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Tappenden, P., Harnan, S., Ren, S. et al. (2016) 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: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *PharmacoEconomics*. ISSN: 1170-7690

<https://doi.org/10.1007/s40273-016-0440-x>

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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: An Evidence Review Group perspective of a NICE Single Technology Appraisal

Short title: Olaparib for PSR OC – an ERG perspective

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ABSTRACT

As part of its Single Technology Appraisal process, the National Institute for Health and Care Excellence (NICE) invited the manufacturer of olaparib (AstraZeneca) to submit evidence on the clinical effectiveness and cost-effectiveness of olaparib for the maintenance treatment of *BRCA1/2* mutated (*BRCAm*), relapsed, platinum-sensitive (PSR) ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy. The Evidence Review Group (ERG) produced a critical review of the evidence contained within the company's submission (CS) to NICE.

The clinical evidence related to one Phase II, double-blind randomised controlled trial which recruited 265 patients with platinum-sensitive recurrent serous ovarian cancer (OC) regardless of *BRCAm* status. Patients received 400mg olaparib b.d. or matched placebo. In the whole population, the primary endpoint of progression-free survival (PFS) was met (hazard ratio= 0.35; 95% confidence interval (CI) 0.25 to 0.49, $p<0.01$) for olaparib versus placebo. The *BRCAm* subgroup analysis (added after the study commenced but one month before the primary analysis was undertaken) reported an HR for PFS of 0.18 (95% CI 0.10 to 0.31, $p<0.0001$) for olaparib versus placebo, though interaction tests appeared inconclusive. Overall survival was not statistically significant in the whole group (HR 0.88 (95% CI 0.64 to 1.21, $p=0.44$) or the *BRCAm* subgroup (0.73 (95% CI 0.45 to 1.17, $p=0.19$), though treatment switching may have confounded results. The exclusion of data from sites allowing crossover resulted in an HR of 0.52 (95% CI 0.28 to 0.97, $p=0.039$) in the *BRCAm* group. Health-related quality of life measures were not significantly different between groups. All *post hoc* exploratory outcomes (time to treatment discontinuation/death, time to first subsequent therapy/death, and time to second subsequent therapy/death) were statistically significantly better in the olaparib arm in the whole population and the *BRCAm* subgroup analyses. Adverse events were more frequent for olaparib, but were largely minor or manageable.

The company's semi-Markov model assessed the cost-effectiveness of olaparib versus routine surveillance in patients with *BRCAm* PSR OC from an NHS/PSS perspective over a lifetime horizon. The model suggested that the incremental cost-effectiveness ratio (ICER) for olaparib versus routine surveillance is expected to be approximately £49,146 per quality-adjusted life year (QALY) gained. The ERG did not consider the company's cost-effectiveness estimates to be credible. Additional ERG analyses suggested that the ICER is likely to be more than £92,214 per QALY gained. Additional analyses provided by the company in patients who have received 3 or more lines of chemotherapy suggested a more favourable cost-effectiveness profile for olaparib. The NICE Appraisal Committee recommended olaparib this subgroup provided the cost of olaparib for people who remain on treatment after 15 months will be met by the company.

KEY POINTS FOR DECISION-MAKERS

- The supporting clinical evidence for olaparib was a subgroup analysis of a Phase II trial, considered to be at moderately high risk of bias overall. The *BRCAM* subgroup was considered clinically plausible, but interaction tests were inconclusive. PFS was significantly better for patients receiving olaparib ($p < 0.0001$). OS was not significantly better ($p = 0.19$) except in the cross-over adjusted analysis ($p = 0.039$), though this analysis did not correct for unlicensed treatment with olaparib beyond PFS.
- Additional work undertaken by the ERG suggested that the ICER for olaparib versus routine surveillance in *BRCAM* PSR OS patients who have received two or more lines of chemotherapy is likely to be greater than £92,214 per QALY gained.
- The NICE Appraisal Committee concluded that the most plausible ICERs for olaparib versus routine surveillance in *BRCAM* PSR OC patients who have received three or more lines chemotherapy were £46,600 to £46,800 per QALY gained.
- Olaparib was recommended within its marketing authorisation for treating adults with *BRCAM* PSR OC and whose disease has responded to platinum-based chemotherapy only if: they have had 3 or more courses of platinum-based chemotherapy, and; the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company.

