time to first subsequent treatment or death	15.6	20.0	4.4	6.2	7.0	0.8
Time to second subsequent treatment or death	23.8	27.0	3.2	15.3	16.0	0.7
Overall survival*	34.9	38.0	3.1	31.9	26.0	5.9

**Note: Model results based on adjustment for PARP inhibitor use in the 'watch and wait' arm. Without adjustment for PARP inhibitor use (trial-based assessment), estimated median OS was 31.0 months*

Within the routine surveillance group, the degree of error between the observed and predicted end points of time to treatment discontinuation or death, time to first subsequent treatment or death and time to second subsequent treatment or death is relatively small. The sizeable difference between the observed and predicted OS in the routine surveillance group, according to the CS,[1] can be explained by the 23% crossover rate in the placebo group. The company's trial-based assessment (without adjustment for PARP inhibitor use) produced an estimated median OS of 31.0 months.

Within the olaparib group however, the differences between the observed and predicted end points is more pronounced. In particular:

- The median time to first subsequent treatment or death predicted within the model is upwardly biased by 4.4 months (0.37 years).
- The median time to second subsequent treatment or death predicted within the model is upwardly biased by 3.2 months (0.27 years).
- The median OS predicted within the model is upwardly biased by 3.1 months (0.26 years).

This issue is further evident by comparing model-predicted OS against that observed within Study 19 (see Figure 24), both including and excluding the re-analyses of the placebo group data to remove the potentially confounding effects of crossover. The figure shows eight OS curves (C1-8); these have been obtained from the model, or digitised from the CS[1] and the company's clarification response:[9]

- Curves 1 and 2 – OS for olaparib and placebo without adjustment for placebo group crossover[1]
- Curves 3 and 4 – OS for olaparib and placebo with adjustment for placebo group crossover using RPSFTM[9]
- Curves 5 and 6 – OS for olaparib and placebo adjusted for placebo group by excluding crossover sites (denoted "CSE-adjusted);[9]
- Curves 7 and 8 – OS predicted by the company's model.

Figure 24: Comparison of observed, crossover-adjusted and modelled survival for the olaparib and routine surveillance groups (CONFIDENTIAL)

A comparison of the modelled and empirical OS curves indicates the following:

- The adjustment of the placebo group data using the RPSFTM method and by excluding crossover sites produces similar projections of OS; this is reassuring. Both of these methods indicate a slightly worse survival prognosis for patients receiving placebo as compared against the unadjusted Kaplan-Meier curve for the placebo group presented within the CS.[1]
- Despite the adjustments for handling placebo group crossover, the apparent slowing of the hazard of death in the placebo group, relative to that in the olaparib group, is maintained in the crossover-adjusted Kaplan-Meier curves for placebo. In other words, the gap between the OS curves for olaparib and placebo appears to close, or nearly close, at around 3-years post-randomisation, irrespective of the crossover method applied. The ERG notes that there is only a small number of patients at risk in the tails of the curves hence they are subject to considerable uncertainty.
- For the olaparib group, the model appears to broadly reflect the empirical Kaplan-Meier OS curve for the first 2 years post-randomisation, but appears to overestimate OS beyond this timepoint.
- In the routine surveillance group, the model does not appear to provide a particularly good fit to the empirical placebo group data using either the crossover site excluded Kaplan-Meier curve or the RPSFTM-adjusted Kaplan-Meier curve.
- Whilst the empirical Kaplan-Meier data, both including and excluding placebo crossover adjustment, appear to suggest that the curves for olaparib and placebo intersect, or nearly intersect, at around 3 years post-randomisation, this is not reflected in the model-predicted OS. Rather, it is around this timepoint within the model whereby the greatest difference between the groups is predicted by the company's model. This suggests that the model does not predict the data well.

These apparent biases in the model-predicted end points are likely to be symptomatic of the issues detailed above, specifically: (i) the use of parametric models which do not provide a good fit to the observed time-to-event data; (ii) the use of potentially inappropriate assumptions of proportional hazards for the outcomes of TTD/D and TFST/D; (iii) the use of potentially inappropriate assumptions regarding the proportional risk of death in those patients experiencing first subsequent therapy and second subsequent therapy events, and; (iv) the use of assumptions of equivalence between the treatment groups in terms of the proportion of second subsequent therapy events that are deaths and the time-to-event curves for the time from first subsequent therapy to second subsequent therapy or death and the time from second subsequent therapy to death. Irrespective of the source of the discrepancy, the ERG considers this to be a significant cause for concern. It is likely that some of this apparent bias could have been avoided by appropriately dealing with crossover and by adopting a model structure which allows for the use of parametric curves directly fitted to these crossover-adjusted OS data.

Overall however, the ERG does not have confidence in the overall survival gains, or consequently, the QALY benefits, predicted for olaparib within the company's model.

(7) Issues surrounding HRQoL within the company's model

The company's model includes four utility scores characterised by patients being progression-free and on treatment (utility=0.77), progression-free following treatment discontinuation (utility=0.71), first subsequent therapy (utility=0.72), and second subsequent therapy (utility=0.65, see Table 28). The progression-free health states were informed by a mapping exercise (from the FACT-O questionnaire to the EQ-5D), whilst the chemotherapy state utilities were based on estimates derived from the literature.[48] The base case model assumes that AEs do not impact upon HRQoL over and above the mapped estimates.

The CS notes that the choice of mapping algorithms was based on a consideration of whether the characteristics of the estimation sample for the mapping algorithm were similar, or at least representative, of the target sample of patients with Study 19. However, the reported characteristics (see Table 30) did not provide sufficient evidence to support this assertion, particularly in terms of severity. The technical report presented information on ECOG status; this shows that Study 19 participants were more likely to report being fully active (79%) compared against the Longworth *et al* sample (23%), thereby indicating a difference in severity. A better comparison would have been based on the FACT-G dimension scores as this is the basis of the mapping function; this would provide a more informed judgement of similarities in the target and estimation samples. The impact of using the

mapping function from Longworth *et al* should also have been tested in the sensitivity analysis by assessing the uncertainty around the predicted values by making use of reported standard errors.

The use of separate utilities for patients who are receiving maintenance therapy and for those who have discontinued is justified within the CS as within the single-factor regression models, only *BRCA* status and treatment discontinuation were statistically significant predictors of health utility (see Table 31, $p<0.05$). Whilst differentiating between "on treatment" utility and "off treatment" utility seems reasonable for the olaparib group, applying this adjustment to the routine surveillance group seems less reasonable as these patients, by definition, are not receiving maintenance therapy and therefore cannot discontinue. It is possible that such a difference in health utility reflects the onset of symptomatic disease, however it may also plausibly reflect a placebo effect within the trial. Consequently, the most appropriate utility values for the "progression-free on treatment" and "progression-free discontinued" states are unclear. The company's response to clarification questions highlights that this assumption does not have a material impact upon the ICER: *"When constant utility values of 0.713 or 0.769 were applied for the PF state (both on/off treatment) in the 'watch and wait' arm, the ICERs varied by less than 5% from the base case ICER."*[9] The ERG is satisfied that this issue does not materially impact upon the ICER for olaparib versus routine surveillance.

The ERG also has concerns regarding the estimates of health utilities for patients in the first subsequent therapy and second subsequent therapy health states within the company's model. The utilities for these states were sourced from the manufacturer's submission within NICE TA222,[38] based on EQ-5D estimates derived from the OVA-301 trial.[48] However, the reported utilities of 0.72 and 0.65 relate to states of "progression-free survival" and "progressed disease" rather than states of "first subsequent therapy" and "second subsequent therapy", respectively. In reality, patients receiving chemotherapy would have a progression-free period and a post-progression period and it is likely that each of these states would be associated with different levels of HRQoL. The ERG considers that the estimates used do not fully reflect the health states included in the company's model but also recognise the lack of alternative relevant preference-based estimates within the literature.

(8) Omission of the cost of BRCA mutation testing from the company's base case analysis

The final NICE scope[10] states that *"The economic modelling should include the cost associated with the diagnostic testing for BRCA1/2m in people with OC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test."* In addition, the NICE Guide to the Methods of Technology Appraisal[44] states that *"If a diagnostic test to establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness. A sensitivity analysis should be provided without the*

cost of the diagnostic test." Whilst the CS[1] includes a sensitivity analysis in which the cost of *BRCA* mutation testing is included, the company's base case analysis excludes the cost of the diagnostic test. The inclusion of the cost of *BRCA* mutation testing increases the company's probabilistic base case ICER for olaparib versus routine surveillance from £81,063 per QALY gained to £84,326 per QALY gained.

(9) Issues surrounding the company's secondary analysis of the cost-effectiveness of olaparib including the wider costs and benefits of BRCA mutation testing for unaffected relatives

The final NICE scope[10] does not indicate that the potential additional health benefits of *BRCA* mutation testing should be included in the economic analysis. In the event that these costs and benefits are deemed relevant to decision-making, the ERG has both practical and theoretical concerns regarding their inclusion.

The ERG has several concerns regarding the appropriateness of combining the results of the company's model and the model developed to inform NICE CG164.[8] Firstly, there are differences between the two models in terms of the treatment pathways assumed for ovarian cancer; specifically, the guideline model does not include olaparib as a treatment option, hence the company's analysis reflects a situation in which *BRCA*-testing and olaparib treatment are available for the index case, but the treatment is not available for relatives; this is somewhat inconsistent. Secondly, the ERG notes that the use of five family pedigrees, combined with average costs and QALYs for unaffected family members, is limited and may not adequately reflect the range of possible family structures within the population under consideration. It is therefore unlikely that the average ICER across the five pedigrees reported by the company is meaningful (see Table 49). Finally, the NICE CG164 cost-effectiveness review specifically highlights the degree of uncertainty surrounding their analysis of the costs and benefits of unaffected relatives and suggests that further evidence on the impact of genetic testing on relatives would be valuable. However, the company's secondary analysis does not take into consideration uncertainty surrounding the costs and benefits of *BRCA* mutation testing.

From a theoretical perspective, the ERG does not believe that the company's secondary analysis includes all relevant comparisons, thereby hindering the correct interpretation of the results. In the case of drugs in which the prior use of a companion diagnostic is a prerequisite, it is important to consider where the value of the joint intervention lies, that is, whether it accrues from the use of the new drug, or whether this value would still exist in its absence. This requires the inclusion of all appropriate comparators within a fully incremental economic analysis i.e. comparing (i) no testing and no drug, (ii) testing and no drug, and; (iii) testing and drug for test-positives. The failure to consider all appropriate comparators within a fully incremental analysis may obscure results and potentially

lead to the inappropriate joint recommendation of tests which are known to be efficient and drugs which are known to be inefficient.

Consider the following hypothetical example of Test X and Drug Y for Disease Z, as illustrated in Table 57. Supposing a patient with Disease Z will gain 2 QALYs and current treatment costs £5,000 over the patient's remaining lifetime. Drug Y costs £50,000 and is associated with 0.5 additional QALYs compared to usual treatment. Without testing, unaffected relatives without the disease have a mean QALY gain of 10 years and will incur £500 in direct health care costs. Test X costs £300 per individual tested and provides, on average, an additional 0.3 QALYs per unaffected relative as a consequence of early knowledge of the disease and preventative treatment. In conjunction with prior genetic testing, the use of Drug Y leads to a mean increase in health gains of 0.1 QALYs and an increase in average costs of £5,000 for relatives. The ICER for Test X alone versus no testing is £1,000 per QALY gained whilst the ICER for Test X plus Drug Y versus Test X alone is £70,000 per QALY gained. Under this scenario, Drug Y does not appear economically attractive. However, if one makes a comparison of Test X plus Drug Y versus no testing, Drug Y appears considerably more economically attractive. This is because the cost-effectiveness of the joint intervention is being driven by the costs and benefits associated with the test rather than the drug itself.

Table 57: Hypothetical example of fully incremental comparisons of drugs and companion diagnostics

Costs and QALYs accrued by index case and relatives						
Beneficiary	**No testing**		**Test X alone**		**Test X plus Drug Y for test-positives**	
	QALYs	**Costs**	**QALYs**	**Costs**	**QALYs**	**Costs**
Index case	2	£5,000	2	£5,000	2.5	£50,000
Relative 1	10	£500	10.3	£800	10.4	£5,800
Relative 2	10	£500	10.3	£800	10.4	£5,800
Relative 3	10	£500	10.3	£800	10.4	£5,800
Relative 4	10	£500	10.3	£800	10.4	£5,800
Relative 5	10	£500	10.3	£800	10.4	£5,800
Total	52	£7,500	53.5	£9,000	54.5	£79,000
Cost-effectiveness comparisons						
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER vs next best comparator**	**ICER vs no testing**
Test X plus Drug Y for test-positives	54.5	£79,000	1.0	£70,000	£70,000	£28,600
Test X alone	53.5	£9,000	1.5	£1,500	£1,000	£1,000
No testing	52.0	£7,500	-	-	-	-

Inc. - incremental; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

The company's secondary analysis compares *BRCA* mutation testing plus olaparib against no *BRCA* mutation testing and routine surveillance. However, the comparison that *should* be made is *BRCA* mutation testing plus olaparib versus *BRCA* mutation testing plus routine surveillance. This comparison is not however considered within the CS.[1] As such, the ERG would urge caution in the interpretation of the company's secondary analysis of olaparib plus *BRCA* mutation testing.

(10) Limited use of sensitivity analysis

The following analyses are purported to have been undertaken within the CS but have not been reported:

- An analysis in which time from first subsequent therapy to second subsequent therapy or death is modelled using the log normal model (mentioned on page 123 of the CS[1]).
- An analysis in which time from first subsequent therapy to second subsequent therapy or death is modelled using the generalised gamma model (mentioned on page 123 of the CS[1]).
- An analysis using follow-up resource use data from NICE TA284[49] whereby patients would have one outpatient visit every month and one CT scan every month (mentioned on page 154 of the CS[1]).

The ERG further notes that the following additional sensitivity analyses would be informative:

(i) An analysis of all potentially plausible parametric survivor functions for the outcome of time from randomisation to treatment discontinuation or death, including/excluding the assumption of proportional hazards between treatment groups.

(ii) An analysis of all potentially plausible parametric survivor functions for the outcome of time from randomisation to first subsequent therapy or death, including/excluding the assumption of proportional hazards between treatment groups.

(iii) An analysis of all potentially plausible parametric survivor functions for the outcome of time from first subsequent therapy to second subsequent treatment or death.

(iv) An analysis of all potentially plausible parametric survivor functions for the outcome of time from second subsequent therapy to death.

(v) The replication of all one-way sensitivity analyses, scenario analyses and PSA including the cost of *BRCA* testing.

5.4 Additional analysis undertaken by the ERG

5.4.1 Exploratory analysis methods

5.4.1.1 Correction of errors within the company's base case model

As noted in Section 5.3, two apparent errors were identified in the implementation of the company's model (the risk of death following the first subsequent therapy event and the frequency of outpatient visits for patients receiving routine surveillance). In addition, the costs of *BRCA* mutation testing should have been included in the company's base case. The ERG corrected these apparent errors and re-ran the deterministic and probabilistic versions of the model; the changes made to the company's model are detailed in Appendix 7. Importantly however, the ERG does not believe that the company's model provides robust estimates of OS or QALY gains (see Section 5.3) and would advise caution in the consideration of any results produced using the company's model.

5.4.1.2 Re-estimation of survival gains and QALY gains for olaparib and routine surveillance using individual patient data

The ERG requested patient-level data from Study 19 in order to re-analyse all survival modelling undertaken by the company without reliance on assumptions of proportional hazards or assumptions of equivalence in event risks between treatment groups (see clarification response[9] question C1). The company declined this request stating: *"In relation to the request for individual patient data, AstraZeneca would consider undertaking further analyses with the provision of a protocol and statistical analyses plan and may consider providing the data if appropriate and after guarantee of safeguarding of the de-identified and anonymised patient data... In general AstraZeneca does consider legitimate requests for patient level data on a case-by-case basis, following consistent*

criteria to establish if and how the information provided will be used for valid scientific purposes and to benefit patients."

Given the problems regarding the company's model structure and the data contained therein, the ERG does not consider that further analyses using the company's model would provide additional value for informing decision-making. Instead, the ERG undertook further exploratory analyses focussing on two questions:

(1) Using the crossover-adjusted OS data provided within the CS[1] and the company's clarification response,[9] what is the expected incremental survival gain for olaparib versus routine surveillance?

(2) Using a simple partitioned survival model approach, together with replicated patient-level time-to-event data on crossover-adjusted OS, time to treatment discontinuation or death and time to first subsequent therapy or death, what is the expected incremental QALY gain for olaparib versus routine surveillance?

Both of these additional analyses required the extrapolation of observed time-to-event data; the methods used to fit these parametric curves are described below.

Survival modelling methods

The ERG did not have the access to the IPD from Study 19. The Kaplan-Meier curves for time to first subsequent therapy or death (CS[1] Figure 7.4), time to discontinuation or death (CS[1] Figure 7.7), OS excluding sites allowing placebo group crossover (clarification response[9]) and OS adjusted using RPSFTM (clarification response[9]) were digitised using GetData Graph Digitizer™ software for both treatment groups. The IPD for these four outcomes were then reconstructed using methods reported by Guyot *et al;*[65] this reconstruction method is based on finding numerical solutions to the inverted Kaplan-Meier equations, given information on the number of patients at risk and/or the number of events.

The reconstructed curves for the four outcomes are plotted in Figures 25 to 28. The estimated median for each curve is presented in Table 58. All ERG-reconstructed IPD have very similar medians compared with values reported within the CS;[1] this shows that the ERG-reconstructed IPD appear to be a good representation of the Study 19 *BRCAm* trial data for these four time-to-event outcomes. However, it was not feasible to check the accuracy of reconstructed IPD for OS adjusted using the RPSFTM method, since the company's clarification response did not provide median values for the RPSFTM-adjusted Kaplan-Meier curves.

Table 58: Comparison of CS reported medians and ERG-reconstructed IPD medians

Outcome	Olaparib group		Placebo group	
	CS reported median (months)	ERG reconstructed IPD median (months)	CS reported median (months)	ERG reconstructed IPD median (months)
1. Time to treatment discontinuation or death	11.0	11.3	4.6	4.8
2. Time to first subsequent therapy or death	15.6	16.9	6.2	6.9
[redacted]	34.9	34.9	26.6	26.6
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IPD – individual patient data; RPSFTM – Rank Preserving Structural Failure Time Model; NR: not reported

In the CS,[1] the proportional hazards model incorporating treatment group as a covariate was used for the outcomes of time to first subsequent therapy or death and time to treatment discontinuation or death (see Section 5.2.4.3). TTP on penultimate platinum therapy, Jewish ethnicity and full versus partial platinum sensitivity were also adjusted in the model for these two outcomes. The ERG's reconstructed IPD were based on the published Kaplan-Meier curves and no information was available about the covariates included in the company survival analyses. Consequently, the ERG could not investigate the effect of these three covariates on the time-to-event outcomes.

The CS[1] explored parametric distributions including generalised gamma, log normal, log logistic, Weibull, exponential and Gompertz for the proportional hazards model. However, among these distributions, only the exponential, Weibull and Gompertz are proportional hazard models. The log normal and log-logistic models are accelerated failure time models which do not produce a single HR, thus the proportional hazards assumption does not hold. It is not clear how the company fitted these non-proportional hazards models assuming proportional hazards. In addition, the log-log plot of cumulative survival versus log of time for time to treatment discontinuation/death (see Figure 9) showed non-parallel curves, hence the proportional hazards assumption does not appear to be valid in this case.

The ERG considered the following parametric distributions for extrapolating the four time-to-event outcomes: (i) generalised F, (ii) generalised gamma, (iii) gamma, (iv) log normal, (v) log logistic, (vi) Weibull, (vii) exponential and (viii) Gompertz. Each model was fitted to each individual arm from the reconstructed IPD, thereby assuming independent hazards.

Survival modelling results

Figures 25 to 28 present the fitted curves for the range of candidate survivor functions considered for each treatment group for all four time-to-event outcomes. Tables 59 to 62 report the AIC statistics for all fitted curves for each outcome. Comparisons of each individual fitted curve against the empirical Kaplan-Meier data can be found in Appendix 8.

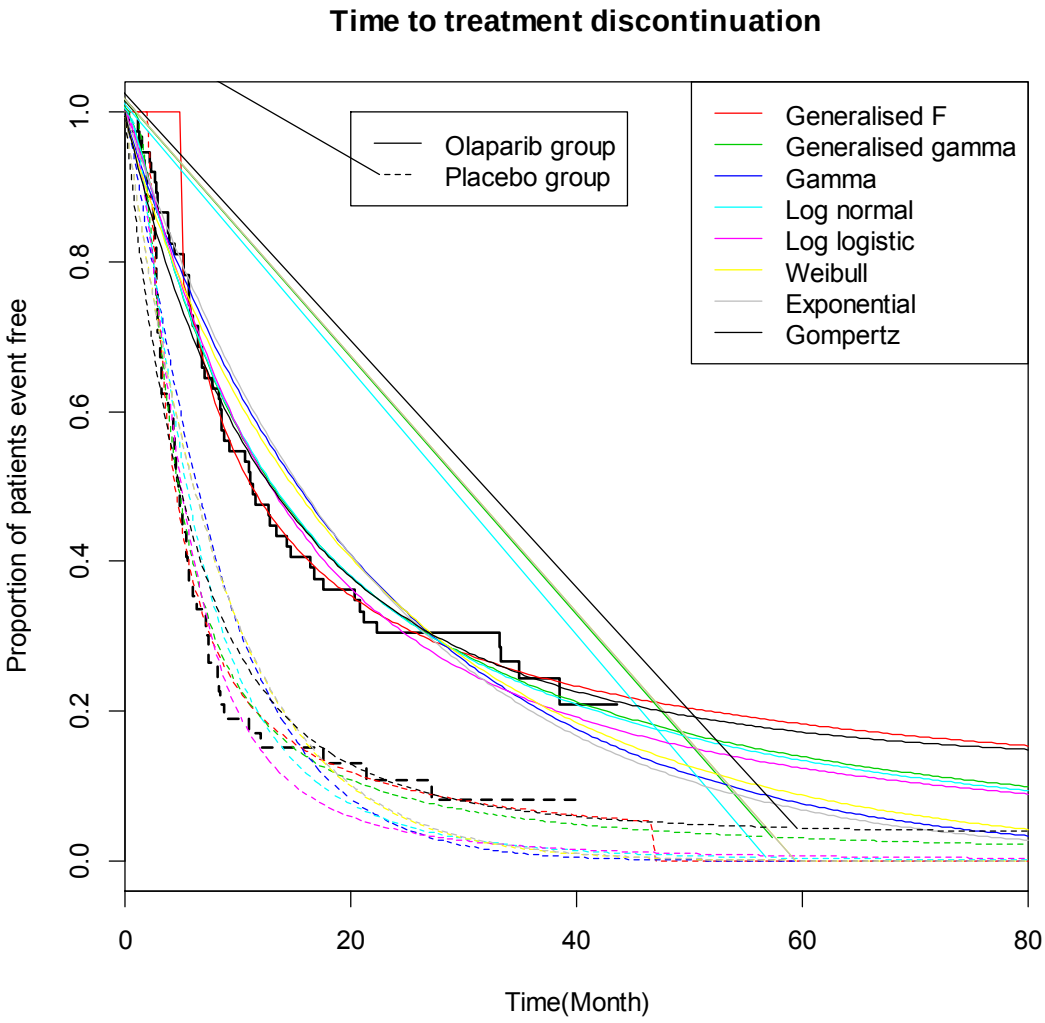
TTE outcome 1 – time from randomisation to treatment discontinuation or death

For the outcome of time to treatment discontinuation or death, the log-log plot of cumulative survival versus log of time (see Figure 9) suggested that the Weibull and exponential models may not be a good choice, since the plotted curves do not follow a straight line and do not have a slope of 1.0. Visual inspection of the fitted Weibull and exponential curves (see Figure 25) and the respective AIC statistics for these curves (see Table 59) also confirm that these are not suitable models. The gamma distribution also has poor fit and relatively higher AIC values, hence this is not a suitable model for both treatment groups. For the olaparib group, the generalised F, generalised gamma, log normal, log logistic and Gompertz functions have similar AIC values, with the generalised F distribution having the lowest AIC. For the placebo group, the generalised F and generalised gamma functions have similar AIC values, with the generalised F distribution having the lowest AIC. However, visual inspection shows that generalised F function may not be the best fit for both treatment groups. On the basis of visual inspection and AIC statistics, the generalised gamma appears to be the most suitable model, however the log normal and log logistic distributions may also be potentially suitable functions.