1. INTRODUCTION

Health technologies must be shown to represent a clinically effective and cost-effective use of resources in order to be recommended for use within the NHS in England. The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with a significant impact. The NICE Single Technology Appraisal (STA) process usually covers new technologies within a single indication, shortly after they have received UK marketing authorisation [1]. Within this process, the company provides NICE with a written submission that summarises the company's estimates of the clinical effectiveness and cost-effectiveness of the technology, together with an executable health economic model. The company's submission (CS) is reviewed by an external organisation independent of NICE, the Evidence Review Group (ERG), which consults with clinical specialists and produces an ERG report. After consideration of the CS, the ERG report and testimony from experts and other stakeholders, the NICE Appraisal Committee formulates preliminary guidance in the form of an Appraisal Consultation Document (ACD) which indicates the Committee's initial recommendations on the use of the technology. Stakeholders are subsequently invited to comment on the submitted evidence and the ACD, after which a subsequent ACD may be produced or a Final Appraisal Determination (FAD) is issued, which is open to appeal. An ACD is not produced when the technology is recommended without restriction; in such instances, the FAD is produced directly. This paper presents a summary of the ERG report [2] and subsequent analyses [3-5] for the STA of olaparib for the maintenance treatment of *BRCA1/2* mutated (*BRCAm*), relapsed, platinum-sensitive (PSR) ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy, and the subsequent development of the NICE guidance for the use of this drug in England [6]. Full details of all relevant appraisal documents can be found on the NICE website (<https://www.nice.org.uk/guidance/indevelopment/ta381/documents>).

2. THE DECISION PROBLEM

Ovarian cancer (OC) represents a group of tumours that arise from diverse types of tissue contained in the ovary. The most common type of OC arises from epithelial cells on the surface of the ovary, and can often spread to any surface within the abdominal cavity including the fallopian tubes and peritoneal cavity. The symptoms of OC commonly include persistent abdominal distension, early satiety and/or loss of appetite, pelvic or abdominal pain and increased urinary urgency and/or frequency [7]. Approximately 6,100 women are diagnosed with OC in England each year [8]. Incidence increases with age and most cases are diagnosed in older postmenopausal women. Most OCs are sporadic. However, the presence of *BRCA* mutations account for more than 10% of all OCs and carriers of *BRCA* mutations have an increased lifetime risk of developing breast cancer and OC. In England and Wales, the 5-year survival rate is approximately 46%, however, prognosis is considerably worse for patients with advanced disease [8]. Approximately 10–15% of women

presenting with advanced disease achieve long-term remission through chemotherapy. However, following initial response to treatment, the majority of patients subsequently relapse.

2.1 Current treatment

There are currently no licensed therapies for the maintenance treatment of PSR OC. Prior to January 2015, bevacizumab was available in England as a maintenance therapy; this is no longer routinely available through the Cancer Drugs Fund (CDF) in the relapsed setting. Current care involves routine surveillance, with further chemotherapy given upon relapse. Surveillance typically involves routine outpatient appointments to assess for symptomatic disease progression. Cancer antigen 125 (CA125), a serum tumour marker, may be used to detect relapse in OC, although the benefits of routine measurement are disputed and its use across England is variable [9]. In people whose disease relapses following initial therapy, NICE recommends paclitaxel in combination with a platinum compound in platinum-sensitive or partially platinum-sensitive disease; pegylated liposomal doxorubicin hydrochloride in partially platinum-sensitive, platinum-resistant or platinum-refractory disease; paclitaxel alone in platinum-refractory or platinum-resistant disease, and; topotecan in platinum-refractory or platinum-resistant disease for people for whom pegylated liposomal doxorubicin hydrochloride and single-agent paclitaxel are considered inappropriate [10].

Olaparib (Lynparza[®]) is a potent inhibitor of poly (ADP-ribose) polymerase (PARP)-1, PARP-2 and PARP-3. Olaparib is licensed for the maintenance treatment of adult patients with PSR *BRCAm* (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy [11]. The recommended dose of olaparib is 400mg (eight 50mg capsules) b.d. Treatment should be continued until disease progression; treatment interruptions and dose reductions may be used to manage adverse reactions [11]. As of June 2016, olaparib had not been listed on the British National Formulary (BNF) [12]. The original anticipated NHS list price was £3,950.00 per pack (448 capsules) [13]. During the appraisal, a Patient Access Scheme (PAS) was agreed whereby the cost of olaparib for people who remain on treatment for more than 18 months will be met by the company. This was subsequently reduced to 15 months and a price of £3,550 per pack was agreed. All results presented here include the original 18-month PAS and original list price.