Table 59: AIC for time from randomisation to treatment discontinuation or death

Survivor function	Placebo group	Olaparib group
Generalised F	**306.90**	**439.78**
Generalised gamma	307.55	442.40
Gamma	338.32	447.48
Log normal	317.57	440.45
Log logistic	315.01	440.20
Weibull	339.80	446.85
Exponential	337.81	445.72
Gompertz	332.94	442.40

Figure 25: Time from randomisation to treatment discontinuation or death using generalised F, generalised gamma, gamma log normal, log logistic, Weibull, exponential and Gompertz models



TTE outcome 2 – time from randomisation to first subsequent therapy or death

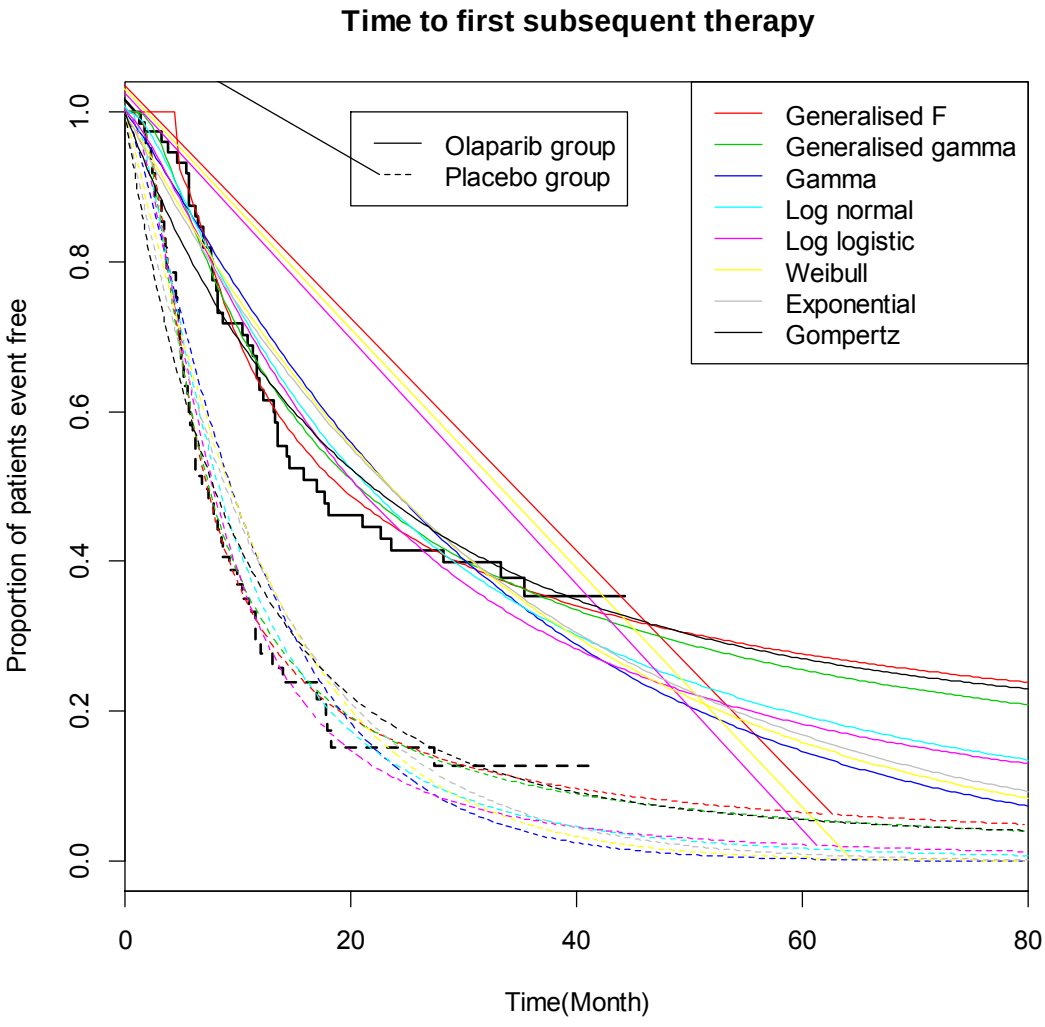
For the outcome of time to first subsequent therapy or death, the log-log plot of cumulative survival versus log of time (see Figure 11) suggests that both the Weibull and exponential models may not be a good choice, since the plotted curves do not follow a straight line and do not have a slope of 1.0. Both visual inspection of the fitted Weibull and exponential curves (see Figure 26) and AIC statistics (see Table 60) confirm that both Weibull and exponential are not suitable for both treatment groups. The gamma and Gompertz distributions also have a poor fit and relatively higher AIC values, hence these are not suitable models for either treatment group. The generalised F, generalised gamma, log normal and log logistic functions have similar AIC values, with the generalised F function having the lowest AIC for the olaparib group and the generalised gamma function having the lowest AIC for the placebo group. On the basis of visual inspection and AIC statistics, the generalised gamma appears to be the

most suitable model, however the log normal and log logistic survivor distributions may also be potentially suitable candidate functions.

Table 60: AIC for time from randomisation to first subsequent therapy or death

Survivor function	Placebo group	Olaparib group
Generalised F	333.27	**379.19**
Generalised gamma	**331.96**	381.77
Gamma	349.66	391.90
Log normal	336.12	383.29
Log logistic	335.97	385.50
Weibull	351.68	392.42
Exponential	350.29	390.50
Gompertz	349.86	389.96

Figure 26: Time from randomisation to first subsequent therapy or death using generalised F, generalised gamma, gamma log normal, log logistic, Weibull, exponential and Gompertz



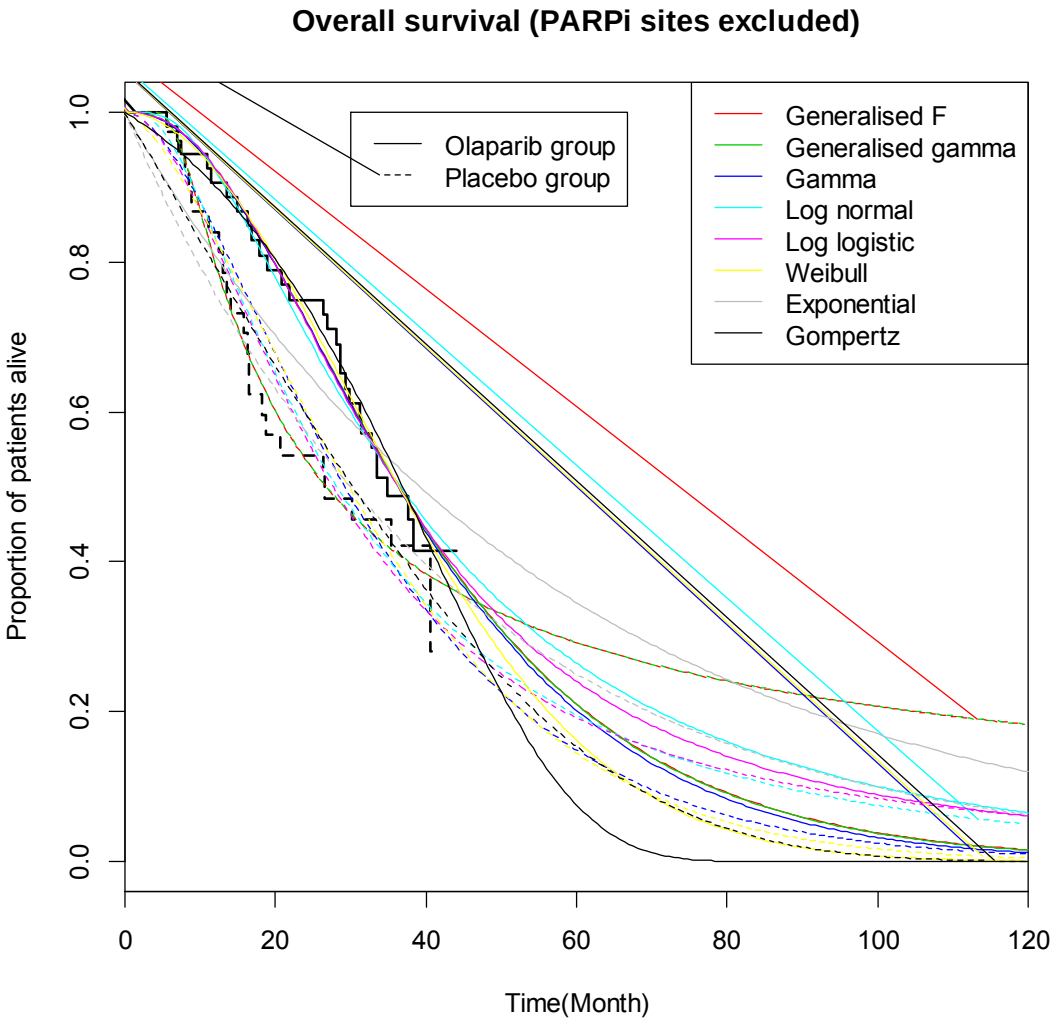
TTE outcome 3 – time from randomisation to death (crossover sites excluded)

For crossover site excluded-OS, using visual inspection of the fitted curves (see Figure 27) and AIC statistics (see Table 61), it is reasonable to suggest that that exponential model is not suitable for both groups and the Gompertz model is not suitable for the placebo arm. The Generalised F and generalised gamma functions suggest a very good fit to the observed data for both arms (see Figure 27 and Appendix 7), however this model results in an intersection of the olaparib and placebo curves at around month 45. The gamma, log normal, log logistic and Weibull all produce a good fit to the olaparib group data; this is confirmed by the similar AIC statistics for these models. However, these models do not fit the placebo group as well as the generalised F and generalised gamma distributions. The fitted curves for the two arms using these models do not intersect, or intersect only slightly around month 70. On the basis of visual inspection and AIC statistics, the generalised F, generalised gamma, gamma, log normal, log logistic and Weibull functions may be potentially suitable models.

Table 61: AIC for overall survival - crossover-sites excluded

Survivor function	Placebo group	Olaparib group
Generalised F	206.52	277.91
Generalised gamma	**204.52**	275.91
Gamma	208.91	**273.91**
Log normal	205.92	274.35
Log logistic	207.67	274.12
Weibull	210.10	274.12
Exponential	211.78	284.07
Gompertz	212.87	276.48

Figure 27: Overall survival (crossover sites excluded) using generalised F, generalised gamma, gamma log normal, log logistic, Weibull, exponential and Gompertz



TTE outcome 4 – time from randomisation to death (RPSFTM-adjusted)

The extrapolation results for the RPSFTM-adjusted OS analysis are similar to those for the crossover site excluded OS analysis described above. Using visual inspection of the fitted curves (see Figure 28) and AIC statistics (see Table 62), it is reasonable to conclude that the exponential model is not suitable for both arms and the Gompertz model is not suitable for the placebo arm. The generalised F and generalised gamma functions provide a very good fit to the observed period of data for both arms (see Figure 28 and Appendix 7), however this model results in an intersection of the two curves at around month 45. The gamma, log normal, log logistic and Weibull functions all provide a good fit to the olaparib group data, which is confirmed by the similar AIC statistics for these models. However, these models do not fit the placebo group data as well as the generalised F and generalised gamma functions. The fitted curves for the two arms using these models do not intersect, or intersect only slightly around month 60. On the basis of visual inspection and AIC statistics, the generalised F,

generalised gamma, gamma, log normal, log logistic and Weibull functions may be potentially suitable models.

Table 62: AIC for overall survival - RPSFTM-adjusted

Survivor function	Placebo group	Olaparib group
Generalised F	348.47	402.33
Generalised gamma	346.51	400.32
Gamma	347.08	**398.38**
Log normal	**344.87**	399.55
Log logistic	346.26	398.66
Weibull	348.44	398.45
Exponential	354.69	419.99
Gompertz	352.57	401.64

Figure 28: Overall survival (RPSFTM-adjusted) using generalised F, generalised gamma, gamma log normal, log logistic, Weibull, exponential and Gompertz CONFIDENTIAL

Methods used to address question 1: What is the expected incremental survival gain for olaparib versus placebo?

Based on the extrapolation of OS detailed in the previous section, the mean survival in each group was estimated using a simple restricted means approach by estimating the AUC for each treatment group over a time period of 15-years (the company's modelled time horizon). Mean incremental survival gains were estimated as the difference in the 15-year restricted mean AUC between the two groups. Mean survival was estimated using the generalised F, generalised gamma, gamma, log normal, log logistic and Weibull models fitted to the empirical OS data. Restricted means estimates were not discounted.

Methods used to address question 2: What is the expected incremental QALY gain for olaparib versus placebo?

A simple partitioned survival model was developed incorporating four health states: (1) alive, not yet progressed to first subsequent therapy, on maintenance therapy; (2) alive, not yet progressed to first subsequent therapy, discontinued maintenance therapy (3) alive, following progression to first subsequent therapy, and (4) dead.

Estimates of the cumulative probability of survival up to time *t* were estimated directly from each potentially plausible candidate parametric survivor function fitted within the ERG's survival modelling exercise detailed above.

The probabilities of not experiencing an event at each timepoint were adjusted to account for two logical inconsistencies which may have resulted from the extrapolation process:

(i) The outcome of initiation of first subsequent therapy or death for a given patient must always occur before, or at the same time as, death due to any cause. If the probability of initiation of first subsequent therapy at time *t* was greater than the probability of OS at time *t*, the probability of initiation of first subsequent therapy or death at time *t* was set to zero.

(ii) The outcome of treatment discontinuation or death for a given patient must always occur before, or at the same time as, the initiation of first subsequent therapy or death. If the probability of treatment discontinuation or death at time *t* was greater than the probability of initiation of first subsequent therapy or death at time *t*, the probability of treatment discontinuation or death at time *t* was set to zero. A similar adjustment to TTD/D was made within the company's model.

The probability of residing in each of the model health states at each timepoint was calculated as follows.

The probability of being alive, not having progressed to first subsequent therapy, and being on maintenance therapy (i.e. in State 1) at time *t* was calculated as:

$S(t_i)_{TTD}$ [i]

The probability of being alive, not having progressed to first subsequent therapy, having discontinued maintenance therapy (i.e. in State 2) at time *t* was calculated as:

$S(t_i)_{TFST} - S(t_i)_{TTD}$ [ii]

The probability of being alive, following progression to first subsequent therapy (i.e. in State 3) at time *t* was calculated as:

$S(t_i)_{OS} - S(t_i)_{TFST}$ [iii]

The probability of being dead (i.e. in State 4) at time *t* was calculated as:

$1-S(t_i)_{OS}$ [iv]

A half cycle correction was applied to adjust for the timing of events. Mean QALYs in each treatment group were estimated by applying utility values drawn from the company's base case analysis.[1] As a single utility value was not available for patients in State 3 (progression to chemotherapy), a simple mean of the two utility values reported by the manufacturer in TA222[38] was assumed (utility=0.68). Health outcomes were discounted at a rate of 3.5% per annum.[44]

The model was analysed across 108 scenarios which reflect the combinations of the most plausible curves fitted within the ERG's survival modelling exercise (see Table 63). In each scenario, the same survivor function was applied to both treatment groups.

Table 63: Candidate survivor functions explored within the ERG's partitioned survival model

Time from randomisation to treatment discontinuation or death	Time from randomisation to first subsequent therapy or death	Time from randomisation to death (OS)
(1) Generalised gamma (2) Log normal (3) Log logistic	(1) Generalised gamma (2) Log normal (3) Log logistic	(1) RPSFTM-adjusted generalised F (2) RPSFTM-adjusted generalised gamma (3) RPSFTM-adjusted gamma (4) RPSFTM-adjusted log normal (5) RPSFTM-adjusted log logistic (6) RPSFTM-adjusted Weibull (7) CSE-adjusted generalised F (8) CSE-adjusted generalised gamma (9) CSE-adjusted gamma (10) CSE-adjusted log normal (11) CSE-adjusted log logistic (12) CSE-adjusted Weibull

RPSFTM – Rank Preserving Structure Failure Time Model; CSE – crossover sites excluded

5.4.2 Results of the ERG's exploratory analysis

5.4.2.1 Corrections applied to the company's base case model

Table 64 presents revised estimates of the company's base case ICER incorporating the corrections to errors identified by the ERG and including the cost of *BRCA* mutation testing. Based on the revised analysis, the probabilistic ICER for olaparib versus routine surveillance is estimated to £83,987 per QALY gained. The analysis based on point estimates of parameters yields a similar ICER for olaparib versus routine surveillance of £85,592 per QALY gained.

Table 64: Corrected base case ICER using the company's model

Central estimates of cost-effectiveness (expectation of the mean)							
Option	**LYGs***	**QALYs**	**Costs†**	**Inc. LYGs***	**Inc. QALYs**	**Inc. Costs**	**ICER**
Olaparib	-	2.61	£85,048	-	0.91	£76,259	**£83,987**
Routine surveillance	-	1.70	£8,788	-	-	-	-
Central estimates of cost-effectiveness (point estimates of parameters)							
Option	**LYGs**	**QALYs**	**Costs**	**Inc. LYGs**	**Inc. QALYs**	**Inc. Costs**	**ICER**
Olaparib	3.55	2.58	£84,945	1.17	0.89	£76,054	**£85,592**
Routine surveillance	2.38	1.69	£8,891	-	-	-	-

** life years gained are not reported as they are not recorded within the company's PSA sub-routine*
† Cost of BRCA mutation testing manually included in total expected cost of olaparib

5.4.2.2 Results for question 1: What is the expected incremental survival gain for olaparib versus routine surveillance?

Table 65 summarises the 15-year restricted means AUC estimates of OS based on parametric curves fitted to the RPSFTM-adjusted and CSE-adjusted Kaplan-Meier data presented within the company's clarification response.[9] The analysis indicates that for some scenarios (using the generalised gamma and generalised F functions), olaparib is predicted to have a lower OS than placebo; this is a consequence of the placebo curve intersecting the olaparib curve. All other estimates of OS are positive (i.e. olaparib produces additional survival gains as compared against placebo). The highest estimate of incremental OS is produced by the CSE-adjusted log normal curve (incremental survival for olaparib versus placebo = 0.68 LYGs). It is noteworthy that this most optimistic estimate is considerably lower than the survival gain predicted by company's base case model (company's model undiscounted LYGs = 1.36).

Table 65: Restricted means AUC analysis of overall survival

OS survivor function	Olaparib	Placebo	Incremental life years gained (olaparib vs placebo)
RPSFTM-adjusted generalised F	[redacted]	[redacted]	[redacted]
RPSFTM-adjusted generalised gamma	[redacted]	[redacted]	[redacted]
RPSFTM-adjusted gamma	[redacted]	[redacted]	[redacted]
RPSFTM-adjusted log normal	[redacted]	[redacted]	[redacted]
RPSFTM-adjusted log logistic	[redacted]	[redacted]	[redacted]
RPSFTM-adjusted Weibull	[redacted]	[redacted]	[redacted]
CSE-adjusted generalised F	3.51	4.68	-1.17
CSE-adjusted generalised gamma	3.51	4.68	-1.18
CSE-adjusted gamma	3.46	2.93	0.53
CSE-adjusted log normal	4.03	3.34	0.68
CSE-adjusted log logistic	3.94	3.39	0.54
CSE-adjusted log Weibull	3.25	2.88	0.37

5.4.2.3 Methods for question 2: What is the expected incremental QALY gain for olaparib versus routine surveillance?

Table 66 presents the estimated discounted QALY gains for olaparib and routine surveillance using the ERG's partitioned survival model.

Table 66: Estimated discounted QALY gains for olaparib and routine surveillance using the ERG's model

Scenario	Survivor function			Mean QALYs		Incremental QALYs (olaparib vs routine surveillance)
	Time to treatment discontinuation	Time to first subsequent therapy	Overall survival	Olaparib	Routine surveillance	
1	gen. gamma	gen. gamma	RPSFTM gen. F	2.16	2.54	-0.38
2	gen. gamma	gen. gamma	RPSFTM gen. gamma	2.16	2.36	-0.20
3	gen. gamma	gen. gamma	RPSFTM gamma	2.20	1.92	0.28
4	gen. gamma	gen. gamma	RPSFTM log normal	2.44	2.16	0.27
5	gen. gamma	gen. gamma	RPSFTM log logistic	2.40	2.17	0.23
6	gen. gamma	gen. gamma	RPSFTM Weibull	2.10	1.87	0.23
7	gen. gamma	gen. gamma	CSE gen. F	2.36	2.80	-0.44
8	gen. gamma	gen. gamma	CSE gen. gamma	2.35	2.80	-0.45
9	gen. gamma	gen. gamma	CSE gamma	2.32	1.93	0.40
10	gen. gamma	gen. gamma	CSE log normal	2.63	2.15	0.48
11	gen. gamma	gen. gamma	CSE log logistic	2.57	2.16	0.41
12	gen. gamma	gen. gamma	CSE Weibull	2.20	1.90	0.30
13	log normal	gen. gamma	RPSFTM gen. F	2.16	2.53	-0.37
14	log normal	gen. gamma	RPSFTM gen. gamma	2.16	2.35	-0.19
15	log normal	gen. gamma	RPSFTM gamma	2.20	1.91	0.29
16	log normal	gen. gamma	RPSFTM log normal	2.44	2.15	0.29
17	log normal	gen. gamma	RPSFTM log logistic	2.40	2.16	0.24
18	log normal	gen. gamma	RPSFTM Weibull	2.10	1.86	0.24
19	log normal	gen. gamma	CSE gen. F	2.36	2.79	-0.43
20	log normal	gen. gamma	CSE gen. gamma	2.35	2.79	-0.44
21	log normal	gen. gamma	CSE gamma	2.32	1.92	0.41
22	log normal	gen. gamma	CSE log normal	2.63	2.14	0.49
23	log normal	gen. gamma	CSE log logistic	2.57	2.15	0.43
24	log normal	gen. gamma	CSE Weibull	2.20	1.89	0.31
25	log logistic	gen. gamma	RPSFTM gen. F	2.16	2.53	-0.37
26	log logistic	gen. gamma	RPSFTM gen. gamma	2.16	2.35	-0.19
27	log logistic	gen. gamma	RPSFTM gamma	2.20	1.91	0.29
28	log logistic	gen. gamma	RPSFTM log normal	2.44	2.15	0.28
29	log logistic	gen. gamma	RPSFTM log logistic	2.40	2.16	0.24
30	log logistic	gen. gamma	RPSFTM Weibull	2.10	1.86	0.24
31	log logistic	gen. gamma	CSE gen. F	2.35	2.79	-0.43
32	log logistic	gen. gamma	CSE gen. gamma	2.35	2.79	-0.44
33	log logistic	gen. gamma	CSE gamma	2.32	1.92	0.41
34	log logistic	gen. gamma	CSE log normal	2.62	2.13	0.49
35	log logistic	gen. gamma	CSE log logistic	2.57	2.14	0.43
36	log logistic	gen. gamma	CSE Weibull	2.20	1.89	0.31
37	gen. gamma	log normal	RPSFTM gen. F	2.17	2.52	-0.35
38	gen. gamma	log normal	RPSFTM gen. gamma	2.17	2.34	-0.17
39	gen. gamma	log normal	RPSFTM gamma	2.21	1.91	0.30
40	gen. gamma	log normal	RPSFTM log normal	2.45	2.14	0.31
41	gen. gamma	log normal	RPSFTM log logistic	2.41	2.16	0.26
42	gen. gamma	log normal	RPSFTM Weibull	2.10	1.86	0.24
43	gen. gamma	log normal	CSE gen. F	2.37	2.78	-0.41
44	gen. gamma	log normal	CSE gen. gamma	2.36	2.78	-0.42
45	gen. gamma	log normal	CSE gamma	2.33	1.92	0.42

Scenario	Survivor function			Mean QALYs		Incremental QALYs (olaparib vs routine surveillance)
	Time to treatment discontinuation	Time to first subsequent therapy	Overall survival	Olaparib	Routine surveillance	
46	gen. gamma	log normal	CSE log normal	2.65	2.13	0.52
47	gen. gamma	log normal	CSE log logistic	2.59	2.14	0.45
48	gen. gamma	log normal	CSE Weibull	2.22	1.89	0.32
49	log normal	log normal	RPSFTM gen. F	2.17	2.53	-0.35
50	log normal	log normal	RPSFTM gen. gamma	2.17	2.34	-0.18
51	log normal	log normal	RPSFTM gamma	2.21	1.92	0.29
52	log normal	log normal	RPSFTM log normal	2.45	2.15	0.31
53	log normal	log normal	RPSFTM log logistic	2.41	2.16	0.25
54	log normal	log normal	RPSFTM Weibull	2.10	1.86	0.24
55	log normal	log normal	CSE gen. F	2.37	2.78	-0.42
56	log normal	log normal	CSE gen. gamma	2.36	2.79	-0.42
57	log normal	log normal	CSE gamma	2.33	1.92	0.41
58	log normal	log normal	CSE log normal	2.65	2.13	0.52
59	log normal	log normal	CSE log logistic	2.59	2.15	0.45
60	log normal	log normal	CSE Weibull	2.22	1.90	0.32
61	log logistic	log normal	RPSFTM gen. F	2.17	2.52	-0.35
62	log logistic	log normal	RPSFTM gen. gamma	2.17	2.34	-0.18
63	log logistic	log normal	RPSFTM gamma	2.21	1.91	0.29
64	log logistic	log normal	RPSFTM log normal	2.45	2.14	0.31
65	log logistic	log normal	RPSFTM log logistic	2.41	2.16	0.25
66	log logistic	log normal	RPSFTM Weibull	2.10	1.86	0.24
67	log logistic	log normal	CSE gen. F	2.36	2.78	-0.42
68	log logistic	log normal	CSE gen. gamma	2.36	2.78	-0.42
69	log logistic	log normal	CSE gamma	2.33	1.92	0.41
70	log logistic	log normal	CSE log normal	2.64	2.13	0.52
71	log logistic	log normal	CSE log logistic	2.59	2.14	0.44
72	log logistic	log normal	CSE Weibull	2.21	1.89	0.32
73	gen. gamma	log logistic	RPSFTM gen. F	2.17	2.52	-0.35
74	gen. gamma	log logistic	RPSFTM gen. gamma	2.17	2.34	-0.17
75	gen. gamma	log logistic	RPSFTM gamma	2.21	1.91	0.30
76	gen. gamma	log logistic	RPSFTM log normal	2.45	2.14	0.31
77	gen. gamma	log logistic	RPSFTM log logistic	2.41	2.15	0.26
78	gen. gamma	log logistic	RPSFTM Weibull	2.10	1.86	0.24
79	gen. gamma	log logistic	CSE gen. F	2.37	2.78	-0.41
80	gen. gamma	log logistic	CSE gen. gamma	2.36	2.78	-0.42
81	gen. gamma	log logistic	CSE gamma	2.33	1.92	0.42
82	gen. gamma	log logistic	CSE log normal	2.65	2.13	0.52
83	gen. gamma	log logistic	CSE log logistic	2.59	2.14	0.45
84	gen. gamma	log logistic	CSE Weibull	2.22	1.89	0.33
85	log normal	log logistic	RPSFTM gen. F	2.17	2.52	-0.35
86	log normal	log logistic	RPSFTM gen. gamma	2.17	2.34	-0.17
87	log normal	log logistic	RPSFTM gamma	2.21	1.91	0.30
88	log normal	log logistic	RPSFTM log normal	2.45	2.15	0.31
89	log normal	log logistic	RPSFTM log logistic	2.41	2.16	0.25
90	log normal	log logistic	RPSFTM Weibull	2.10	1.86	0.24
91	log normal	log logistic	CSE gen. F	2.37	2.78	-0.42
92	log normal	log logistic	CSE gen. gamma	2.36	2.78	-0.42
93	log normal	log logistic	CSE gamma	2.33	1.92	0.41

Scenario	Survivor function			Mean QALYs		Incremental QALYs (olaparib vs routine surveillance)
	Time to treatment discontinuation	Time to first subsequent therapy	Overall survival	Olaparib	Routine surveillance	
94	log normal	log logistic	CSE log normal	2.65	2.13	0.52
95	log normal	log logistic	CSE log logistic	2.59	2.15	0.45
96	log normal	log logistic	CSE Weibull	2.22	1.90	0.32
97	log logistic	log logistic	RPSFTM gen. F	2.17	2.52	-0.35
98	log logistic	log logistic	RPSFTM gen. gamma	2.17	2.34	-0.17
99	log logistic	log logistic	RPSFTM gamma	2.21	1.91	0.30
100	log logistic	log logistic	RPSFTM log normal	2.45	2.14	0.31
101	log logistic	log logistic	RPSFTM log logistic	2.41	2.16	0.25
102	log logistic	log logistic	RPSFTM Weibull	2.10	1.86	0.24
103	log logistic	log logistic	CSE gen. F	2.36	2.78	-0.42
104	log logistic	log logistic	CSE gen. gamma	2.36	2.78	-0.42
105	log logistic	log logistic	CSE gamma	2.33	1.92	0.41
106	log logistic	log logistic	CSE log normal	2.64	2.13	0.52
107	log logistic	log logistic	CSE log logistic	2.59	2.14	0.44
108	log logistic	log logistic	CSE Weibull	2.21	1.89	0.32

QALY – quality-adjusted life year; gen.– generalised; RPSFTM – Rank Preserving Structural Failure Time Model; CSE – crossover sites excluded

The results presented in Table 66 indicate that the greatest discounted incremental QALY gain achievable using the ERG's model is approximately 0.52 QALYs. This scenario is based on the generalised gamma distribution for TTD/D, the log normal distribution for TFST/D and the log normal distribution applied to the crossover site excluded OS dataset. The most favourable incremental QALY estimate generated by the ERG's model is considerably lower than that produced by the company's model (ERG's model = 0.52 QALYs versus company's model = 0.90 QALYs).