In order to receive olaparib, patients must have confirmation of *BRCAm*. Current NICE guidelines recommend *BRCA* testing for women with OC in whom the combined *BRCA1/2m* carrier probability is 10% or more [14]. Currently, the use of *BRCAm* testing across England remains variable.

In November 2014, NICE issued a final scope to appraise the clinical effectiveness and cost-effectiveness of olaparib within its licensed indication for the maintenance treatment of *BRCA1/2m*,

PSR ovarian, fallopian tube and peritoneal cancer in people whose relapsed disease has responded to platinum-based chemotherapy [15].

3. INDEPENDENT ERG REVIEW

The company (AstraZeneca) provided a submission to NICE on the clinical effectiveness and cost-effectiveness of olaparib for the maintenance treatment of *BRCA1/2m* PSR OC [13]. This submission was critically appraised by the ERG. In addition, the ERG identified areas requiring clarification, for which the company provided additional evidence prior to completion of the ERG report [2, 16].

3.1.1 Clinical evidence submitted by the company

The CS included an unpublished systematic review of studies in patients with OC of any *BRCAm* status. The scope of this review was wider than that required by the decision problem. One relevant study was identified for inclusion (Study 19 [17]).

3.1.1.1 Clinical trial design

Population and trial design: Study 19 was a pivotal Phase II, double-blind RCT. The study recruited 265 patients aged 18 years or older, with a histological diagnosis of recurrent, high-grade (grade 2 or 3) serous OC (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), and regardless of *BRCAm* status. Patients who had received previous PARP inhibitor (PARPi) therapy were excluded. Patients had to have an Eastern Co-operative Oncology Group (ECOG) performance status ≤ 2 , a life expectancy of at least 16 weeks and a CA125 measurement below the upper limit of normal, or if above, not significantly rising over time.

Intervention and comparator: Patients were randomised by an interactive voice response system (IVRS) to 400mg olaparib b.d. or matched placebo. Interruptions and dose reductions were permitted to address toxicity or adverse events (AEs), but re-treatment was not allowed. Continuation of treatment was permitted for patients who were still benefitting. Some concomitant medications were allowed, and patients in the placebo arm could crossover to receive a PARPi after the study endpoint was reached.

Outcomes: The primary outcome was progression-free survival (PFS) as assessed by the Response Evaluation Criteria in Solid Tumours (RECIST) criteria or death. Pre-specified secondary outcomes relevant to the scope included overall survival (OS), AEs and health-related quality of life (HRQoL) by the Trial Outcome Index (TOI), the Functional Assessment of Cancer Therapy - Ovarian (FACT-

O) and the FACT/NCCN Ovarian Symptom Index (FOSI). Additional *post hoc* exploratory analyses were reported for the safety population, including: time to treatment discontinuation/death (TTD/D), time to first subsequent therapy/death (TFST/D) and time to second subsequent therapy/death TSST/D (Figure 1). Only TFST/D was listed in the NICE scope, with TSST/D presented as a proxy for PFS2. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [18].

Figure 1: Outcome measurement in Study 19

[INSERT FIGURE 1 HERE]

Analysis plan: The pivotal data for this assessment was a subgroup analysis of *BRCAm* patients from Study 19 [13, 19]. The testing of all patients for *BRCAm* status, a subgroup analysis of PFS in *BRCAm* patients, and a global interaction test were added to the statistical plan approximately one month before the PFS data cutoff (DCO) point was reached (June 2010). This replaced the subgroup analysis of patients who had homologous-recombination-deficient (HRD) tumours (of which *BRCA* mutations are a subset), as an HRD test was not developed in time. Additional analyses of all other clinical endpoints in this subgroup 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 after the DCO. 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.