Given that the incremental cost for olaparib versus routine surveillance is almost entirely comprised of the additional acquisition costs associated with olaparib, applying the ERG-corrected base case incremental costs of £76,259 (see Table 64) to the ERG's most optimistic incremental QALY gain for olaparib indicates that the ICER for olaparib versus routine surveillance is likely to be in excess of £145,000 per QALY gained, but may be considerably higher.

As noted in Section 5.4.1.2, the ERG's partitioned survival model does not include separate states for first and second subsequent chemotherapy, hence it was not possible to assume exactly the same utility values as the company's base case model. However, the company's model indicates that the contribution of these states to the overall incremental QALY gain is small (see Table 47). Table 67 presents a sensitivity analysis of the ERG's partitioned survival model assuming the two post-progression utility values used in the company's base case model (first subsequent therapy utility = 0.72; second subsequent therapy utility = 0.65). This analysis indicates that the QALY estimates estimated using the ERG's partitioned survival model are not materially influenced by the post-progression utility value.

Table 67: Sensitivity analysis assuming alternative post-progression utility values

Scenario	Most optimistic incremental QALY gain (olaparib versus routine surveillance)	Implied ICER for olaparib versus routine surveillance (assuming incremental cost = £76,259)
Post-progression utility = 0.68	0.5238	£145,594
Post-progression utility = 0.72	0.4899	£155,657
Post-progression utility = 0.65	0.5557	£137,220

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

The ERG sought the views of three clinical experts (also authors of this report) regarding their views on which of the extrapolated curves may be considered most plausible. This exercise was undertaken via email using a standardised questionnaire form. The clinical advisors' preferences are summarised in Table 68.

Table 68: Clinical advisors' preferred extrapolated curves

Respondent	Outcome	Preferred curve (s)	Reason given
Clinical advisor 1	TTD/D	Generalised gamma	*"Curves follow the data most accurately. Curves most clinically believable."*
	TFST/D	Generalised gamma	*"Curves represent an accurate overview of the individual data set (same number of "points" above and below the curves). Most clinically plausible."*
	RPSFTM-adjusted OS	Gamma	*"Most clinically "sensible", Closest representation of KM data. Extrapolation most believable."*
	CSE-adjusted OS	Gamma	*"Most feasible clinically. Curves follow data most accurately. Extrapolation most believable."*
Clinical advisor 2	TTD/D	Generalised gamma	*"Best fit with Kaplan-Meier, projected outcomes after 40 months look reasonable."*
	TFST/D	Generalised F	*"Best fit with Kaplan-Meier, projected outcomes after 40 months look reasonable.*
	RPSFTM-adjusted OS	Gamma	*"Best fit with Kaplan-Meier, projected outcomes after 40 months look reasonable. Doesn't produce an unlikely cross over between treatment arms."*
	CSE-adjusted OS	Gamma	*"Best fit with Kaplan-Meier, projected outcomes after 40 months look reasonable. Doesn't produce an unlikely cross over between treatment arms."*
Clinical advisor 3	TTD/D	Generalised gamma	*"Generalised f has an odd step, the others control drop to zero too quickly"*
	TFST/D	Generalised F	*"Looks to fit data better"*
	RPSFTM-adjusted OS	Log normal or generalised gamma	*"Very difficult as data curves so similar – log normal or generalised gamma looks better!"*
	CSE-adjusted OS	Gamma, log normal or log logistic	*"Even more difficult – coarser data similar curves. More realistic looking esp. time to reach near zero and fit to data."*

Using the crossover-site excluded OS data, the first clinical advisor's preferred survival curves imply an incremental gain of 0.28 QALYs for olaparib versus routine surveillance. Assuming incremental costs of £76,259 for olaparib versus routine surveillance, this implies an ICER of £270,268 per QALY gained. Using the RPSFTM-adjusted OS data, the first clinical advisor's preferred survival curves imply an incremental gain of 0.40 QALYs for olaparib versus routine surveillance. Assuming incremental costs of £76,259 for olaparib versus routine surveillance, this implies an ICER of £191,979 per QALY gained.

Using the crossover-site excluded OS data, the second clinical advisor's preferred survival curves imply an incremental gain of 0.38 QALYs for olaparib versus routine surveillance. Assuming incremental costs of £76,259 for olaparib versus routine surveillance, this implies an ICER of £201,103 per QALY gained. Using the RPSFTM-adjusted OS data, the second clinical advisor's preferred survival curves imply an incremental gain of 0.26 QALYs for olaparib versus routine surveillance. Assuming incremental costs of £76,259 for olaparib versus routine surveillance, this implies an ICER of £288,985 per QALY gained.

The third clinical advisor's views were more tentative and did not indicate a single preferred curve for OS adjusted using either crossover method. This advisor stated a preference for the log normal and generalised gamma functions for the RPSFTM-adjusted OS data, and the gamma, log normal or log logistic functions for the crossover site excluded OS data. The resulting QALY gains implied by the clinical advisor's preferred survival functions range from -0.22 QALYs (RPSFTM-adjusted generalised gamma OS curve, olaparib dominated by routine surveillance) to 0.38 QALYs (CSE-adjusted log-logistic OS curve, implied ICER = £199,694 per QALY gained for olaparib versus routine surveillance).

5.5 Discussion

The CS[1] includes a systematic review of published economic studies of treatments for ovarian cancer together with a *de novo* model-based economic evaluation to assess the incremental cost-effectiveness of olaparib versus routine surveillance in women with *BRCA1/2* mutated (germline and/or somatic), PSR high-grade serous ovarian, fallopian tube or peritoneal cancer whose relapsed disease has responded to platinum-based chemotherapy.

One previously published economic evaluation of olaparib (with or without prior *BRCA* mutation testing) versus routine surveillance in patients with PSR high-grade serous ovarian cancer after a partial or complete response to a platinum-containing regimen was included in the company's review. Within this analysis, the authors reported the ICER for *BRCA1/2* testing followed by olaparib treatment for *BRCA* mutation carriers compared with routine surveillance to be $193,442 per PFLYS.

This study is however subject to a number of limitations including the use of a short time horizon, the use of PFS as the metric of health benefit, and the omission of downstream health benefits associated with platinum-based chemotherapies.

The company developed a *de novo* model to assess the cost-effectiveness of olaparib versus routine surveillance in PSR ovarian cancer. The health economic analysis contained within the CS is comprised of two evaluations:

(i) The base case economic evaluation of olaparib maintenance treatment versus routine surveillance in patients with *BRCAm* PSR ovarian cancer. This analysis excludes the costs of *BRCA* mutation testing and considers costs and benefits relating to the index *BRCAm* ovarian cancer patient only.

(ii) A broader economic evaluation that also accounts for: (a) the costs of *BRCA* mutation testing in PSR ovarian cancer patients, and; (b) the costs and benefits of expanding *BRCA* mutation testing to family members of relapsed *BRCAm* ovarian cancer patients undergoing *BRCA* mutation testing as a prerequisite in consideration of olaparib as a potential treatment option. This analysis considers costs and benefits relating to the index *BRCAm* ovarian cancer patient and family members.

The company's base case analysis adopts a semi-Markov approach and evaluates costs and benefits from the perspective of the NHS and Personal Social Services (PSS) over a 15-year time horizon. The model includes five health states: (i) progression-free (on maintenance treatment); (ii) progression-free (discontinued maintenance treatment); (iii) first subsequent chemotherapy (on treatment or discontinued); (iv) second subsequent chemotherapy (on treatment or discontinued), and; (v) dead. Clinical input parameters were estimated using data from the *BRCAm* subgroup within Study 19.[27] For the progression-free states, health utilities were mapped from the FACT-O to the EQ-5D using a published algorithm; other utilities were taken from the manufacturer's submission for NICE TA 222.[38] Resource use estimates were taken from Study 19, previous NICE appraisals, guidelines, other literature and assumptions. Unit costs were derived from standard sources. The additional costs and benefits of *BRCA* mutation testing within the wider secondary economic analysis were taken from the cost-effectiveness review report published as part of NICE CG164.[62]

The probabilistic version of the company's base case analysis suggests that olaparib is expected to produce an additional 0.90 QALYs at an additional cost of £72,232 compared against routine surveillance. The probabilistic ICER for olaparib versus routine surveillance is expected to be £79,953 per QALY gained. The results of the model based on point estimates of parameters are similar, with olaparib yielding an ICER of £81,063 per QALY gained compared against routine surveillance. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that olaparib

produces more net benefit than routine surveillance is approximately zero. Assuming a willingness to pay threshold of £50,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately 0.05. The company's secondary analysis which includes the costs and benefits of *BRCA* mutation testing for unaffected relatives suggests a lower average deterministic ICER for olaparib plus *BRCA* mutation testing versus routine surveillance without *BRCA* mutation testing of £61,159 per QALY gained.

The ERG critically appraised the company's economic analysis and double-programmed the company's health economic model. The ERG's rebuild of the company's economic model did not reveal any significant programming errors. However, the ERG has several concerns regarding the model and the evidence used to inform it. The most pertinent of these relate to: concerns regarding company's model structure and use of outcomes data from Study 19 (particularly the exclusion of outcomes relating to time from randomisation to death and PFS); potential confounding of end points used in the company's model; concerns regarding the methods for modelling of time-to-event outcomes, discordance between model predictions and observed data from Study 19, and; concerns regarding the comparison made within the company's secondary analysis of the cost-effectiveness of olaparib plus *BRCA* testing for unaffected relatives. Overall, the ERG has concerns that the various assumptions employed within the company's model are likely to overestimate the incremental health gains for olaparib versus routine surveillance.

In order to further explore the likely magnitude of potential biases in the company's approach to synthesising evidence from Study 19 to estimate survival benefits for olaparib and routine surveillance, the ERG requested patient-level data (IPD) from the *BRCAm* subgroup within Study 19 with the intention of re-fitting the time-to-event curves, taking into account the exclusion of crossover sites and avoiding the company's assumption of proportional hazards between treatment groups. The company declined the ERG's data request. Instead, the ERG replicated the patient-level data from Study 19 using methods reported by Guyot *et al*[65] and fitted a range of potential candidate survivor functions to the replicated IPD data on (i) time to treatment discontinuation or death; (ii) time to first subsequent therapy or death; (iii) OS adjusted using RPSFTM, and; (iv) OS adjusted by excluding crossover sites. This analysis was used to address two questions: (1) What is the expected incremental survival gain for olaparib versus routine surveillance? (2) What is the expected incremental QALY gain for olaparib versus routine surveillance? With respect to the first question, the ERG used a restricted means AUC approach using the ERG-fitted parametric models of crossover-adjusted OS for olaparib versus placebo. With respect to the second question, the ERG developed a four state partitioned survival model in which OS duration is directly informed by parametric curves fitted to the crossover-adjusted Kaplan-Meier curves provided by the company.

The ERG's restricted means analysis produced a most optimistic estimate of undiscounted incremental survival for olaparib of 0.68 LYGs, based on the CSE-adjusted log normal curve. This estimate is considerably lower than the estimated 1.36 incremental LYGs for olaparib versus routine surveillance generated by the company's base case model. This analysis suggests that it is highly likely that the company's model substantially overestimates the incremental survival benefits associated with olaparib.

The ERG's partitioned survival model suggests that the most optimistic discounted incremental QALY gain for olaparib versus routine surveillance is approximately 0.52 QALYs. This scenario is based on a generalised gamma distribution for TTD/D, a log normal distribution for TFST/D and the log normal distribution for crossover site excluded OS. The most favourable QALY estimate generated by the ERG's model is considerably lower than the estimated 0.90 discounted incremental QALYs generated by the company's model. Assuming that the incremental cost for olaparib versus routine surveillance estimated by the company's model, which is largely comprised of the acquisition costs of the drug, is reasonable, this implies that the ICER for olaparib versus routine surveillance is likely to be in excess of £145,000 per QALY gained, but may be considerably higher. Based on the preferred survivor functions selected by the clinical advisors to the ERG, the implied ICER for olaparib versus routine surveillance is estimated to be, at best, £191,979 per QALY gained. One clinical advisor stated a preference for a combination of survivor functions which led to olaparib being dominated by routine surveillance.

6. END OF LIFE CONSIDERATIONS

NICE end-of-life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
- The treatment is licensed or otherwise indicated, for small patient populations.

The company believes that olaparib should be considered as a "life extending treatment at the end of life." The company requests that NICE consider the end-of-life criteria in light of:

(i) The significant unmet need

(ii) The lack of maintenance treatment options in this patient population

(iii) The small eligible patient population

Table 69 presents additional information from the CS[1] relating the available evidence to NICE's end-of-life criteria.

The ERG notes that the company's modelled estimates of the expected survival duration for the routine surveillance group predicted by the company's model do not appear to be reliable. The ERG-reconstructed IPD for the Study 19 *BRCAm* subgroup suggests the median RPSFTM-adjusted OS duration for the placebo group was approximately 28.4 months (see Table 58). Excluding crossover sites produced an estimated median OS duration for placebo of approximately 26.6 months. The company's health economic model suggests a mean survival duration of approximately 30 months (undiscounted). The ERG's restricted-means analysis suggests that the mean undiscounted survival duration in the placebo group is at least [redacted] months, based on the RPSFTM-adjusted Weibull survivor function.

Table 69: Additional information relating to the consideration of olaparib as an end-of-life treatment (adapted from CS[1] Table ES1)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Patients with relapsed OC have been shown to have a poor survival, with median OS of 17.6 months at first relapse.[66] The most relevant data, in the licensed population for olaparib, available in literature comes from a subgroup analysis of an Australian observational study of OC in 1001 patients.[2] Patients with *BRCAm* PSR ovarian cancer, not treated with a PARP inhibitor, were well matched on several characteristics with the licensed population for olaparib. In this group, a median OS of 21.9 months was observed. This finding is supported by data from the placebo arm in Study 19. In this group, 23% of patients received a PARP inhibitor following progression. When adjusting for this post progression crossover, the estimated median OS was 26.6 months for patients not receiving PARP inhibitors. Median OS without adjustment for crossover was 31.9 months. The median OS of 21.9 months observed in a real-world population supported by the 26.6 months observed in the adjusted analysis in Study 19 indicates that the licensed population has a short life expectancy of approximately 24 months with current standard of care.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In Study 19, the interim analysis of OS (52% maturity) in the licensed population resulted in a HR of 0.73 (P=0.19). The difference in median OS was 3 months (34.9 months for olaparib versus 31.9 months for placebo).[22] When adjusting for post progression crossover in an exploratory analysis, the HR for OS was 0.52 (nominal P value=0.039). The difference in median OS was 8.3 months (34.9 months for olaparib versus 26.6 months for placebo). The adjusted analysis is supported by the economic model in which a median difference in OS of 12 months (38 months for patients receiving olaparib vs 26 months for patients on placebo) is estimated. Taken together, these analyses provide sufficient evidence demonstrating olaparib offers an extension to life of at least 3 months in the licensed population.
The treatment is licensed or otherwise indicated for small patient populations	Olaparib has European orphan drug designation.[67] In England and Wales, AstraZeneca anticipates that no more than 450 patients per year will become eligible for treatment with olaparib for *BRCA*-mutated high-grade serous PSR ovarian cancer.

7 CONCLUSIONS

7.1 Conclusions on the clinical effectiveness and cost-effectiveness of olaparib

The results of study 19 showed a statistically significant benefit for the whole population in terms of PFS, with a HR of 0.35 (95% c.i. 0.25 to 0.49, $p<0.01$) for olaparib versus placebo. Median PFS was 8.4 months for olaparib and 4.8 months for placebo (95% c.i. NR). This is supported by no detrimental effect on OS. However, no statistically significant improvement in OS was observed either, with a HR for death of 0.88 (95% c.i. 0.64 to 1.21, $p=0.44$) for olaparib versus placebo. Median survival was 29.8 months (95% c.i. 27.2 to 35.7) in the olaparib arm versus 27.8 months (95% c.i. 24.4 to 34.0) in the placebo arm at 58% maturity. TTD/D, TFST/D and TSST/D were all favourable for olaparib, though these outcomes were defined *post hoc* and TTD/D and TSST/D were not listed as outcomes in the final NICE scope. HRQoL was unaffected by olaparib treatment, and AEs appeared largely minor or manageable in nature.

For the *BRCAm* subgroup, the HR for PFS was superior to that for the whole group, at 0.18 (95% c.i. 0.10 to 0.31, $p<0.0001$) for olaparib versus placebo, Median PFS was 11.2 months (95% c.i. 8.3 to "not calculable") for olaparib versus 4.3 months (95% c.i. 3.0 to 5.4) for placebo. OS was not statistically different in a naïve analysis of the study results, but was statistically significant in a cross-over analysis which excluded study sites which allowed placebo group crossover with a HR of 0.52 (0.28 to 0.97, nominal $p=0.039$). In this crossover-adjusted analysis, median survival was 34.9 months in the olaparib arm and 26.6 months in the placebo arm [redacted] The results of the outcomes TTD/D, TFST/D, TSST/D, HRQoL and AEs were similar to the results observed for the whole population.

Whilst there are good theoretical reasons why *BRCAm* patients may be clinically distinct from non-*BRCAm* patients in their reaction to olaparib (as outlined in the introduction of the CS[1]), the evidence base for olaparib in *BRCAm* patients is very limited. The pivotal evidence comes from a subgroup analysis of a Phase II trial. The subgroup itself was not defined before the study commenced, but was instead defined approximately one month before the primary outcome analysis DCO, more than a year after the study commenced. The interaction tests performed appear to be inconclusive regarding the statistical significance of the subgroup in comparison to the rest of the study population. In addition, multiple potential sources of bias and confounding were identified that may have impacted on estimates of efficacy, including: multiple mid-trial changes to the study protocol; a lack of a clear definition of the *BRCAm* subgroup; problems with the randomisation stratification system leading to unbalanced groups; un-blinding of around 20% of patients after PFS but potentially before TTD/D, TFST/D and TSST/D; protocol deviations; continuation of patients on treatment after progression,

and; crossover of placebo patients to PARP inhibitors after progression. The generalisability of the trial results is also unclear due to: the definition of progression used; a lack of clarity regarding timing of treatment initiation after progression; the inclusion of *tBRCAm* patients, and; the continuation of patients on treatment after progression.

In summary, the large number of potential sources of bias and confounding along with issues around generalisability reduces the certainty that can be placed on the results of the trial in relation to the decision problem. In addition, whilst PFS benefits have been demonstrated in both the whole population and the *BRCAm* subgroup, this remains a proxy for OS. A delay in progression may in itself be beneficial to patients, if it results in fewer rounds of chemotherapy overall. However, as the validity of the subgroup remains under question, so too does the effect on OS, as efficacy for this outcome has only been demonstrated in the *BRCAm* subgroup. As such, and with consideration of the multiple potential sources of bias and confounding identified, the only relatively safe (but still not free of all sources of bias) conclusion to draw is that PFS was improved by olaparib in patients with relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer who have responded to platinum-based chemotherapy.

The probabilistic version of the company's base case analysis suggests that olaparib is expected to produce an additional 0.90 QALYs at an additional cost of £72,232 compared against routine surveillance. The probabilistic ICER for olaparib versus routine surveillance is expected to be £79,953 per QALY gained. The company's secondary analysis which compares *BRCA* mutation testing plus olaparib versus no *BRCA* testing plus routine surveillance suggests a lower average deterministic ICER of £61,159 per QALY gained.

The ERG has concerns regarding the robustness of the magnitude of incremental survival benefits and QALY gains for olaparib predicted by the company's model. The ERG's exploratory analysis suggests that the most optimistic estimate of undiscounted incremental survival for olaparib versus routine surveillance, based on parametric curves directly fitted to the available crossover-adjusted OS data, is approximately 0.68 LYGs. This estimate is considerably lower than the estimated 1.36 incremental LYGs for olaparib generated by the company's base case model. The ERG's partitioned survival model suggests that the most optimistic incremental QALY gain for olaparib versus routine surveillance is approximately 0.52 QALYs. The most favourable QALY estimate generated by the ERG's model is considerably lower than the QALY gain predicted by the company's model (discounted incremental QALYs generated by the company's model=0.90). Assuming that the incremental cost for olaparib versus surveillance estimated by the company's model, which is largely comprised of the acquisition costs of the drug, is reasonable, this implies that the ICER for olaparib versus routine surveillance is likely to be in excess of £145,000 per QALY gained, but may be

considerably higher. Based on the preferred survivor functions selected by the clinical advisors to the ERG, the implied ICER for olaparib versus routine surveillance is estimated to be, at best, £191,979 per QALY gained. One clinical advisor stated a preference for a combination of survivor functions which led to olaparib being dominated by routine surveillance.

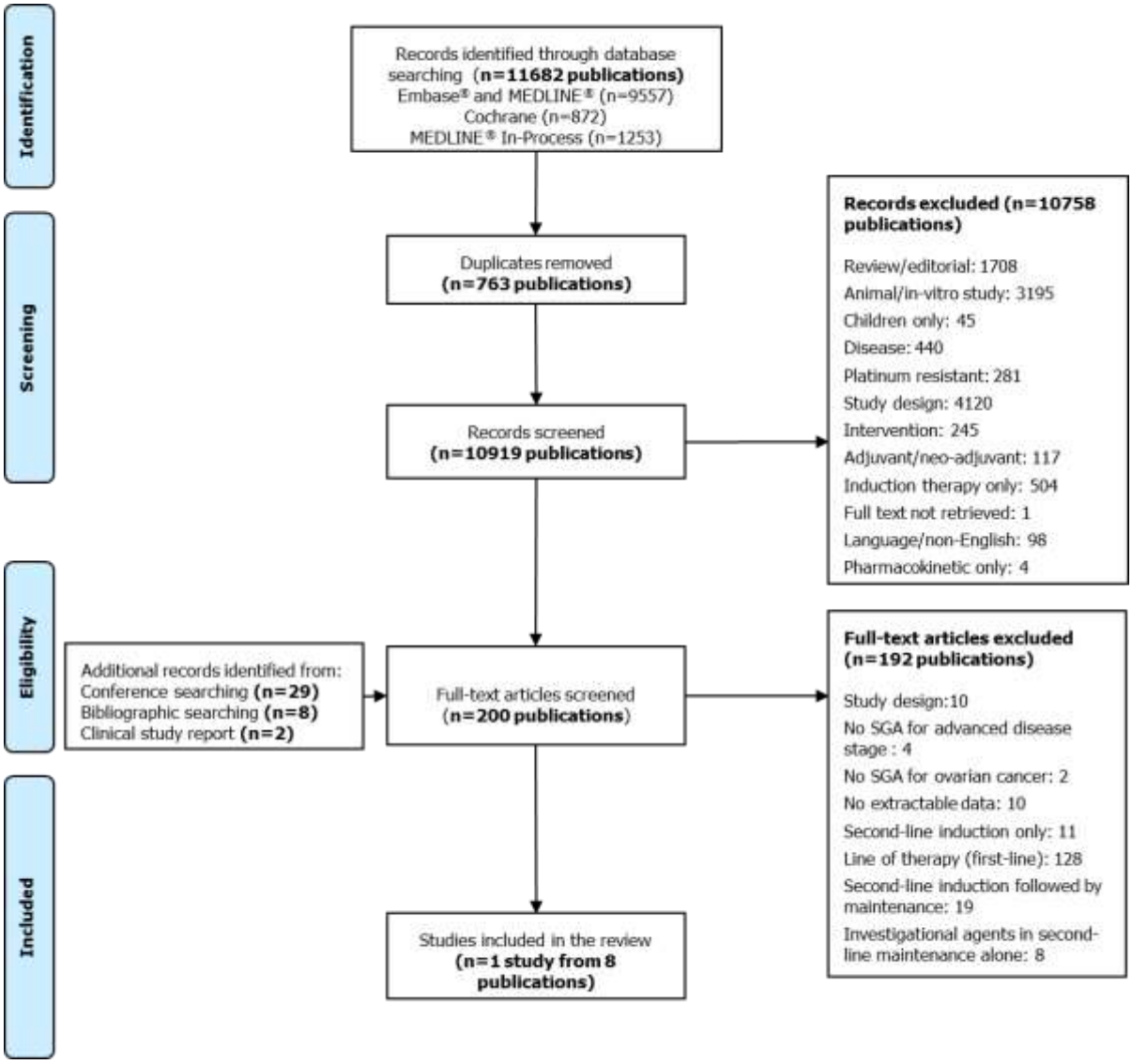
7.2 Implications for research

The ERG considers the available evidence on the clinical effectiveness of olaparib versus placebo for *BRCAm* PSR ovarian cancer to be weak. A prospective Phase III trial of olaparib versus placebo, with sufficient power to detect a difference in OS and which includes the collection of HRQoL data using a preference-based measure (e.g. the EQ-5D), would be valuable in reducing existing uncertainties regarding the clinical benefits of olaparib. The findings of such a study should be used to inform estimates of cost-effectiveness for olaparib versus routine surveillance. The ERG notes that a Phase III trial (clinicaltrials.gov identified - NCT01874353) is currently ongoing but has not yet reported. This study is however powered according to PFS rather than OS.