3.1.1.2 Clinical study results

Patient characteristics: The most notable imbalances in patient characteristics related to objective response to the most recent platinum-based chemotherapy, and to a lesser extent, in ECOG performance status. Adjustments for imbalances were applied in Cox proportional hazards model analyses in the full analysis set (FAS); it was unclear if adjustment was applied to the *BRCAm* subgroup.

PFS: In the whole population analysis, the primary study endpoint was met, with a hazard ratio (HR) for PFS of 0.35 (95% confidence interval [C.I]. 0.25 to 0.49, $p < 0.01$) for olaparib versus placebo. Median PFS was 8.4 months for olaparib versus 4.8 months for placebo (95% CI not reported [NR]). The *BRCAm* subgroup analysis reported an HR for PFS of 0.18 (95% CI 0.10 to 0.31, $p < 0.0001$) for olaparib versus placebo; median PFS was 11.2 months for olaparib (95% CI 8.3 to “not calculable”) versus 4.3 months for placebo (95% CI 3.0 to 5.4). A treatment-subgroup interaction test was not presented within the CS but was reported in the Clinical Study Report (CSR) and the European Public Assessment Report (EPAR); each reports a significant interaction 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 non-treatment covariates was performed [20, 21].

OS: Within the whole population, OS was not significantly different between groups at either analysis point. The HR for death was 0.94 (95% CI 0.63 to 1.39; $p=0.75$) for olaparib versus placebo (median OS 29.7 months versus 29.9 months respectively, 95% CI NR) at the June 2010 DCO [17]. At 58% OS data maturity (November 2012), the HR for death was 0.88 (95% CI 0.64 to 1.21, $p=0.44$) for olaparib versus placebo, with a median survival of 29.8 months (95% CI 27.2 to 35.7) in the olaparib arm versus 27.8 months (95% CI 24.4 to 34.0) in the placebo arm [20, 21]. For the *BRCAM* subgroup, OS was reported only at the November 2012 DCO (52% maturity); the HR for death was 0.73 (95% CI 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 in which sites allowing placebo group crossover to PARPis reported a significant OS difference (HR=0.52, 95% CI 0.28 to 0.97, nominal $p=0.039$) [22]. No correction was applied for patients in the olaparib arm who continued to receive olaparib beyond disease progression.

HRQoL: Study 19 reported “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 therapy [23].

Other outcomes: All *post hoc* exploratory outcomes (TTD/D, TFST/D and TSST/D) were statistically significant for the whole population and the *BRCAM* subgroup. In the whole population, the HR for TTD/D was 0.39 (95% CI 0.30 to 0.51) for olaparib versus placebo, and 0.36 (95% CI 0.24 to 0.53) for olaparib versus placebo in the *BRCAM* subgroup. In the whole population, the HR for TFST/D was 0.41 (95% CI 0.31 to 0.54) for olaparib versus placebo, and 0.33 (95% CI 0.22 to 0.50) for olaparib versus placebo in the *BRCAM* subgroup. In the whole population, the HR for TSST/D was 0.54 (95% CI 0.41 to 0.72) for olaparib versus placebo, and 0.44 (95% CI 0.29 to 0.67) for olaparib versus placebo in the *BRCAM* subgroup.

AEs occurred more often in the olaparib group, but were largely minor and manageable with dose reductions or interruptions. More patients receiving olaparib suffered severe AEs such as fatigue, anaemia and neutropenia compared with placebo. Serious AEs occurred in 21.6% of olaparib patients versus 9.7% of placebo patients. These included anaemia, small bowel obstruction, dyspnoea and gastritis.

3.1.2 Critique of clinical effectiveness evidence and interpretation

3.1.2.1 Critique of systematic review

Adaptations to the systematic review were made by the company to bring it in line with the NICE scope. Whilst unclear from the CS, clarifications provided by the company suggest that the review was well conducted. The ERG concluded that all relevant evidence had been identified.

3.1.2.2 Critique of clinical evidence

Study 19 had several limitations, both methodologically and with respect to its relevance to the decision problem.

Population: The inclusion criteria for the FAS were considered broadly appropriate by the ERG and their clinical advisors [11]. Two ERG advisors thought the criteria requiring stable CA125 status to be reasonable, and considered that CA125 status would likely be used in clinical practice as this biomarker is used to monitor response to chemotherapy. Baseline imbalances were considered likely to be due to problems with the IVRS which led to mis-stratification of patients; whilst these were corrected using Cox model analyses for the FAS, it remained unclear whether all *BRCAm* analyses were also adjusted.

The *BRCAm* subgroup was considered clinically relevant, but the study used both germline (blood test) and tumour (tissue sample test) *BRCAm* testing to select patients. Tumour testing is not routinely performed in England and it is unclear whether this will be possible on a large scale. Consequently, this may potentially lead to problems regarding generalisability.

Intervention: The intervention was considered largely appropriate, with the exception of the continuation of olaparib beyond progression (which is not in accordance with the licence), and the assessment of progression (halting treatment in most cases) using RECIST rather than CA125 (which generally indicates progression before RECIST). These factors are likely to mean that treatment was administered in the trial for longer than would be the case in usual clinical practice in England.

Comparator: The ERG concluded that the comparator reflected clinical practice. Data on differences in concomitant treatments (e.g. ascites drainage, pain relief) between groups were not presented.

Outcomes: The primary outcome was considered appropriate, though it was noted that PFS is a proxy for OS, and that OS is the most relevant outcome. The ERG argued that as Study 19 is being used as pivotal evidence, it should conform to EMA guidelines for Phase III trials [24]; these state that PFS should be supported by a trend toward OS benefit, or outcomes such as PFS2 or time to next line therapy. In Study 19, TFST/D and TSST/D were considered by the ERG to be suitable supporting endpoints instead of PFS2, despite not being listed in the NICE scope. However, the clinical advisors were concerned that practice in the countries included in Study 19 may be to commence subsequent

therapy earlier than in England, thus truncating these outcomes. Furthermore, these outcomes were added to the study plan after PFS data had been collected, hence they are at high risk of bias.

Conversely, continuation of treatment beyond PFS and the use of RECIST criteria rather than CA125 means that TTD/D and PFS may be longer than would be expected in clinical practice. Other outcomes such as TFST/D, TSST/D, OS and AEs may have been affected by the increased dose allowed in the trial, unblinding of study participants, and by placebo group crossover. Generalisability was therefore a concern to the ERG.

AE measurement was largely adequate, despite a lack of clarity in the methods of elicitation. The choice of HRQoL measures appeared appropriate, though a preference-based measure was not used and measurement was only performed during the treatment phase of the trial.

Study design: The multiple changes to the statistical analysis plan, particularly the timing of OS measurement and the addition of the *BRCAM* subgroup analyses, were a matter of concern as they were performed *post hoc*. The company's rationale for selecting the *BRCAM* subgroup was thought to have clinical plausibility by the ERG's clinical advisors, though interaction tests were inconclusive. Based on published quality assessment criteria [25], the ERG scored the study as low risk for 4 domains (allocation concealment, imbalances in dropouts between groups, outcome reporting bias and analysis methods), but high risk for randomisation (due to problems with the IVRS) and balance between groups in prognostic factors at baseline, and unclear risk for blinding as some patients were unblinded under an emergency protocol.

As 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 ERG concluded that the study results were associated with considerable uncertainty in relation to their accuracy and generalisability. To compound these issues further, the history of changes to the study protocol and the *post hoc* definition of the *BRCAM* subgroup and inconclusive interaction tests means that the hypothesis that olaparib has superior efficacy in *BRCAM* patients compared with other patients had not been robustly tested or proved. The ERG noted that a Phase III trial of olaparib in *BRCAM* OC patients was ongoing (clinicaltrials.gov identifier - NCT01874353) and would provide the required confirmation of the study's results. The lack of conclusive 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 olaparib confers a survival benefit or not.

3.2 Cost-effectiveness evidence submitted by the company

The company submitted a *de novo* health economic model to assess the cost-effectiveness of olaparib versus routine surveillance in patients with *BRCAM* PSR OC. The company's economic analysis was comprised of two related evaluations:

- (i) The base case economic evaluation of olaparib maintenance treatment versus routine surveillance in patients with *BRCAM* PSR OC. This excludes the costs of *BRCAM* testing and considers costs and benefits relating to the index *BRCAM* OC patient.
- (ii) A broader economic evaluation that also accounts for: (a) the costs of *BRCAM* testing in *BRCAM* PSR OC patients, and; (b) the costs and benefits of expanding *BRCAM* testing to family members of relapsed *BRCAM* OC patients undergoing *BRCAM* testing as a prerequisite in consideration of olaparib as a potential treatment option. This analysis considers costs and benefits relating to the index *BRCAM* OC patient and family members.