8. APPENDICES

Appendix 1: Revised review PRISMA flow chart

Reproduction of Figure A4.1 from the company's clarification response: Revised PRISMA flow diagram of olaparib comparative effectiveness systematic review process[9]



Appendix 2: Definition of severity of adverse events used in Study 19, taken from Table 7 of the study protocol[27]

Mild Grade 1 – Does not interfere with the patient's usual function (awareness of symptoms or signs, but easily tolerated (acceptable)).

Moderate Grade 2 – Interferes to some extent with the patient's usual function (enough discomfort to interfere with the usual activity (disturbing)).

Severe Grade 3 – Interferes significantly with the patient's usual function (incapacity to work or to do usual activities (unacceptable).

Life-threatening Grade 4 – Results in risk of death, organ damage or permanent disability (unacceptable)

Death Grade 5 – Event has a fatal outcome

Note: It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE

Appendix 3: Subgroup analysis critique according to Rothwell 2005[31]

Trial design	**Criteria met?**
Subgroups analyses should be defined before starting the trial and should be limited to a small number of clinically important questions.	No – Data collection had commenced and the first DCO nearly reached before the subgroup was defined.
Expert clinical input into the design of subgroup analyses is needed to ensure that all relevant baseline clinical and other data are recorded.	Unclear
The direction and magnitude of anticipated subgroup effects should be stated at the outset. The exact definitions and categories of the subgroup variables should be defined explicitly at the outset in order to avoid post hoc data-dependent variable or category definitions. For continuous or hierarchical variables the cutoff points for analysis should be predefined.	No – the subgroup was not defined until part-way through the study. The subgroup was defined before un-blinding of study data (unclear if any blinded analysis had taken place), but it is not clear if a direction of effect was specified. It is also unclear whether the subgroup was defined in a manner commensurate with the *BRCAm* subgroup presented in the CS[1] in that tumour *BRCA* patients were added later.
Stratification of randomisation by important subgroup variables should be considered.	Unclear
If important subgroup-treatment effect interactions are anticipated, trials should ideally be powered to detect them reliably.	No – the study was not powered for the *BRCA* subgroup or for interaction tests, but for the subgroup of HRD patients.
Trial stopping rules should take into account anticipated subgroup-treatment effect interactions and not simply the overall effect of treatment.	Unclear
If relative treatment effect is likely to be related to baseline risk, the analysis plan should include a stratification of the results by predicted risk. The risk score or model should be selected in advance so that the relevant baseline data can be recorded.	Unclear – ERG do not have access to statistical analysis plan
Analysis and reporting	
The above design issues should be reported in the methods section along with details of how and why subgroups were selected.	No - This has not been provided in the CS[1]
Significance of the effect of treatment in individual subgroups should not be reported; rates of false negative and false positive results are extremely high. The only reliable statistical approach is to test for a subgroup treatment effect interaction.	No – No subgroup treatment effect interaction tests were presented in the CS[1], though evidently some were done during the course of the trial, but as far as the ERG can tell, were non-significant (Table 7, CSR)[24]
All subgroup analyses that were done should be reported - i.e., not only the number of subgroup variables but also the number of different outcomes analysed by subgroup, different lengths of follow-up etc.	No – Table 7 of the CSR[24] suggests that "stratification factors" (i.e. time to disease progression on penultimate platinum-based chemotherapy; OR to last platinum-based chemotherapy; ethnic descent) were subject to the same tests in 2010 as *BRCA*, but these are not mentioned in the CS.[1]
Significance of pre hoc subgroup-treatment effect interactions should be adjusted when multiple subgroup analyses are done.	No – not mentioned in CS[1]
Subgroup analyses should be reported as absolute risk reductions and relative risk reductions. Where	Not applicable

relevant the statistical significance of differences in absolute risk reductions should be tested.	
Ideally, only one outcome should be studied and this should usually be the primary trial outcome, irrespective of whether this is one outcome or a clinically important composite outcome.	No – all outcomes were analysed, after discussion with the EMA. *Post hoc* outcomes (TTD, TFST and TSST) were also analysed, and contribute to the model.
Comparability of treatment groups for prognostic factors should be checked within subgroups.	No, the potential prognostic factor of OR was not balanced between groups
If multiple subgroup-treatment effect interactions are identified, further analysis is needed to check whether their effects are independent.	Unclear
Interpretation	
Reports of the significance of the effect of treatment in individual subgroups should be ignored, especially reports of lack of benefit in a particular subgroup in a trial in which there is overall benefit, unless there is a significant subgroup treatment effect interaction	No – only the significance of the effect of treatment in individual subgroups was reported. The interaction test was not reported
Genuine unanticipated subgroup-treatment effect interactions are rare (assuming that expert clinical opinion was sought in order to pre-define potentially important subgroups) and so apparent interactions that are discovered post hoc should be interpreted with caution. No test of significance is reliable in this situation.	Unclear – it is unclear whether the *BRCA* subgroup represents a subgroup of the HRD patients originally planned as a subgroup
Pre hoc subgroup analyses are not intrinsically valid and should still be interpreted with caution. The false positive rate for tests of subgroup-treatment effect interaction when no true interaction exists is 5% per subgroup.	No – interaction tests were not presented.
The best test of validity of subgroup-treatment effect interactions is their reproducibility in other trials.	No – no subsequent trial has been conducted
Few trials are powered to detect subgroup effects and so the false negative rate for tests of subgroup-treatment effect interaction when a true interaction exists will usually be high.	N/A

APPENDIX 4: ERG's focussed search of RCTs relating to olaparib

Focussed search in Medline (Ovid) for the report (run on 4th February 2015)

1. exp Ovarian Neoplasms/
2. (ovar$ adj5 (cancer$ or oncolog$ or neoplas$ or carcinom$ or malignan$ or tumor$ or tumour$ or mass$ or growth$ or cyst$)).tw.
3. (adenexa$ adj4 mass$).tw.
4. or/1-3
5. (carboplatin or cisplatin or doxorubicin or gemcitabine or paclitaxel or topotecan or bevacizumab or trabectedin platin$ or abagovomab or cediranib or cvac or enzastaurin or farletuzumab or gefitinib or crlx101 or it-101 or lonafarnib or nintedanib or ly2228820 or niraparib or olaparib or oregovomab or pazopanib or panitumumab or rucaparib or sorafenib or tanomastat or trebananib or veliparib or vismodegib or vorinostat or erlotinib or epirubicin or fluorouracil).tw.
6. randomized controlled trial.pt.
7. randomized controlled trial.mp.
8. 6 or 7
9. Animal/ not (Animal/ and Human/)
10. 4 and 5 and 8
11. limit 10 to yr="2000 -Current"
12. 11 not 9

APPENDIX 5: Family pedigrees assumed within the company's analysis of the cost-effectiveness of olaparib and the wider costs and benefits of *BRCA* mutation testing

Figure 29: Pedigree 1

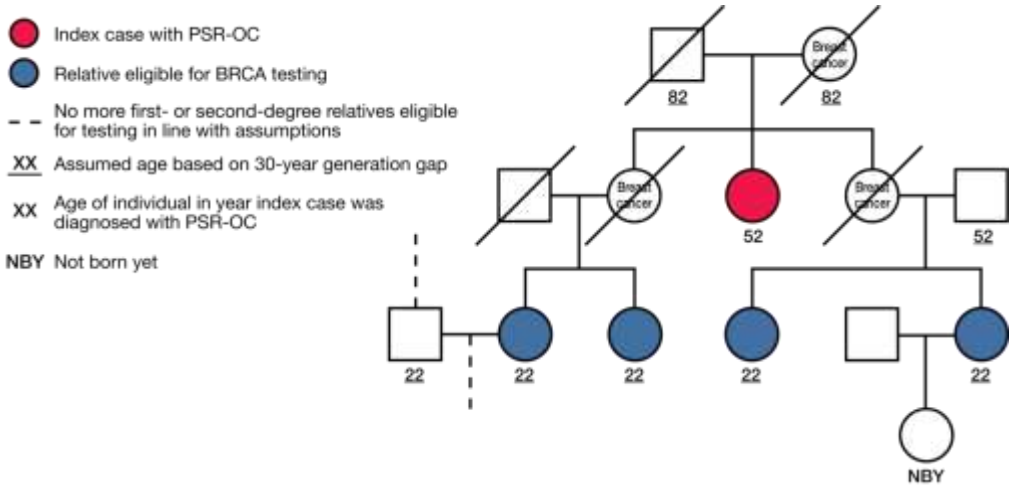


Figure 30: Pedigree 2

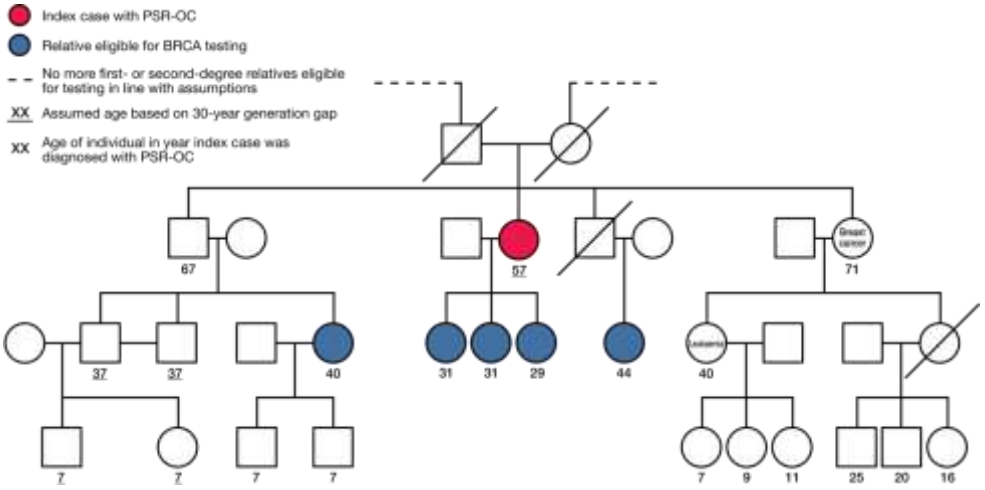


Figure 31: Pedigree 3

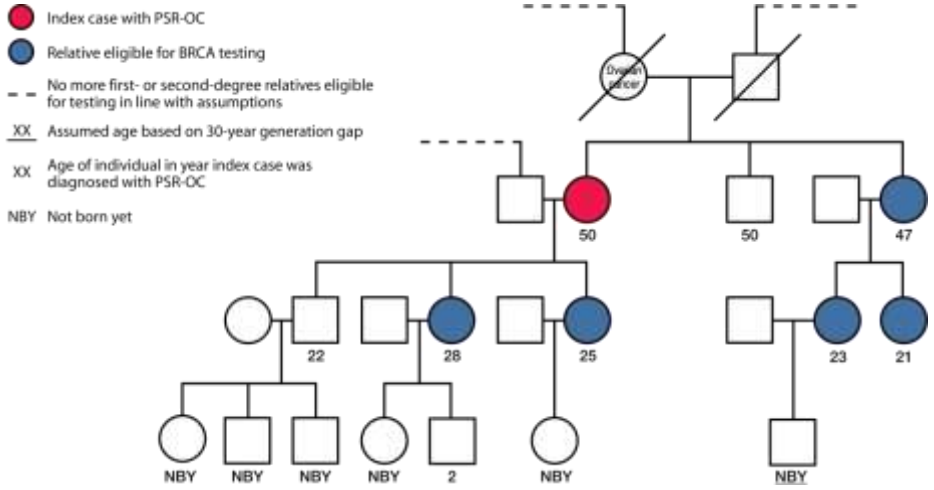


Figure 32: Pedigree 4

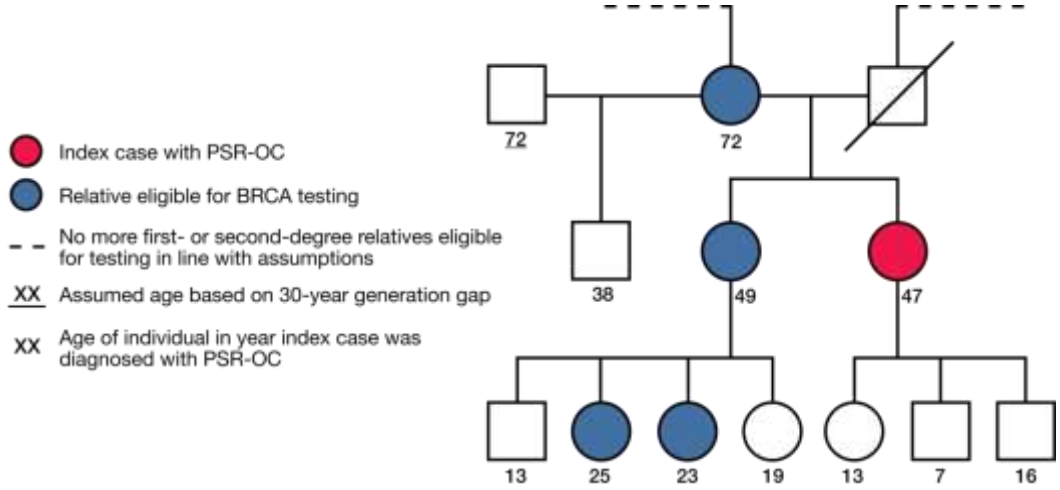
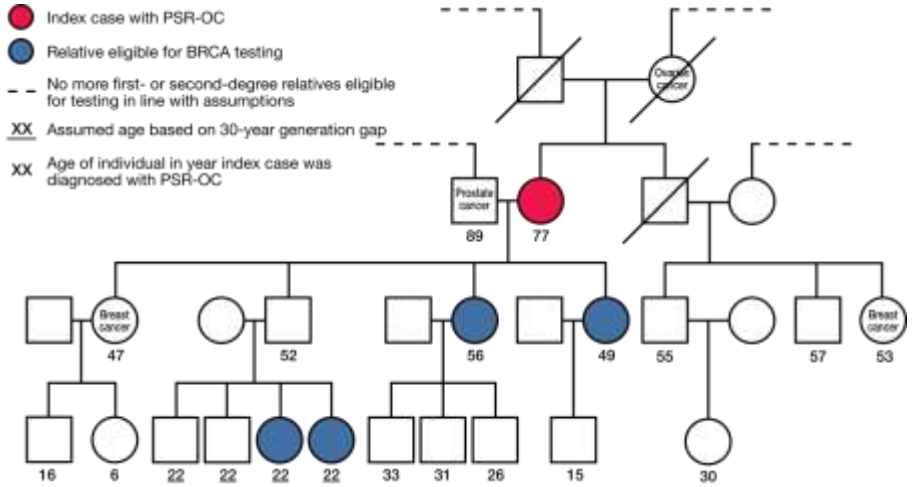


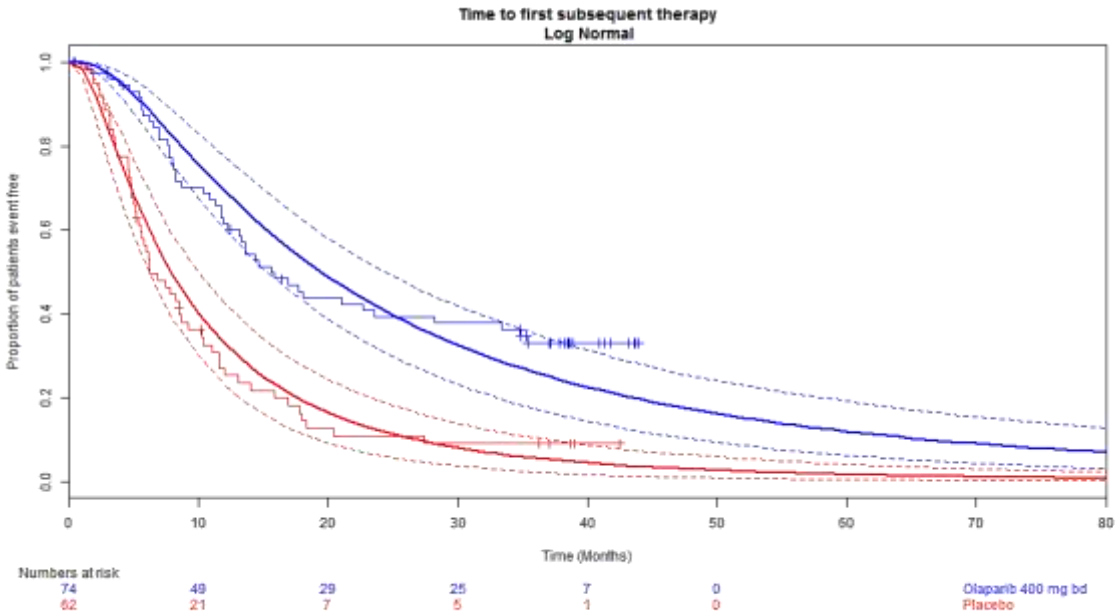
Figure 33: Pedigree 5



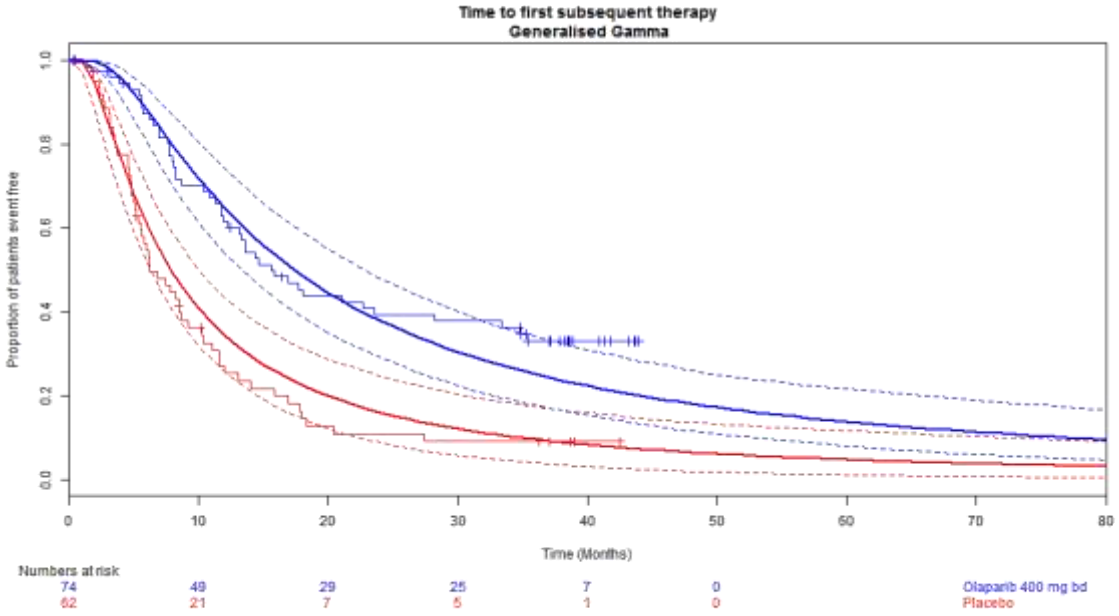
APPENDIX 6: **Graphical plots of alternative survivor functions for the outcomes of time from randomisation to treatment discontinuation or death and time from randomisation to first subsequent therapy or death provided within the company's clarification response**

1. Time to first subsequent therapy or death - treatment-adjusted models

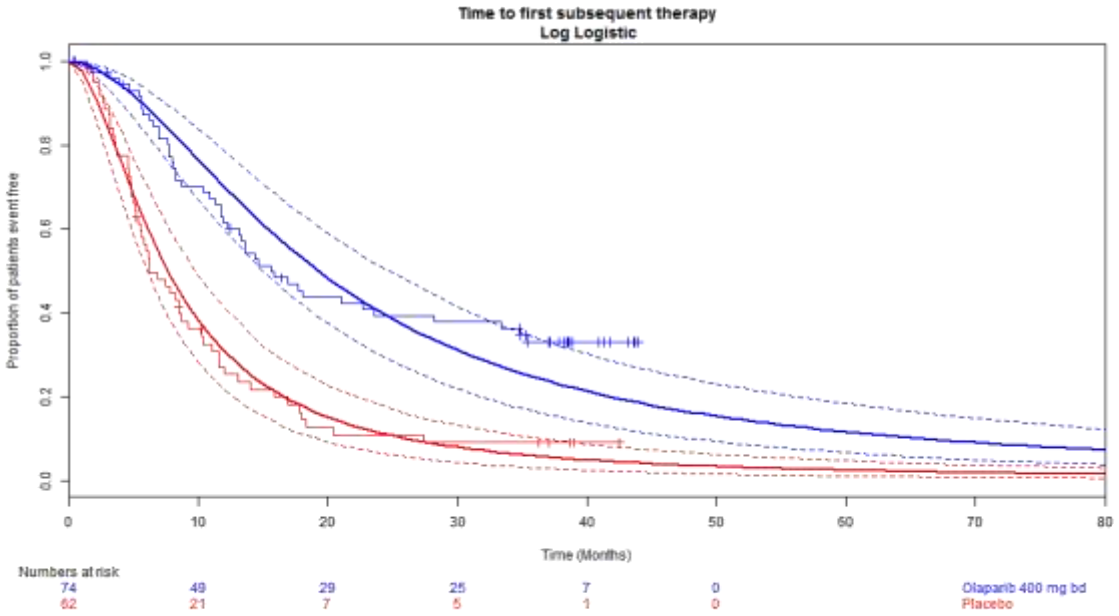
(a) Log Normal (base case)