The company's base case analysis adopts a semi-Markov approach and evaluates costs and health outcomes from a National Health Service (NHS) and Personal Social Services (PSS) perspective over a lifetime horizon (15 years), discounted at a rate of 3.5% per year. The company's model (Figure 2) 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. Transitions between progressive states are modelled using parametric survivor functions fitted to time-to-event data together with fixed estimates of the proportion of these progression events which are deaths. Clinical input parameters were estimated using data from the Study 19 *BRCAM* subgroup [19]. For the progression-free states, health utilities were mapped from the FACT-O to the Euroqol EQ-5D [26]; utilities for subsequent states were sourced from a previous NICE submission [27]. Resource use estimates were based on Study 19 [19], previous appraisals [28], clinical guidelines [14], literature [29-31] and assumptions. Unit costs were derived from NHS Reference Costs 2013-14 [32], the Personal Social Services Research Unit (PSSRU) [33], the NHS Commercial Medicines Unit (CMU) [34] and the BNF [12]. The additional costs and benefits of *BRCAM* testing within the secondary analysis were taken from the cost-effectiveness report published as part of the NICE familial breast cancer guideline [14]. The CS argues that olaparib satisfies NICE's criteria for life-extending therapies at the end of life (EoL) [35].

Figure 2: Company's model structure

[INSERT FIGURE 2 HERE]

The probabilistic version of the company's model suggests that olaparib is expected to produce an additional 0.90 quality-adjusted life years (QALYs) at an additional cost of £72,232 compared with routine surveillance; this corresponds to an incremental cost-effectiveness ratio (ICER) for olaparib

versus routine surveillance of approximately £49,146 per QALY gained. The deterministic model yielded a similar ICER of £49,826 per QALY gained. Assuming willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per QALY gained, the probability that olaparib produces more net benefit than routine surveillance is approximately 0.02 and 0.52, respectively. The company's secondary analysis, which is based on five family pedigrees, suggests a lower average deterministic ICER for *BRCAM* testing plus olaparib versus routine surveillance without *BRCAM* testing of £39,343 per QALY gained.

3.2.1 Critique of cost-effectiveness evidence and interpretation

The ERG critically appraised the company's economic analysis and double-programmed the company's model. No significant programming errors were found. However, the ERG had concerns regarding the model structure and the evidence used to inform the model's parameters.

3.2.1.1 Choice of model structure and use of outcomes data from Study 19 *BRCAM* subgroup

The company's model assumes that all patients who survive their first subsequent therapy event (the "progression-free" period) subsequently receive a first subsequent chemotherapy and that all patients who survive the second subsequent therapy event subsequently receive a second course of chemotherapy. However, for some patients with advanced disease, chemotherapy may offer limited benefit and patients may instead receive supportive care. Furthermore, the model structurally limits the number of lines of subsequent chemotherapy to a maximum of two, yet within the Study 19 *BRCAM* subgroup, more than 36% patients received three or more subsequent lines of therapy [13]. The ERG's main concerns surrounded the outcomes data included in the model and the range of evidence which had been excluded from it. The model is based on the time to first subsequent therapy or death (TFST/D – from randomisation) and time to second subsequent therapy or death (TSST/D – from first subsequent therapy) and survival within those states, with olaparib conferring a clinical benefit in delaying the time to first and second subsequent therapy, and as a consequence, delaying time to death. The modelled "progression-free" interval does not relate to the PFS endpoint, but is instead defined by TFST/D. PFS data are not used in the model. Both TFST/D and TSST/D were *post hoc* exploratory outcomes and may have been influenced by subjective decisions regarding future chemotherapy use, eligibility for treatment and loss of blinding within Study 19. The ERG also had concerns that the observed OS data from Study 19 were not directly used in the company's model. Instead, the model applies the risk of death: (a) as a fixed proportion of time-dependent progression events upon leaving the progression-free and subsequent therapy states, and; (b) as a treatment-independent time-to-event curve for all patients from entry into the second subsequent therapy state. Mortality is therefore captured as a conditional event for patients reaching different health states, rather than by fitting survivor functions to the Kaplan-Meier OS data.