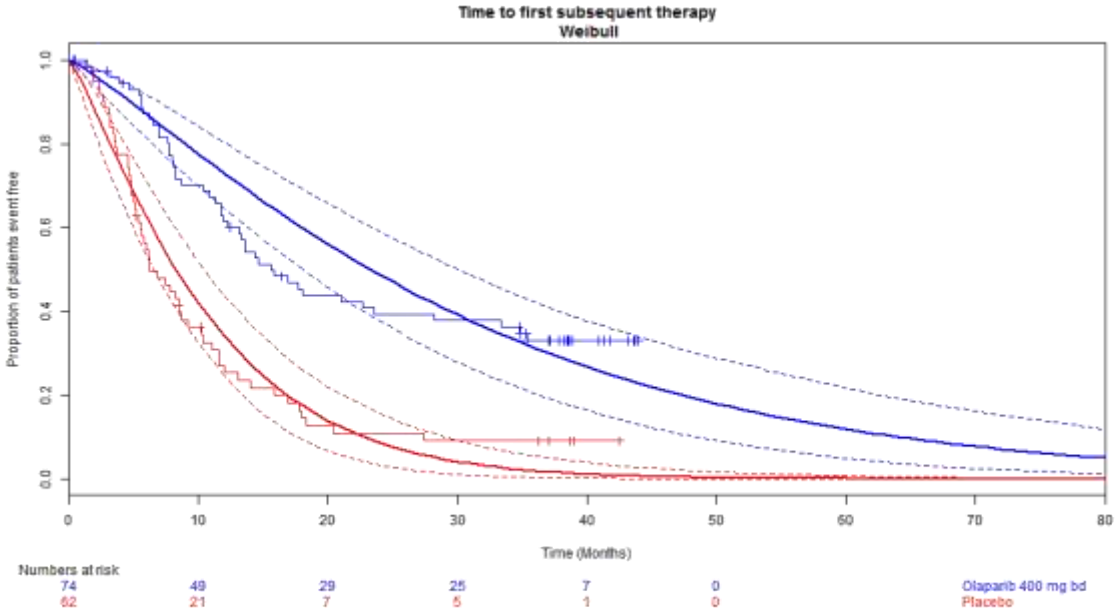
(b) Generalised Gamma



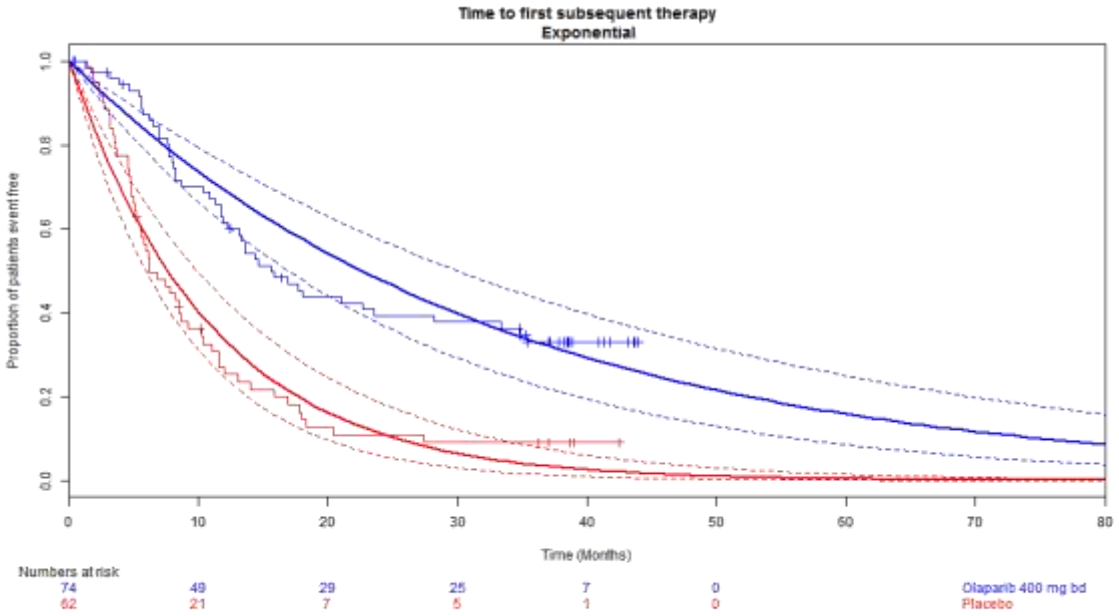
(c) Log Logistic



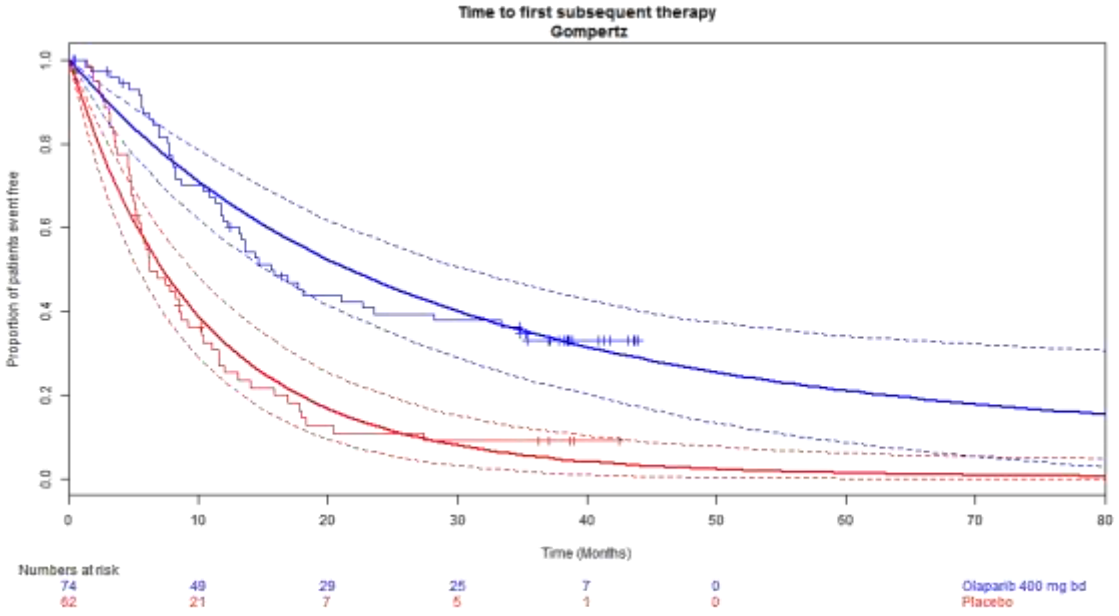
(d) Weibull



(e) Exponential

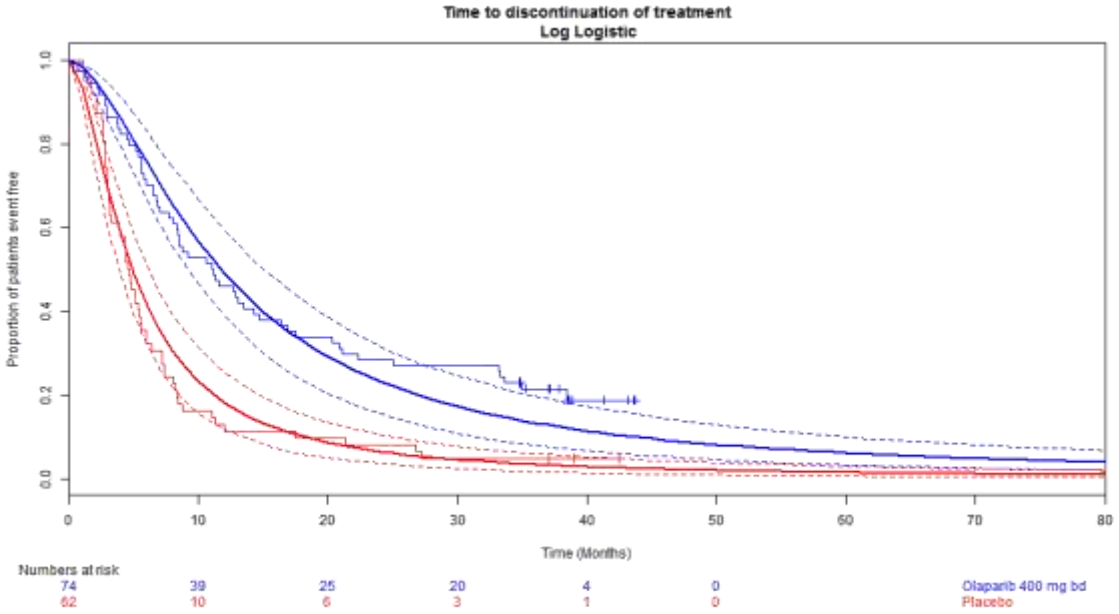


(f) Gompertz

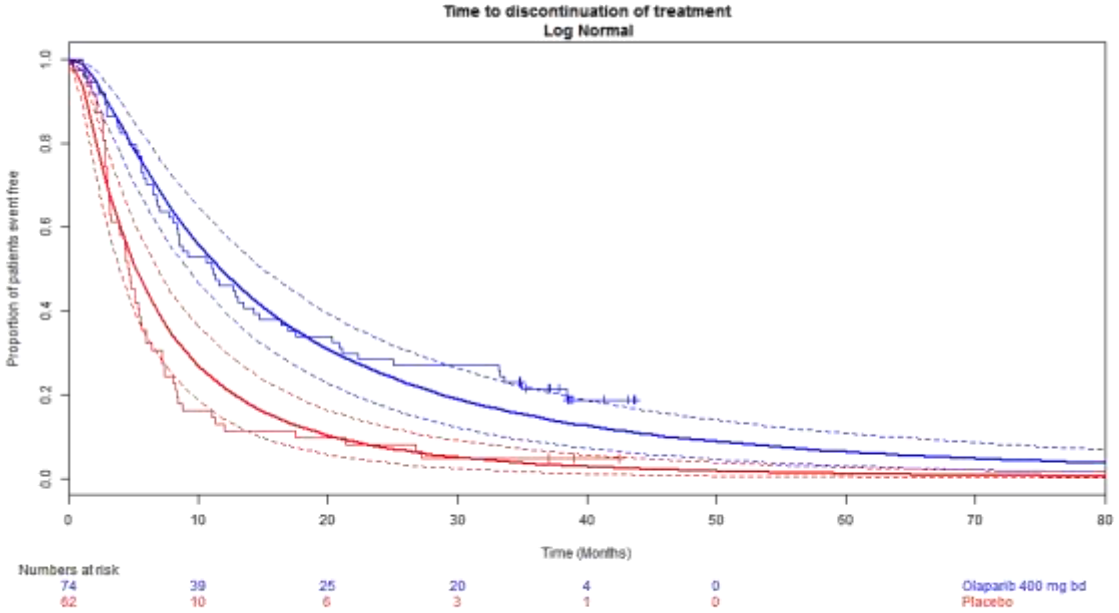


2. Time to treatment discontinuation - treatment-adjusted models

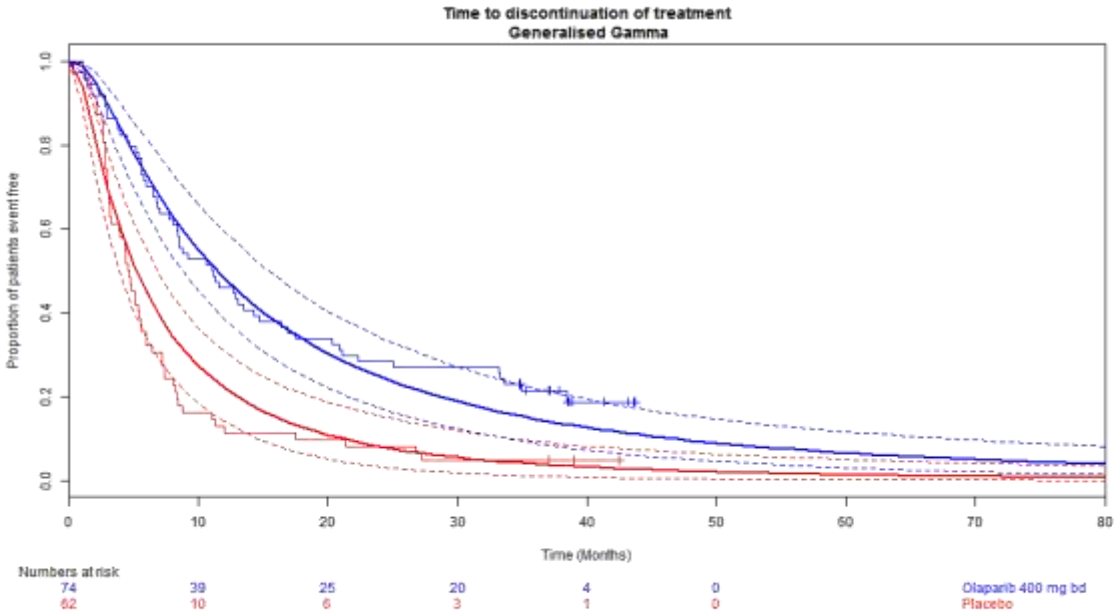
(a) Log Logistic (base case)



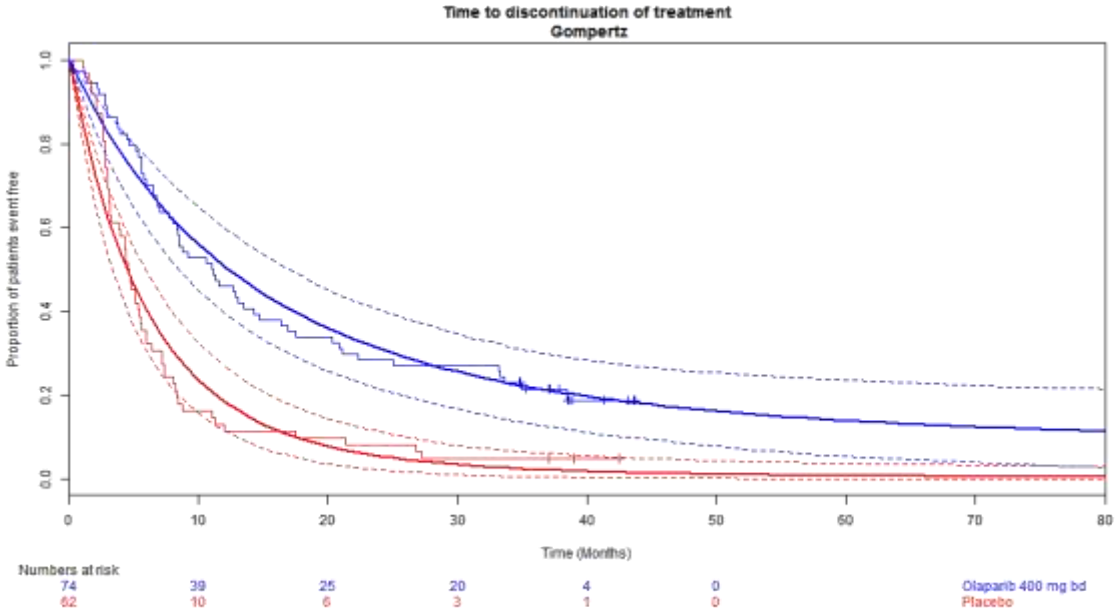
(b) Log Normal



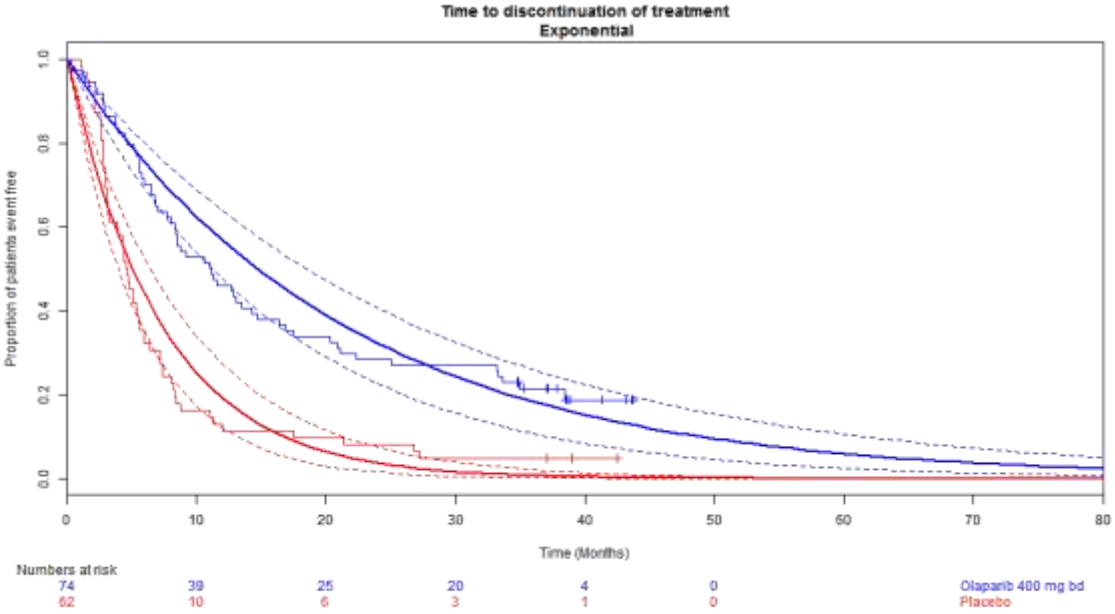
(c) Generalised Gamma



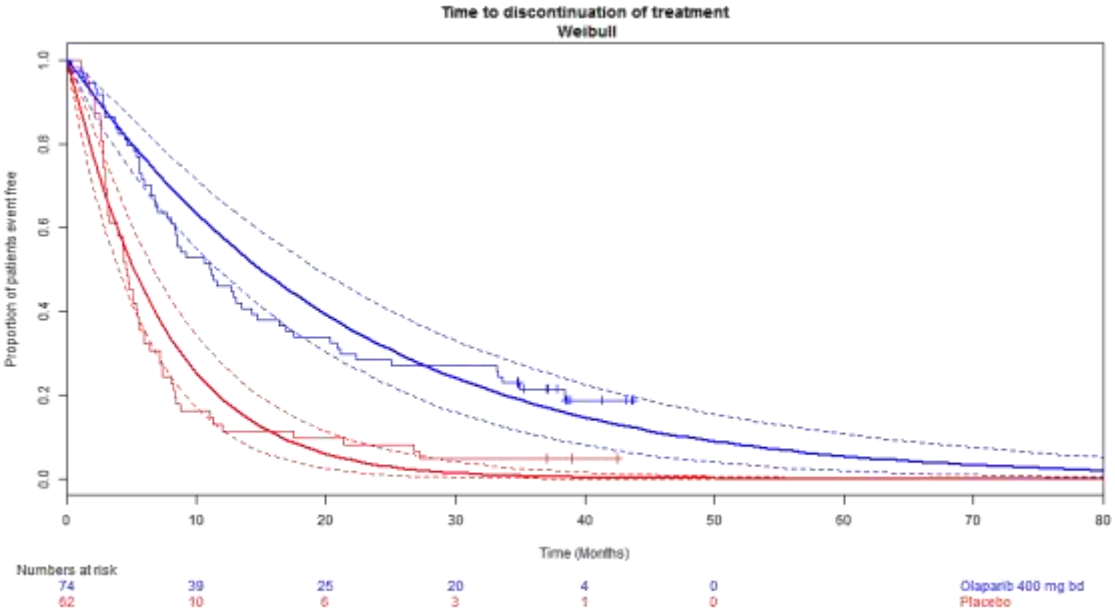
(d) Gompertz



(e) Exponential



(f) Weibull



APPENDIX 7: ERG amendments to correct apparent errors in company's base case

The following amendments were made to the company's base case model:

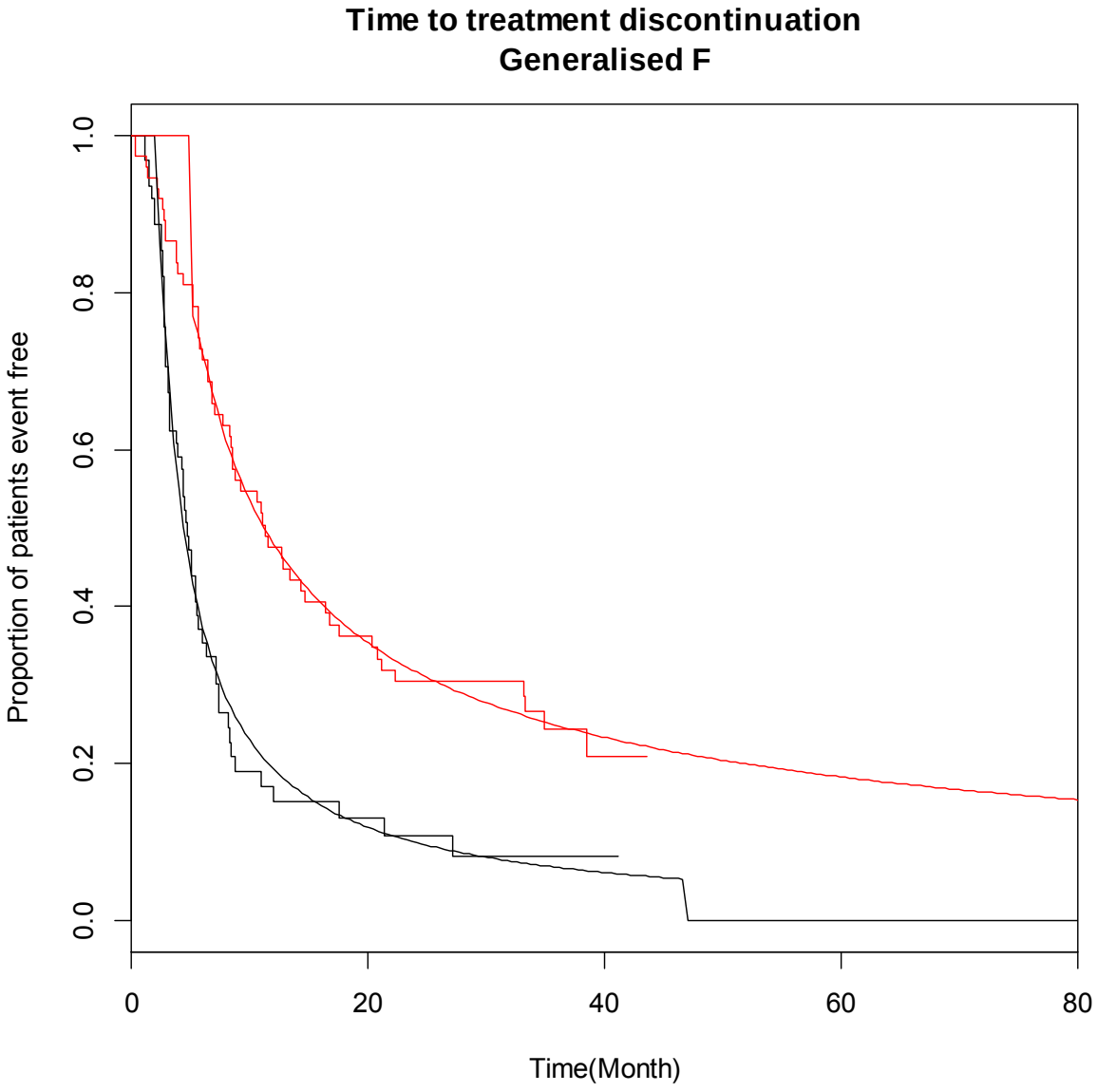
1. Worksheet "Parameter data store" – formula in cell C191 amended to "=2/54"
2. Worksheet "State costs" – value in cell E14 amended to "0.333"
3. Worksheet "PSA results" – formula in cell F12 amended to include additional cost of £2,904 (company's estimate of cost of *BRCA* mutation testing)

APPENDIX 8: Parametric survivor functions fitted by the ERG to replicated individual patient data from the *BRCA*-mutated subgroup within Study 19

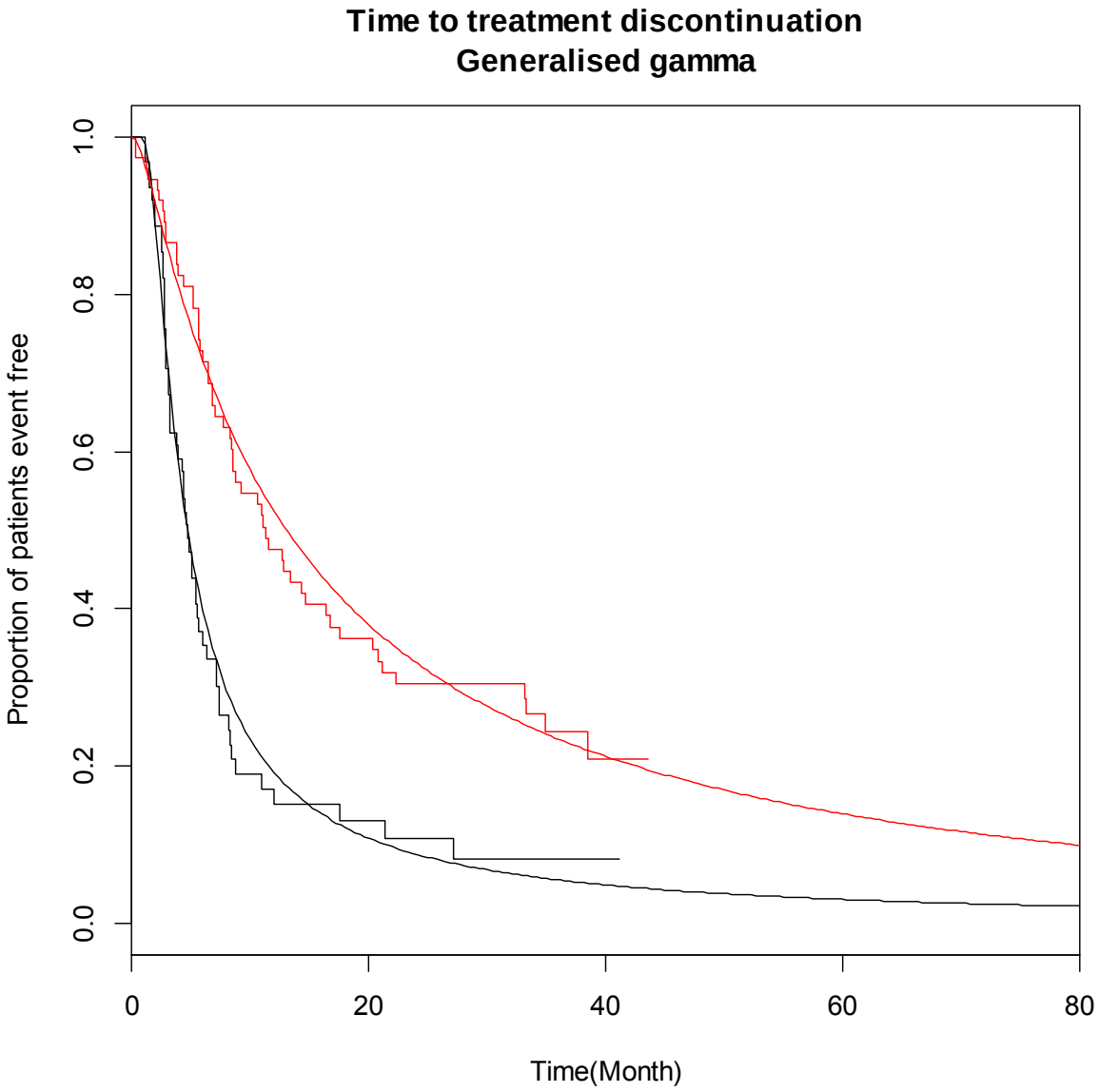
In all plots, red lines indicate olaparib and black lines indicate placebo.

TTE outcome 1: Time from randomisation to treatment discontinuation or death

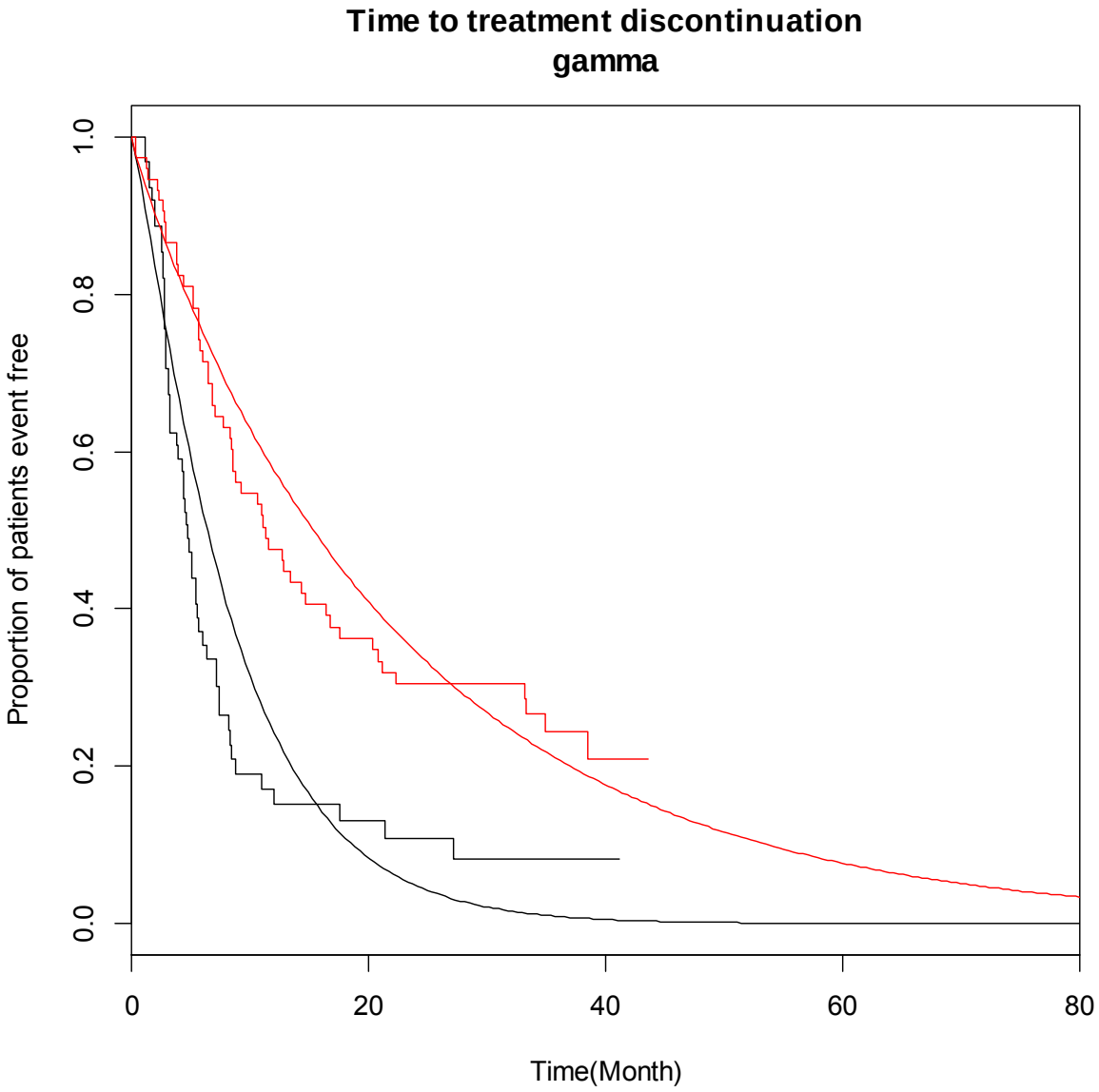
(a) Generalised F



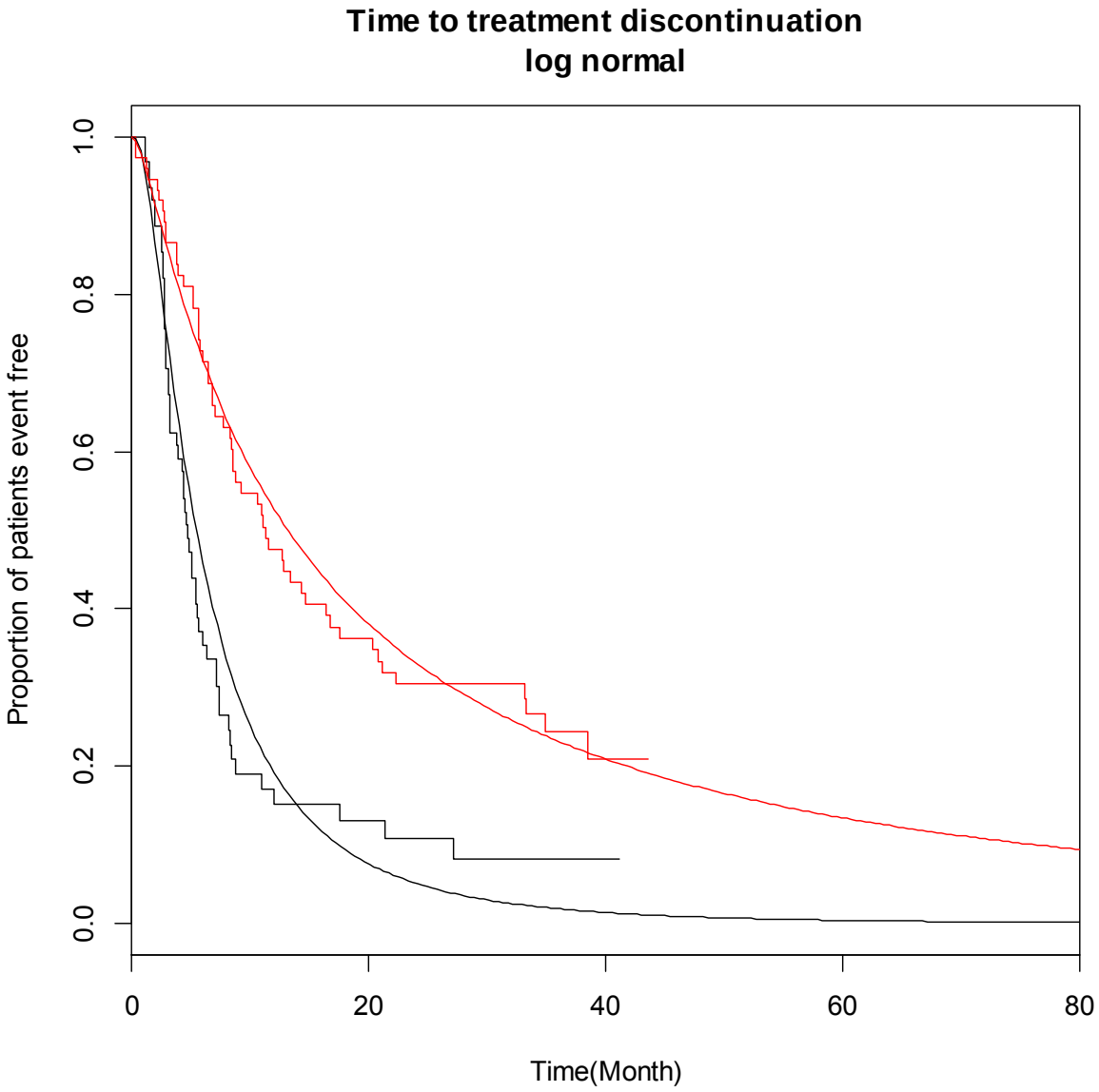
(b) Generalised gamma



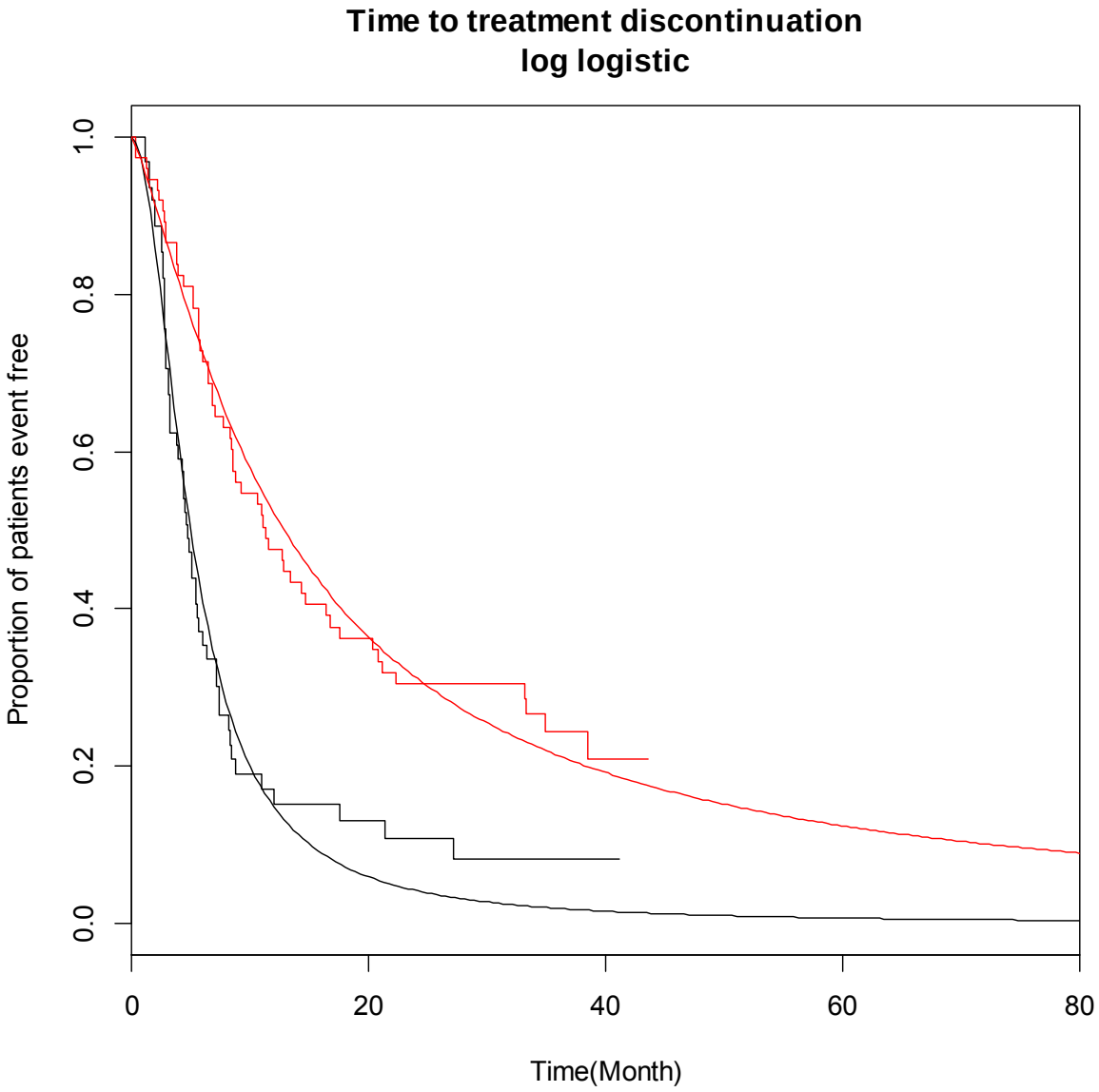
(c) Gamma



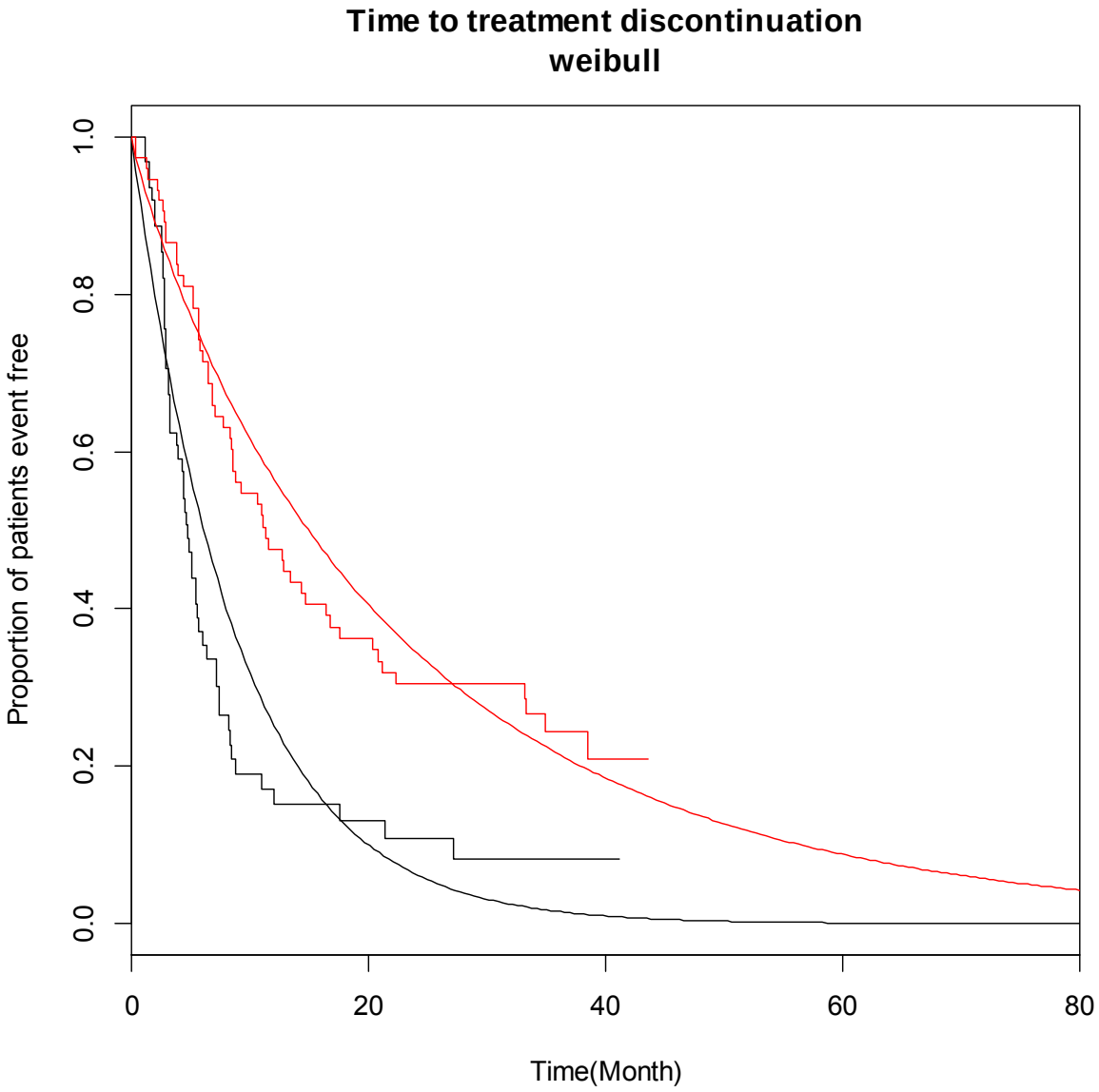
(d) Log normal



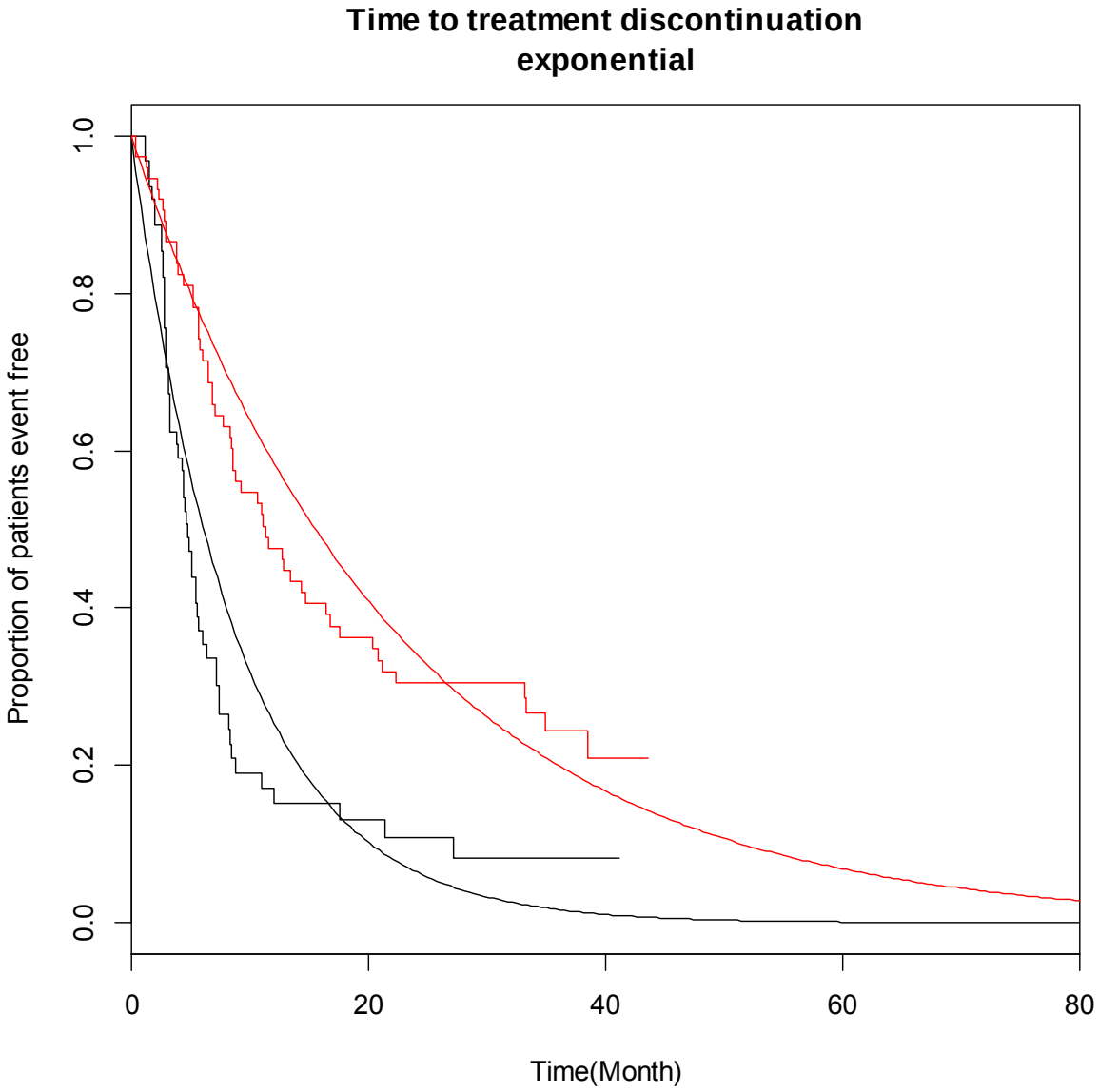
(e) Log logistic



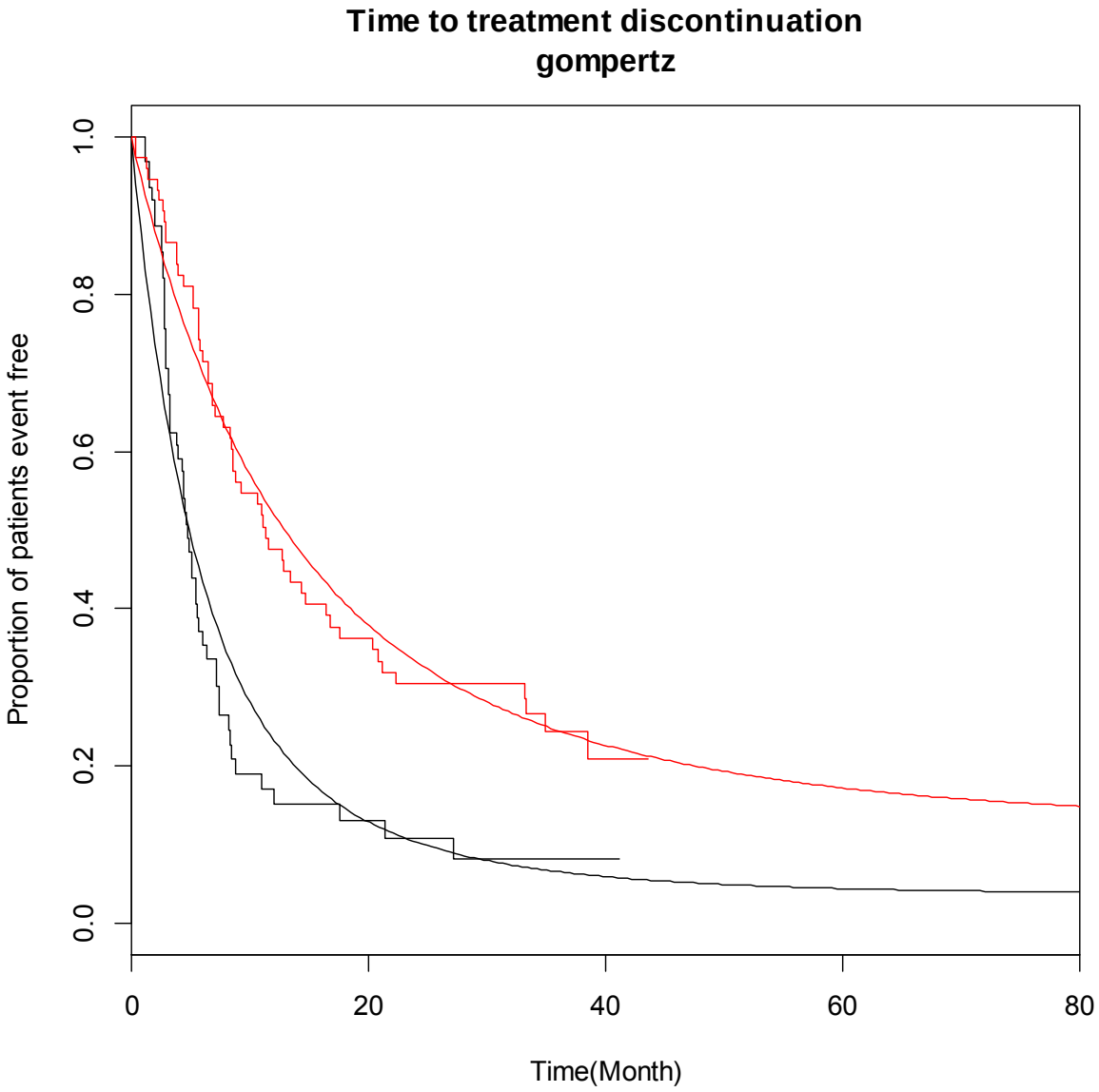
(f) Weibull



(g) Exponential

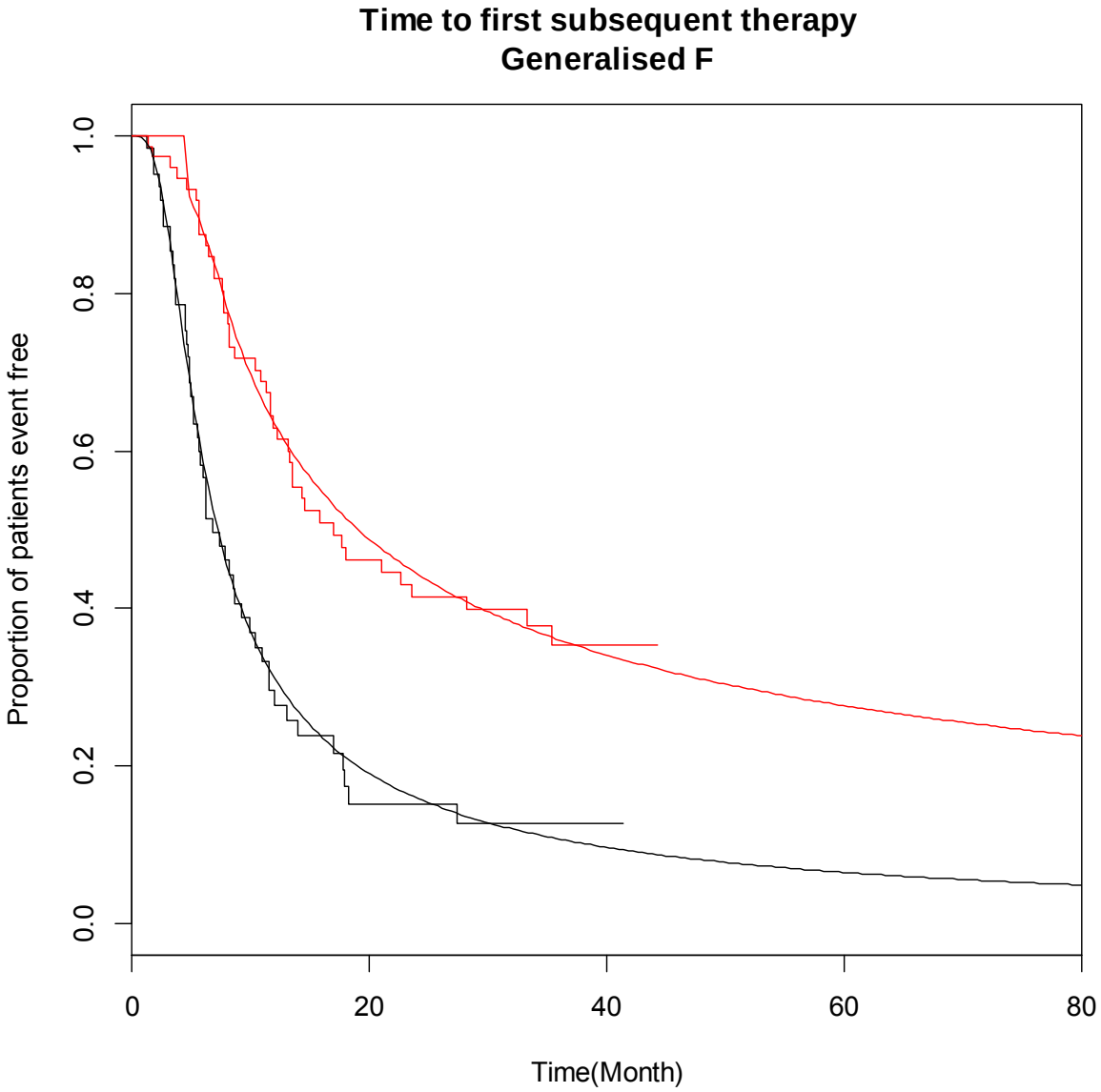


(h) Gompertz

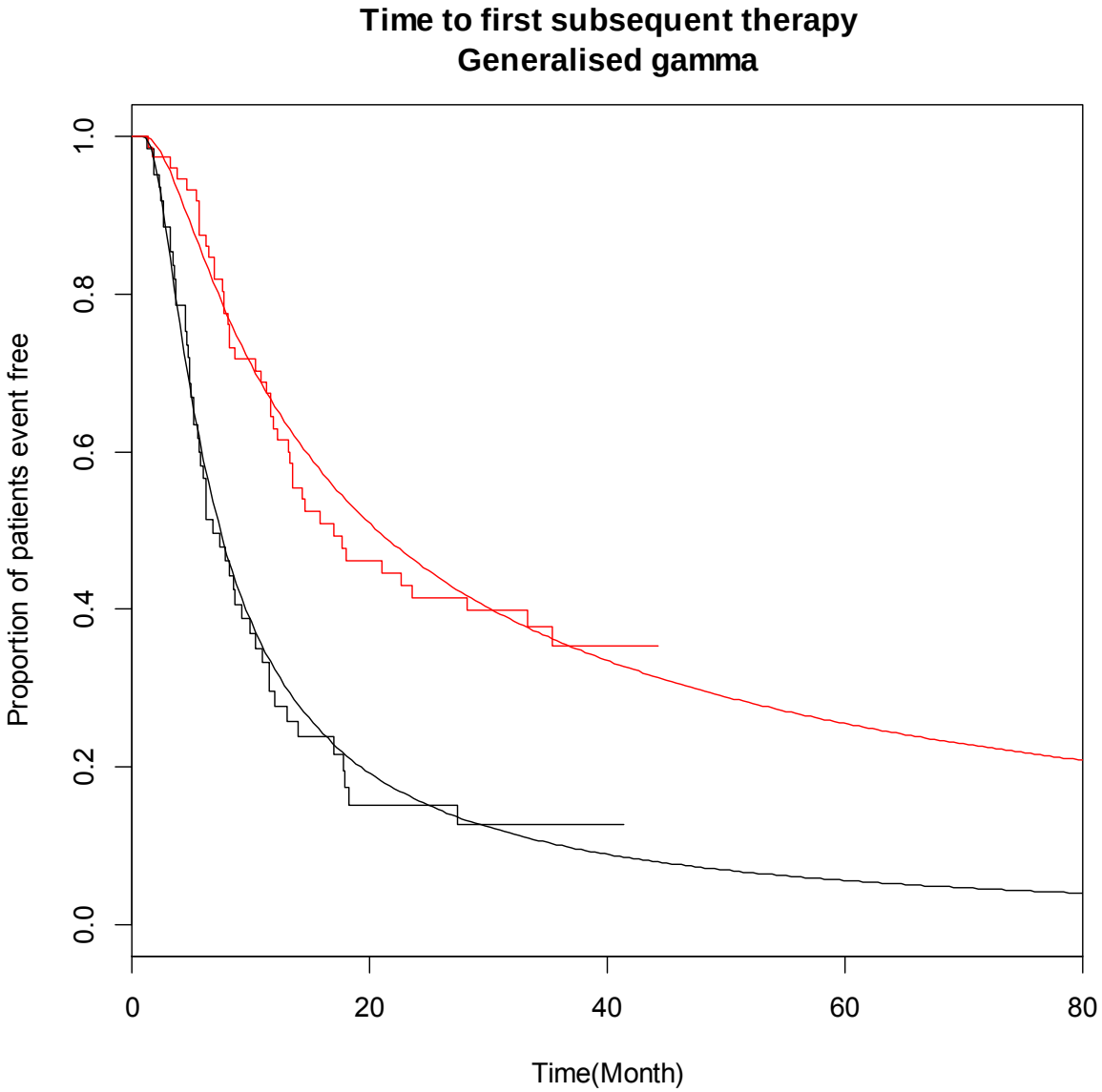


TTE outcome 2: Time from randomisation to first subsequent therapy or death

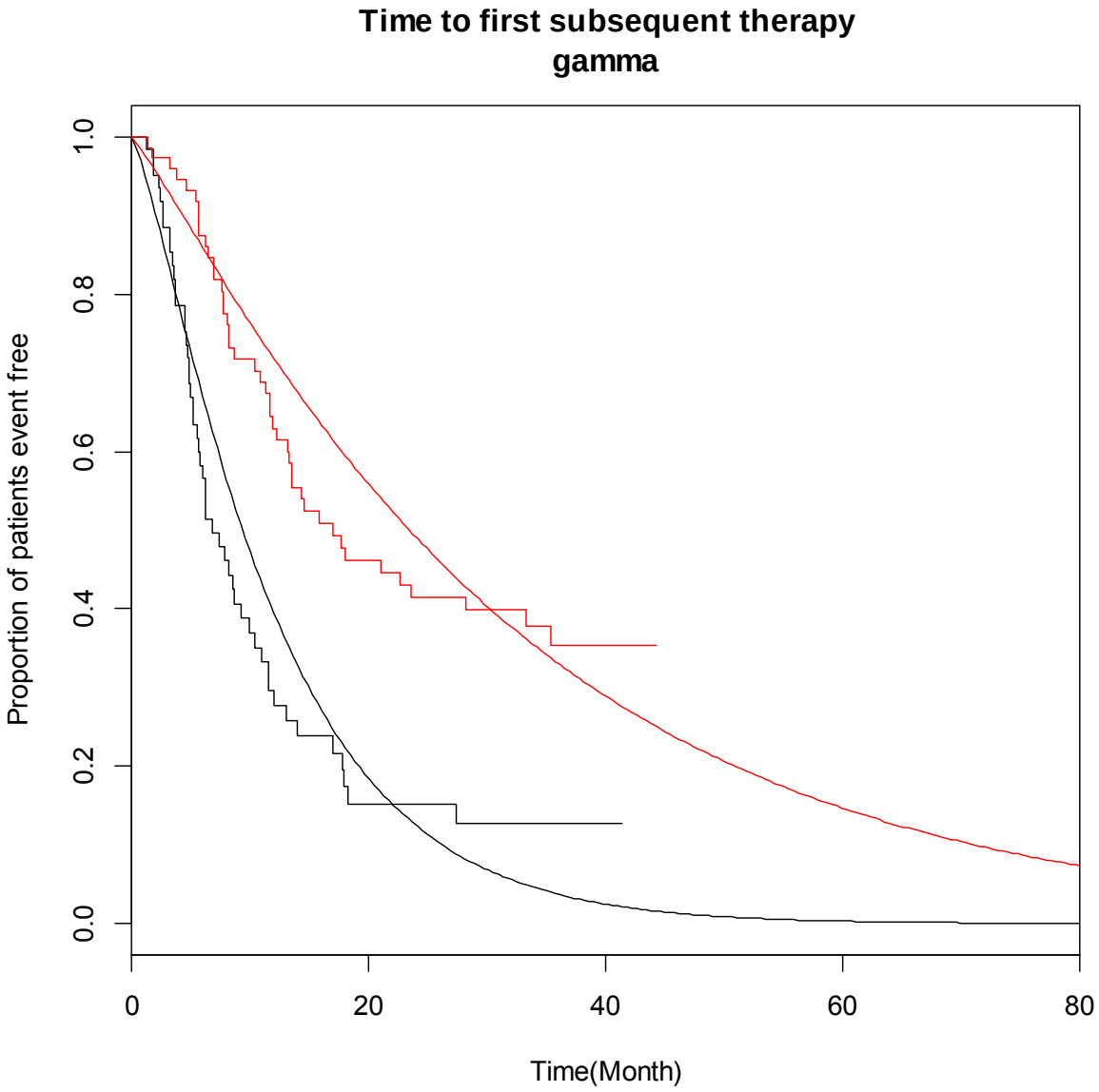
(a) Generalised F



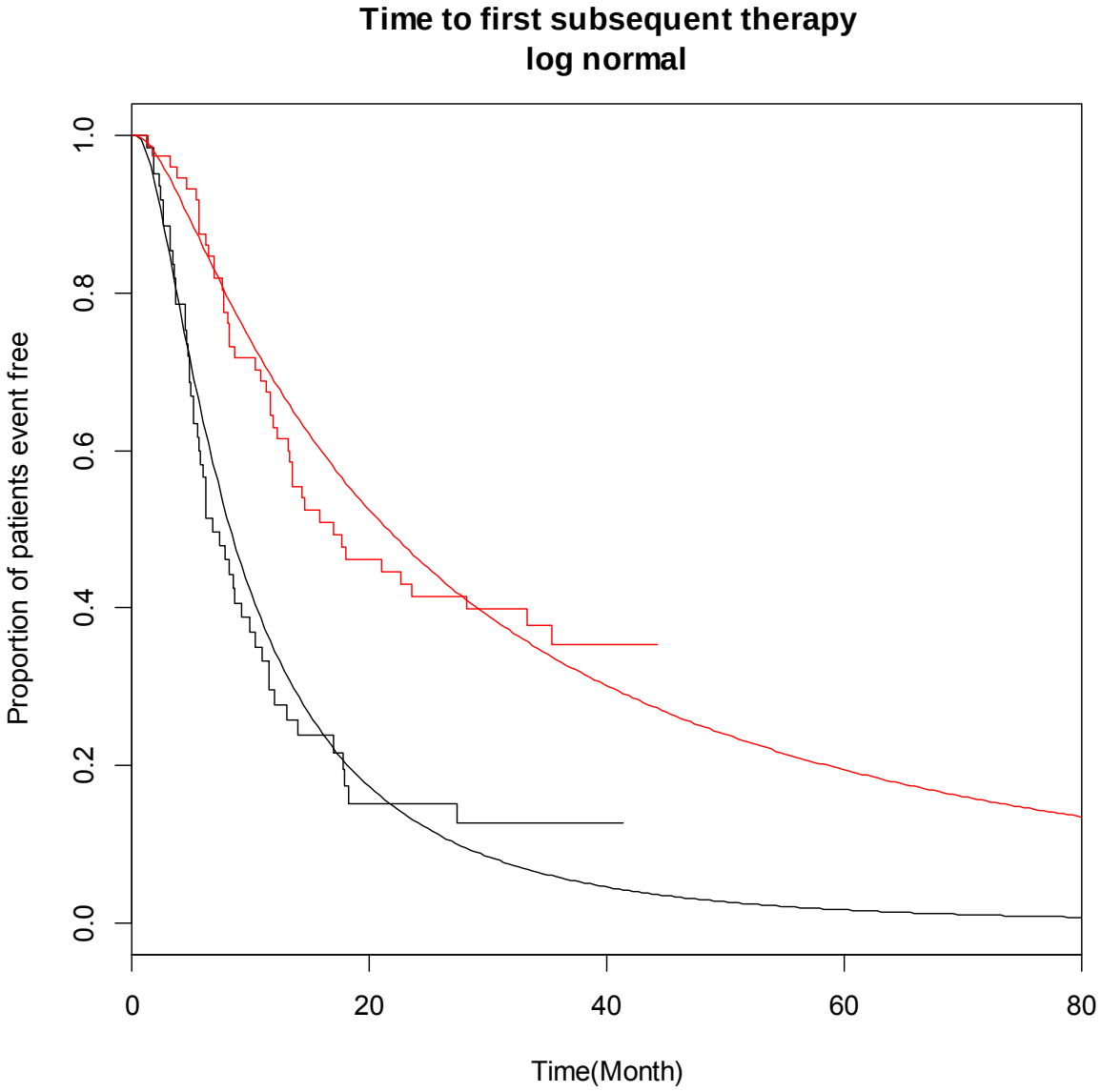
(b) Generalised gamma



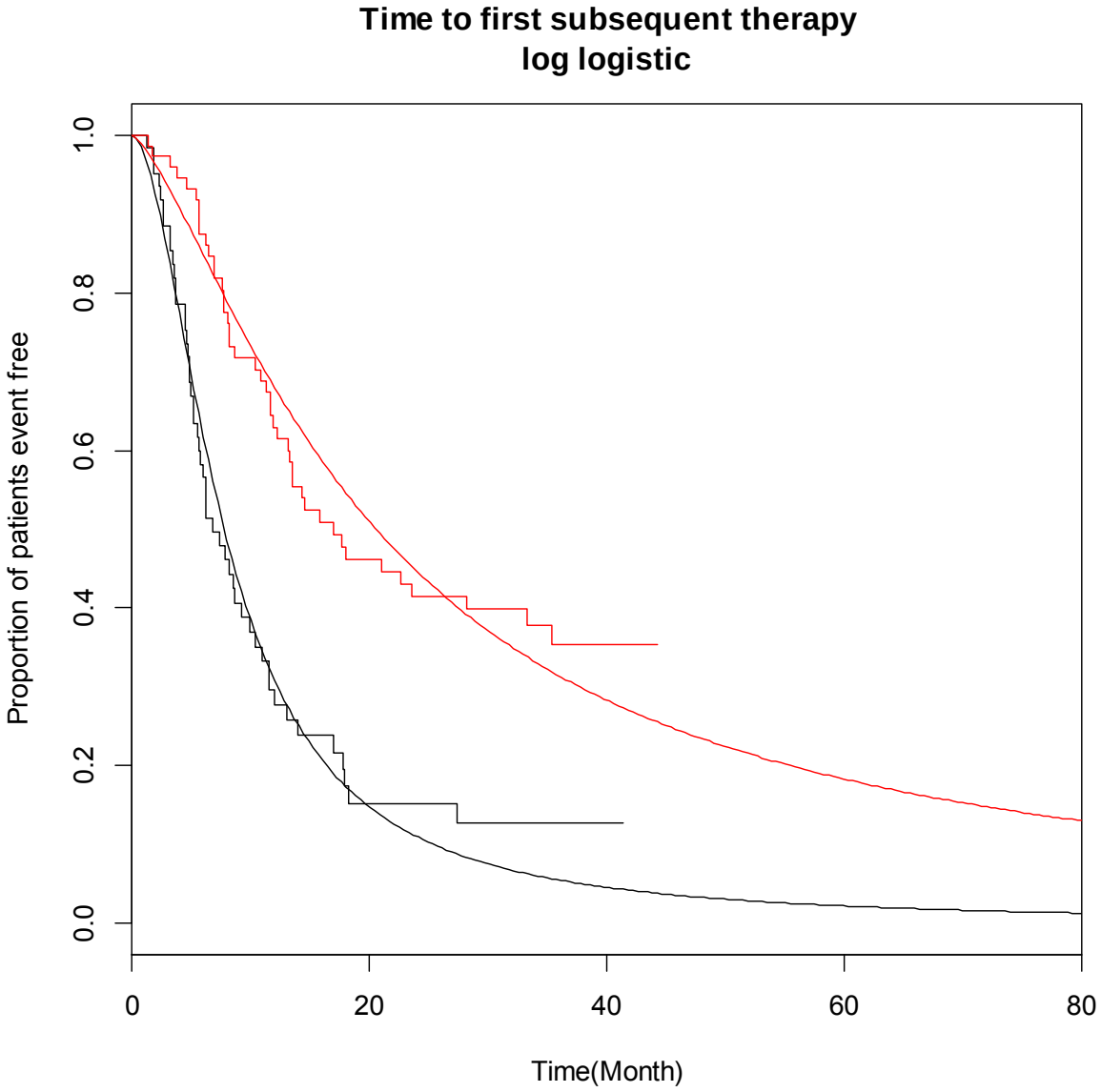
(c) Gamma



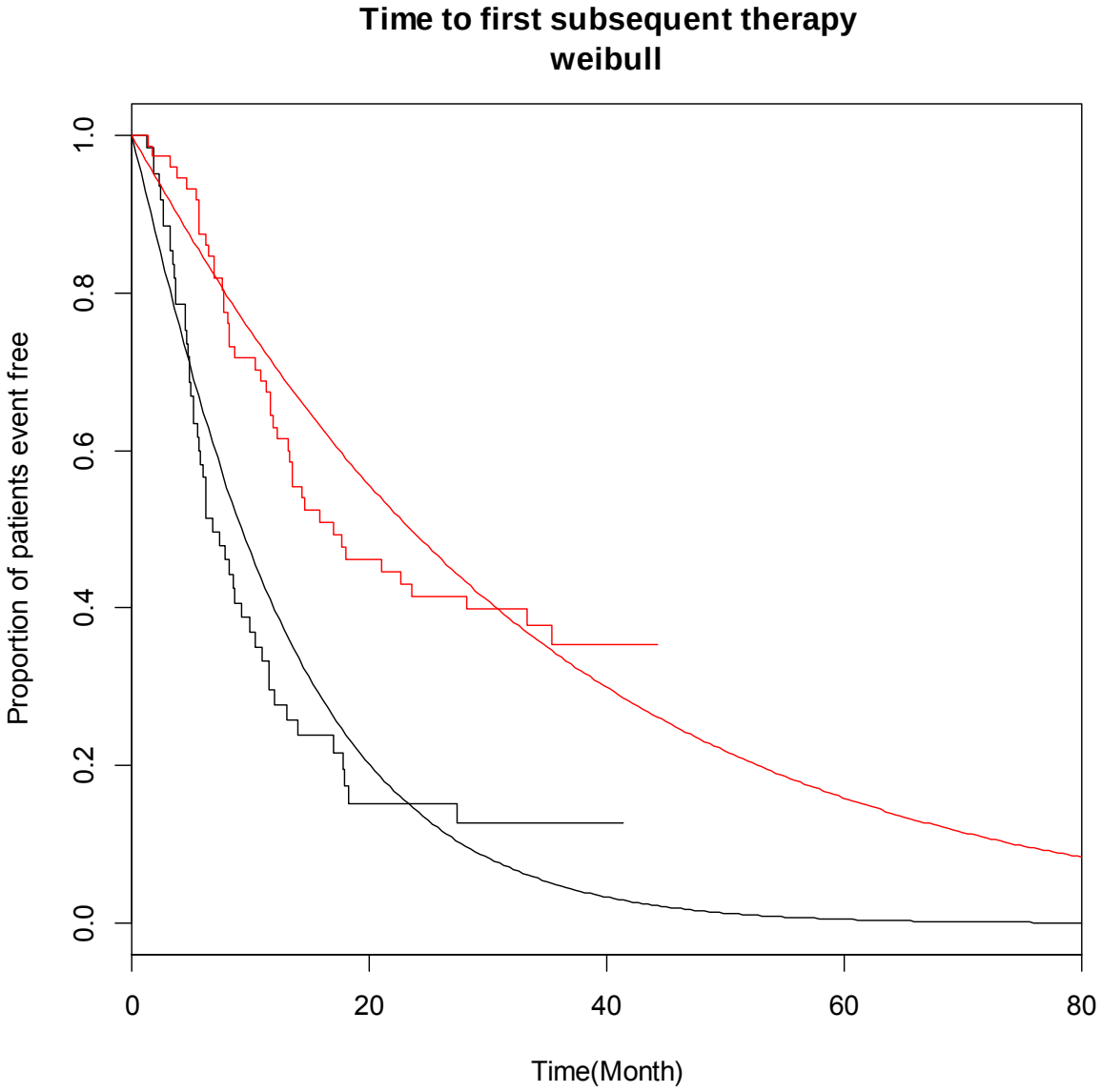
(d) Log normal



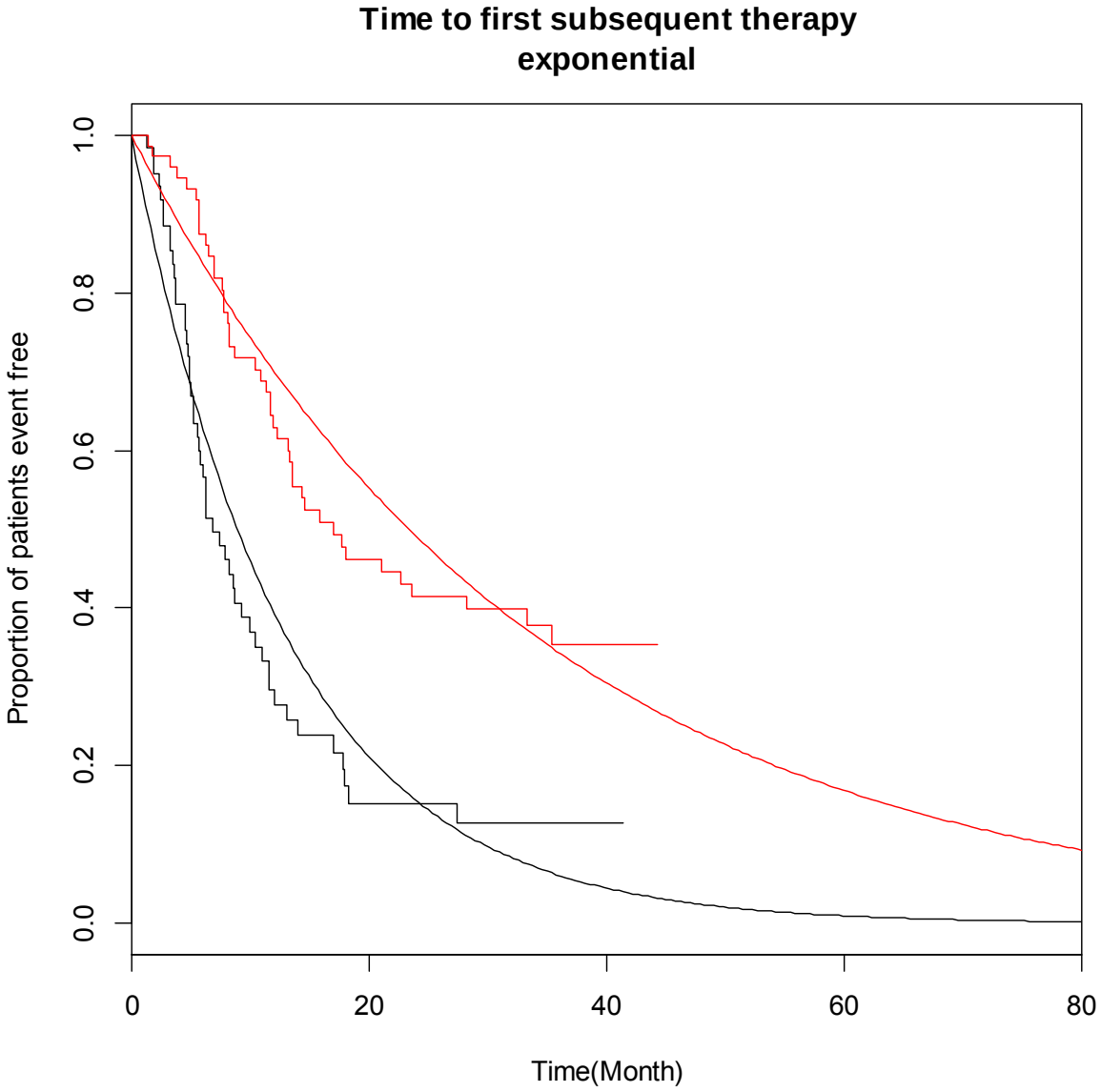
(e) Log logistic



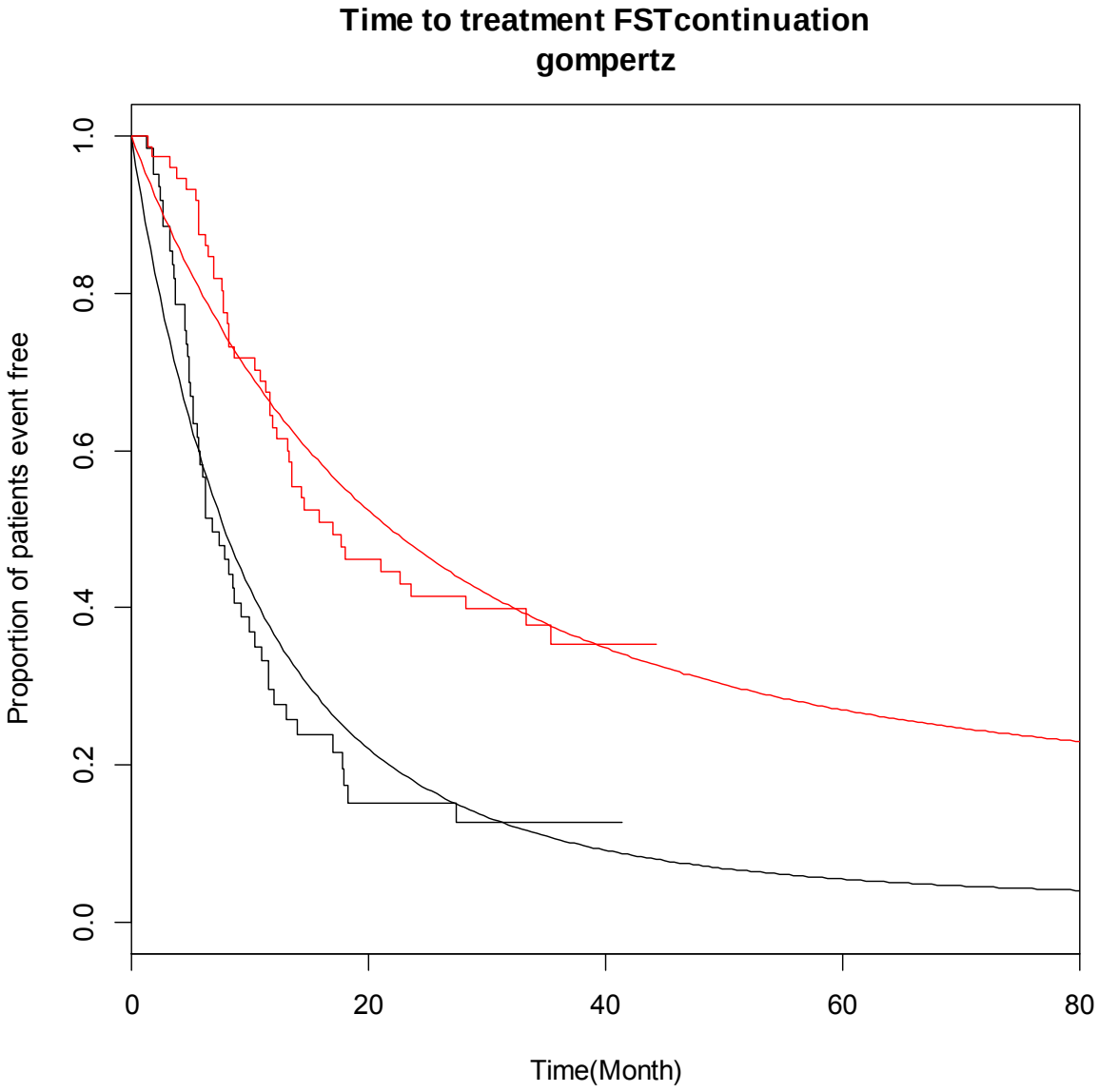
(f) Weibull



(g) Exponential

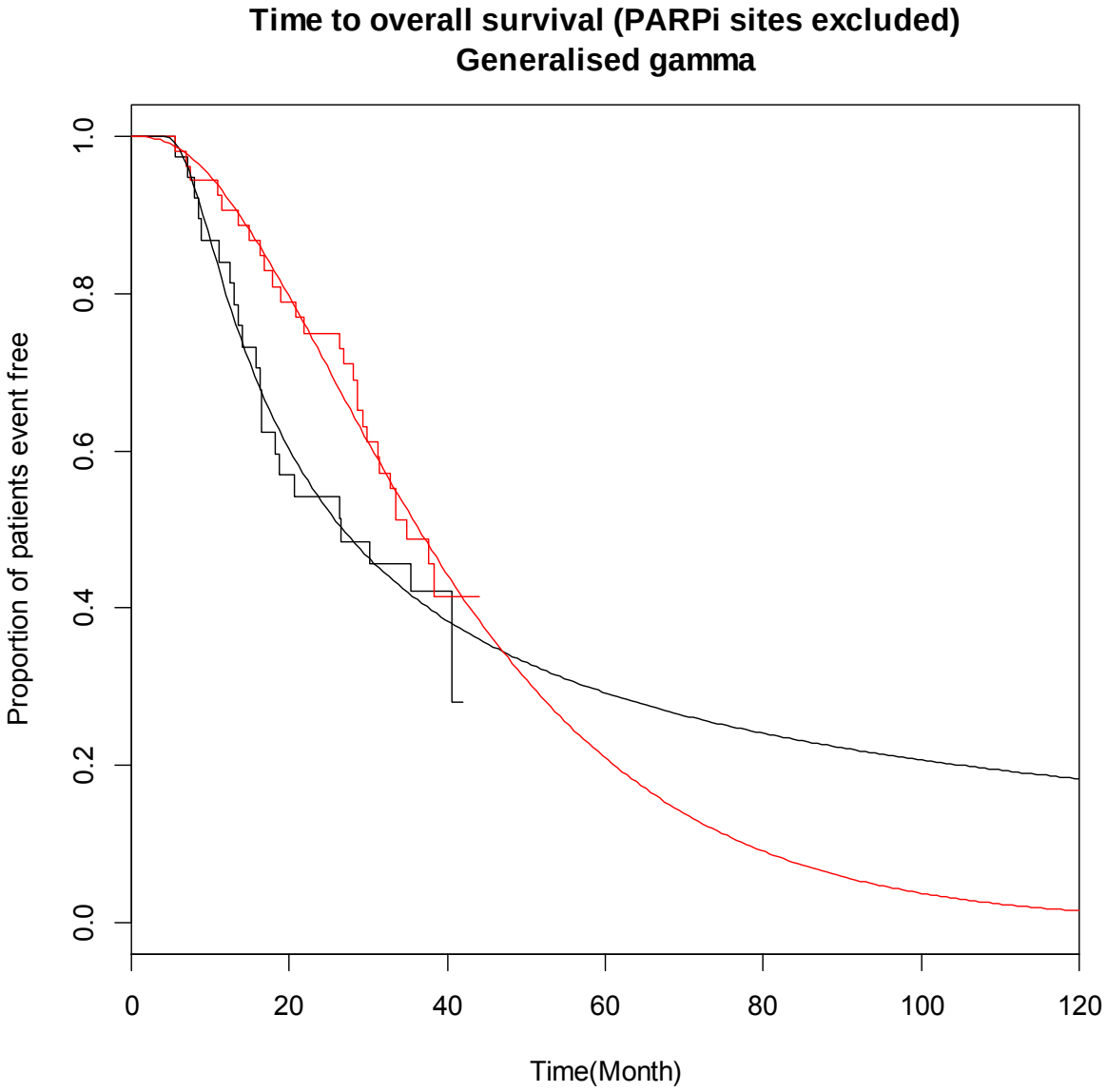


(h) Gompertz

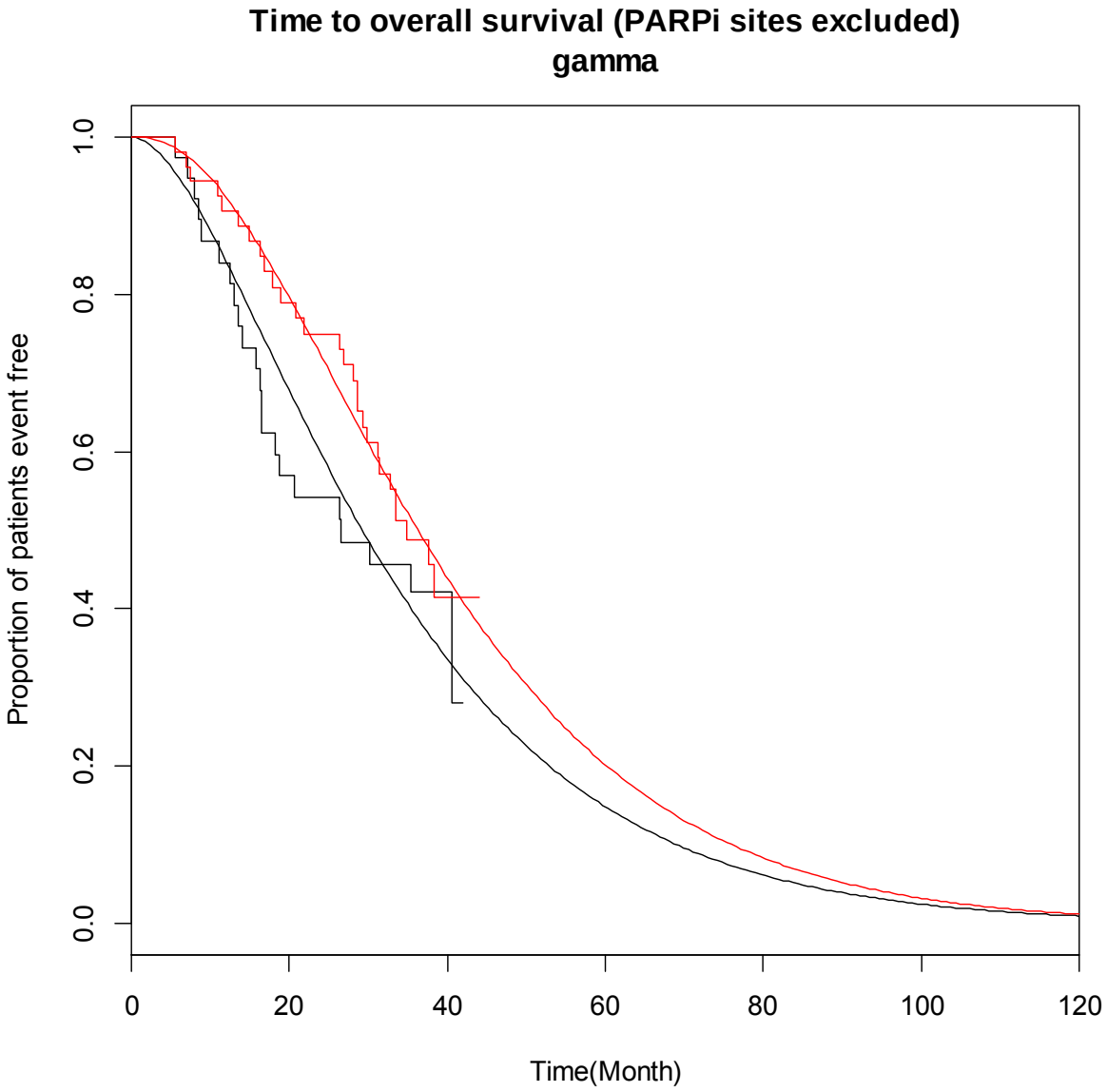


TTE outcome 3: Time from randomisation to death (crossover sites excluded)

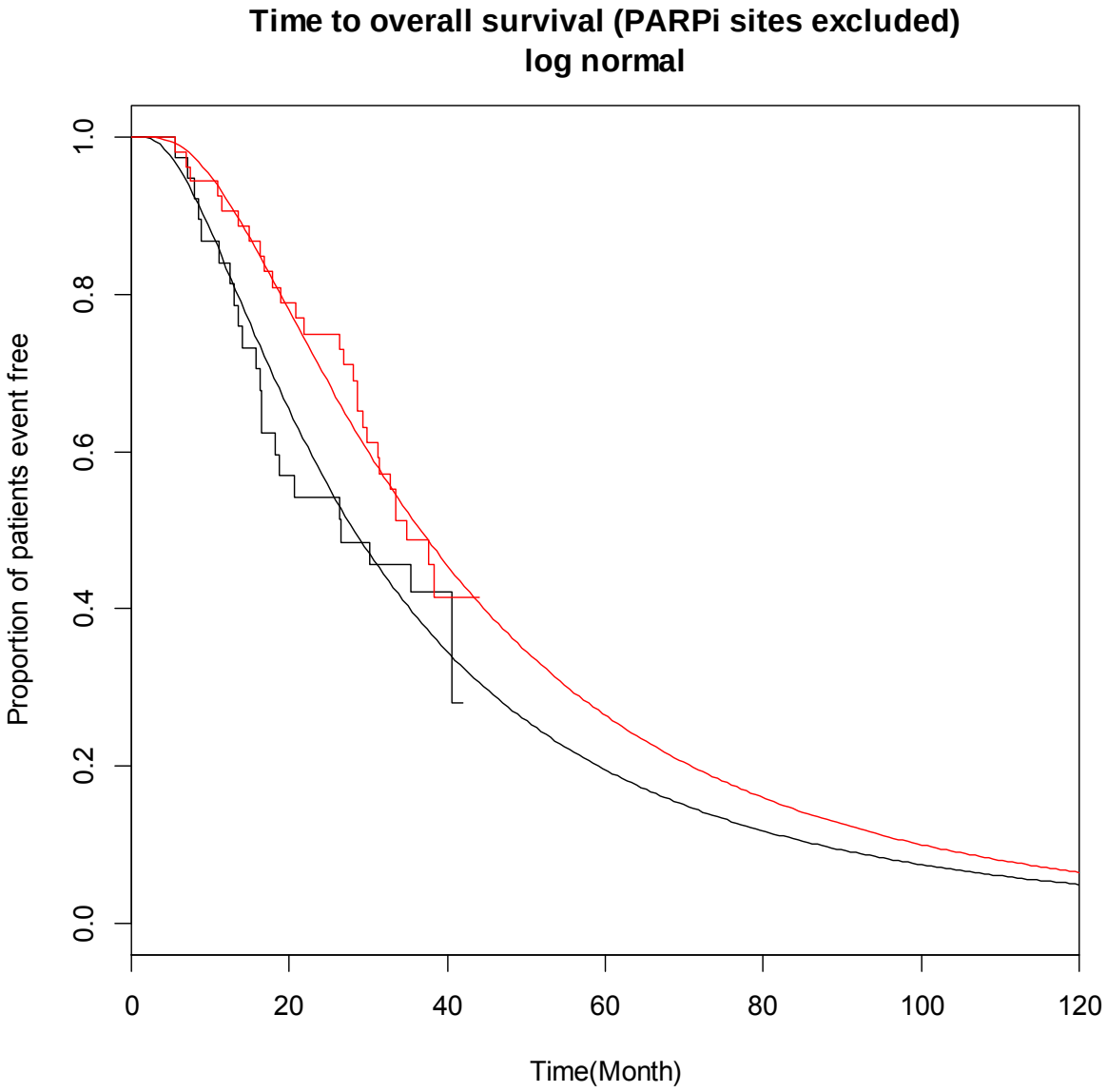
[redacted]**b) Generalised gamma**



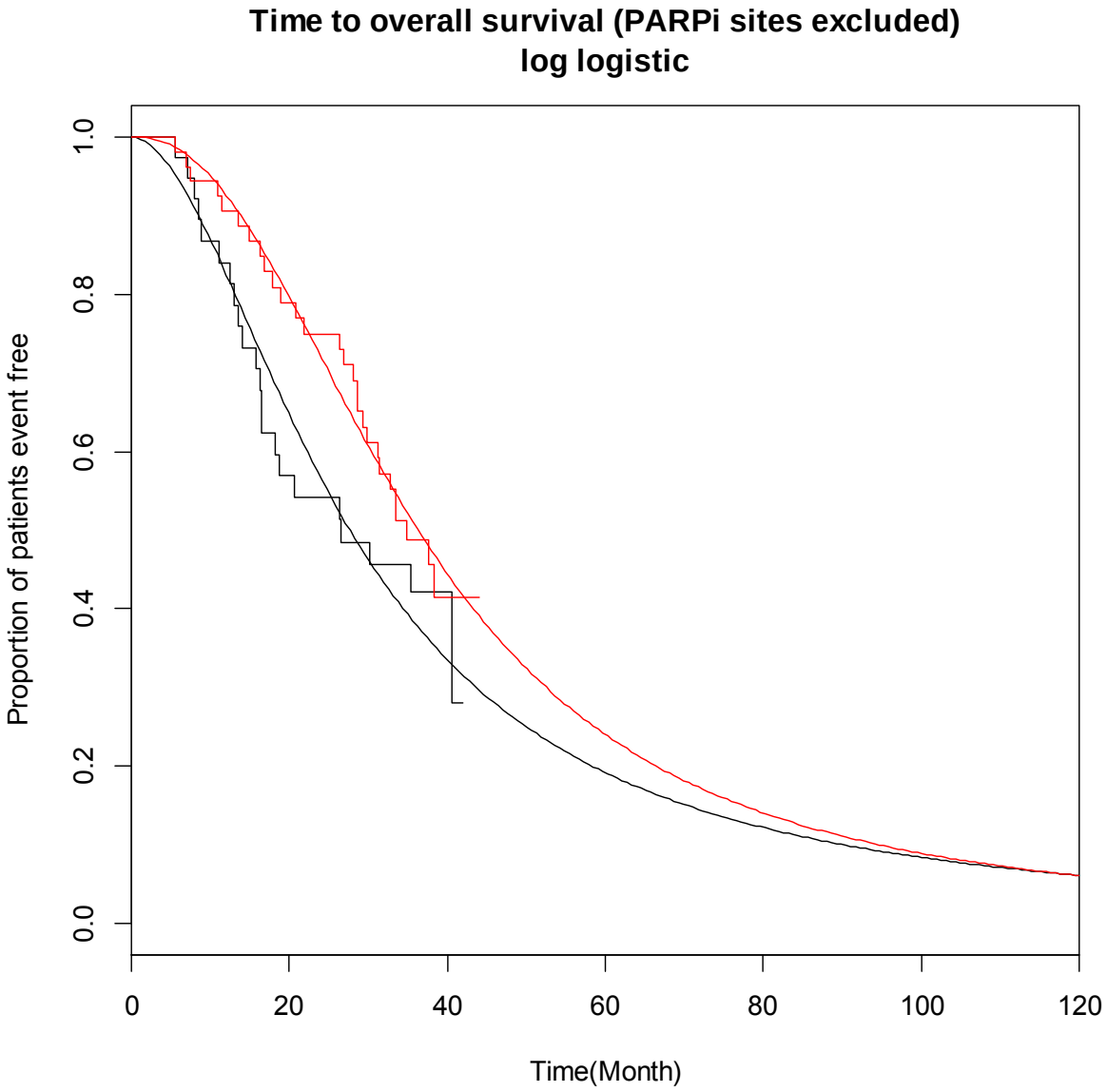
c) Gamma



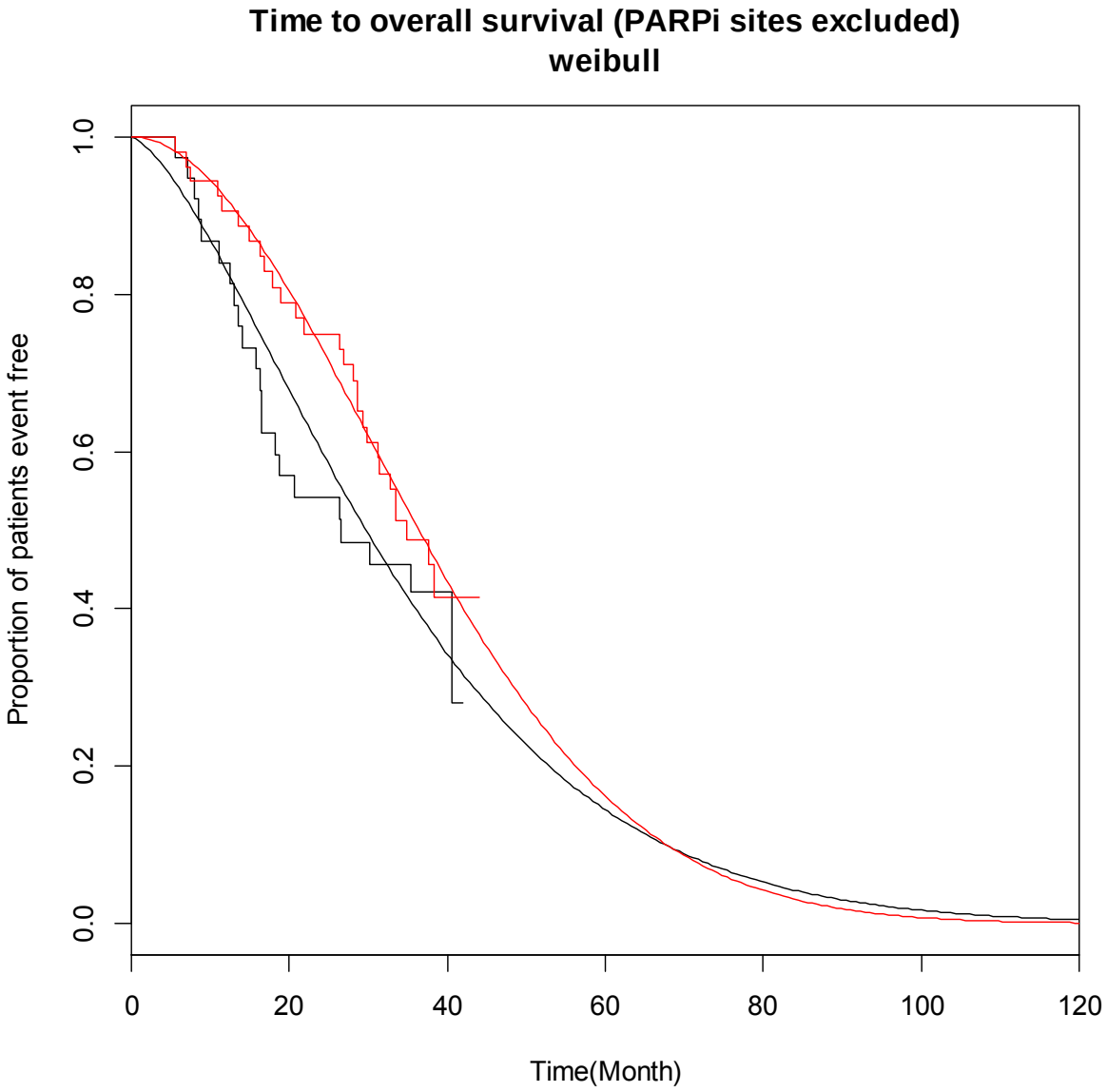
(d) Log normal



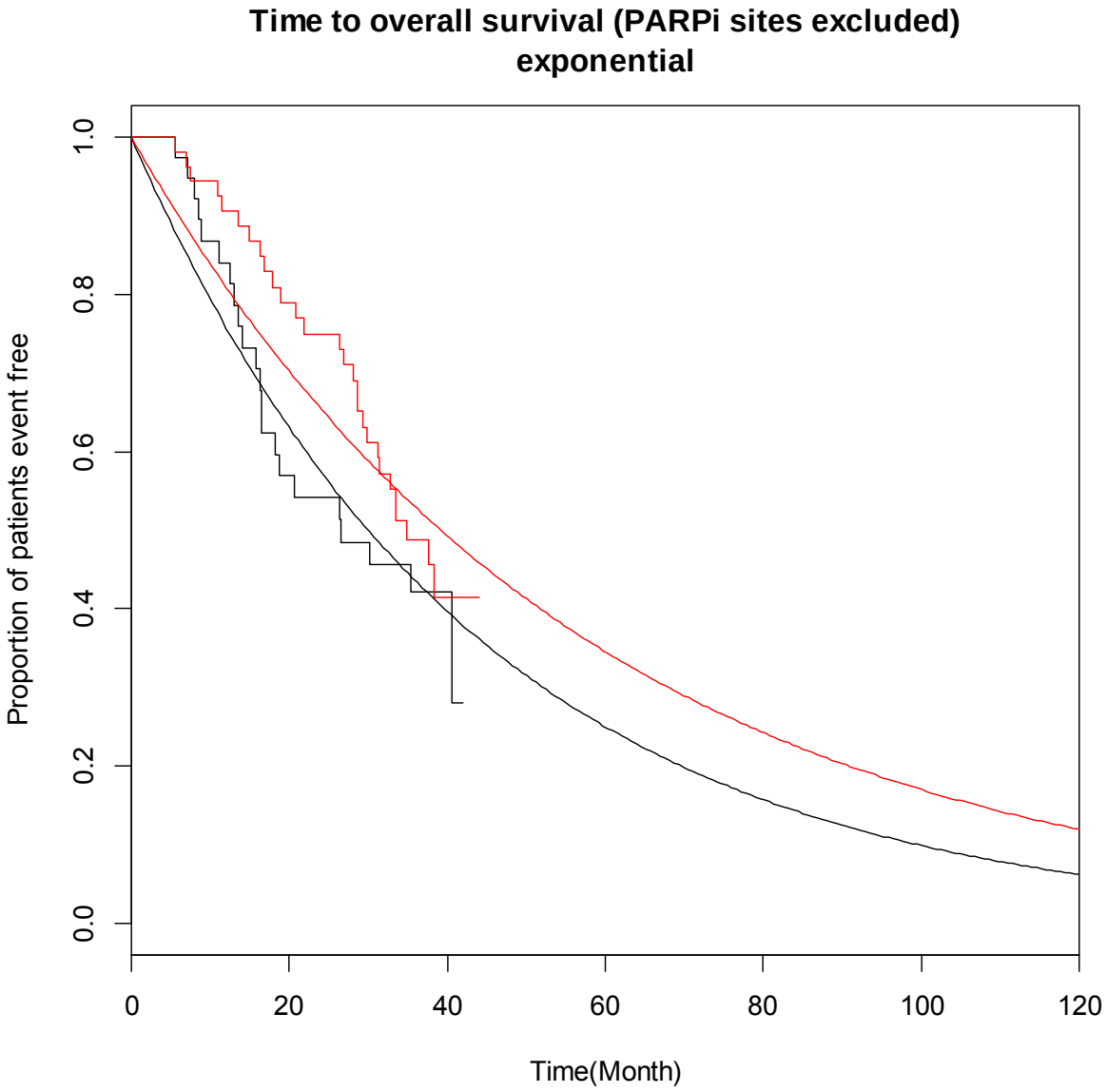
(e) Log logistic



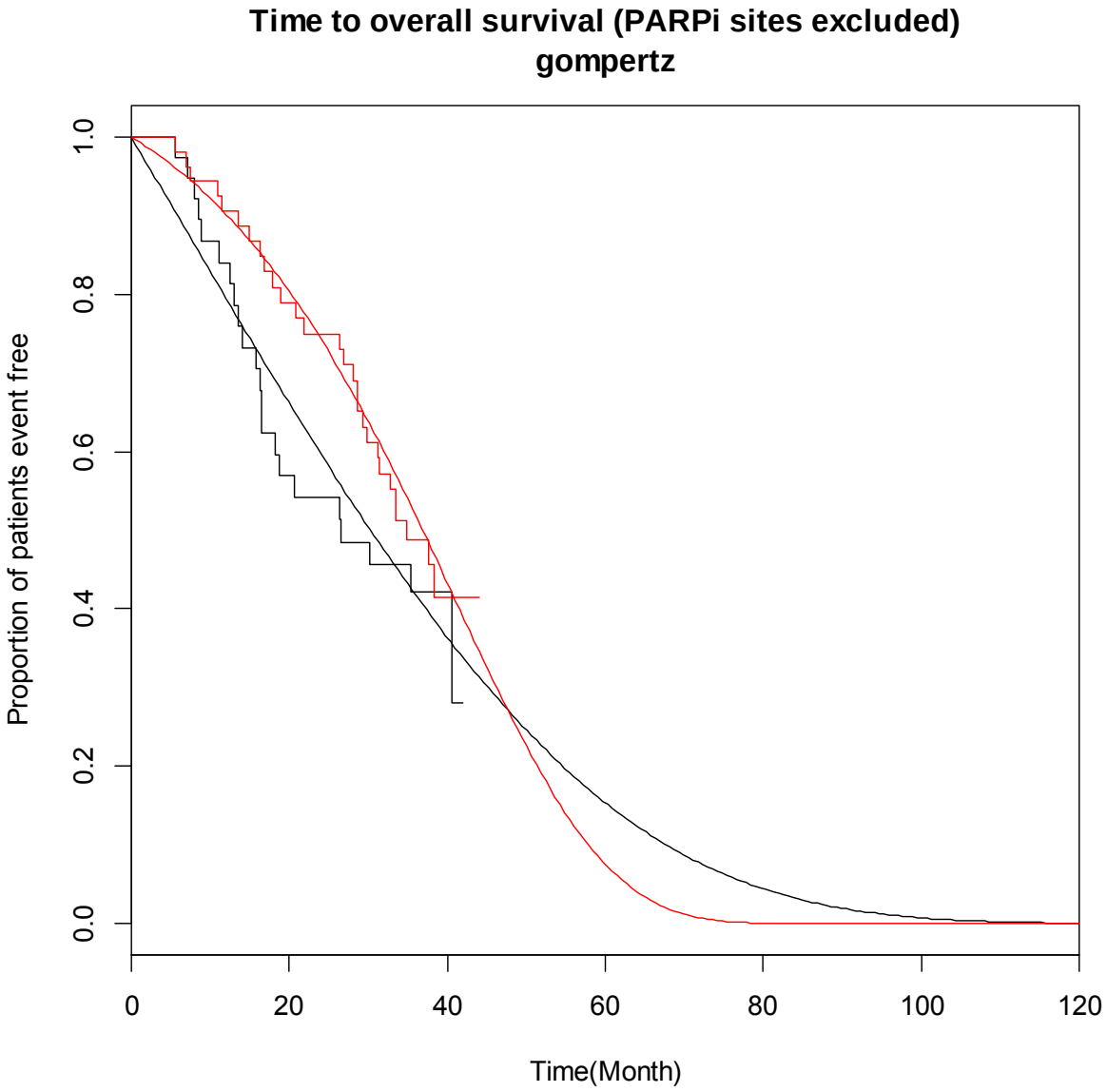
(f) Weibull



(g) Exponential



(h) Gompertz



TTE outcome 4: Time from randomisation to death (RPSFTM-adjusted)

(a) Generalised F (CONFIDENTIAL)

(b) Generalised gamma (CONFIDENTIAL)

(c) Gamma (CONFIDENTIAL)

(d) Log normal (CONFIDENTIAL)

(e) Log logistic (CONFIDENTIAL)

(f) Weibull (CONFIDENTIAL)

(g) Exponential (CONFIDENTIAL)

(h) Gompertz (CONFIDENTIAL)

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