The CS argued that their model structure better represents the benefits of maintenance treatments and the treatment pathway following relapse compared with a simple partitioned survival approach [13]. The ERG argued that the best model is that which: (a) represents clinical reality, and; (b) makes the best use of the evidence available. Excluding PFS, compounding multiple assumptions regarding mortality risks associated with specific health states within and between treatment groups, and limiting the treatment pathway to two lines of chemotherapy does not satisfy both of these criteria.

3.2.1.2 Potential confounding of endpoints used in the company's model

The model attempts to deal with placebo group crossover 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 independent of treatment. The company provided analyses in which placebo group OS was adjusted for treatment switching: (a) by excluding sites allowing placebo group crossover, and; (b) using a Rank Preserving Structural Failure Time Model (RPSFTM) [13, 16]. Kaplan-Meier curves produced using these methods each suggested an apparent OS benefit for olaparib versus placebo, but indicated little difference between the groups by around 3 years post-randomisation. As OS was not directly included as a model input, the impact of using these crossover-adjusted data on the cost-effectiveness of olaparib could not be assessed using the company's model. No attempt was made to correct for confounding due to the continuation of olaparib beyond progression.

3.2.1.3 Concerns regarding the methods for modelling of time-to-event outcomes

According to the CS [13], the process for survival modelling was based on Latimer *et al* [36]. However, the justification for including baseline characteristics as covariates in the model-fitting process was neither justified nor explained, model discrimination did not appear to have included judgements about the plausibility of extrapolations, assumptions of proportional hazards appeared inappropriate, and sensitivity analyses using alternative survivor functions were not presented for outcomes except TFST/D.

3.2.1.4 Discordance between model predictions and observed data from Study 19

Model-predicted OS did not provide a good fit to the observed data, irrespective of whether crossover was adjusted for. Comparing the modelled and empirical OS curves indicated that:

- The crossover-site-excluded (CSE) and RPSFTM-adjusted OS Kaplan-Meier curves were similar.
- Despite adjustment, the gap between the olaparib and placebo curves appears to close, or nearly close, at around 3-years post-randomisation, irrespective of the crossover method applied.

- OS is reasonably predicted for olaparib for the first 2 years post-randomisation but is subsequently overestimated.
- The model does not provide a good fit to the empirical placebo group data irrespective of the method of crossover adjustment.
- Whilst the empirical OS data, both with and without crossover adjustment, 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 company's model predicts the greatest difference between the groups.

These apparent biases in model-predicted OS are likely to be symptomatic of poorly fitting parametric models, inappropriate assumptions regarding proportional hazards, assumptions regarding the proportion of events which are deaths and the equivalence of time-to-event outcomes between groups following the first progression event. Overall, the ERG did not have confidence in the model results.

3.2.1.5 Concerns regarding the nature of the comparison made within the company's secondary analysis

The secondary analysis compared *BRCAM* testing plus olaparib against no *BRCAM* testing and routine surveillance. However, the comparison that should have been made is *BRCAM* testing plus olaparib versus *BRCAM* testing plus routine surveillance; this was absent from the CS. Consequently, much of the apparent benefit of using olaparib suggested by the analysis is conflated with the benefits of *BRCAM* testing.

3.3 Additional work undertaken by the ERG

3.3.1 ERG exploratory analysis methods

The ERG replicated the IPD from the Study 19 *BRCAM* subgroup using methods reported by Guyot *et al* [37] and fitted multiple candidate survivor functions to: (i) TTD/D; (ii) TFST/D; (iii) RPSFTM-adjusted OS, and; (iv) CSE-adjusted OS. The analyses focussed on addressing two questions: (1) "What is the expected incremental OS gain for olaparib versus routine surveillance?" and (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 partitioned survival model in which parametric curves were fitted directly to the crossover-adjusted OS data. Uncertainty was explored across 108 combinations of candidate parametric functions.

3.3.2 Restricted mean survival

The most optimistic estimate of undiscounted incremental survival benefit for olaparib versus routine surveillance produced by the ERG's restricted means analysis was 0.68 life years; this is considerably lower than the 1.36 additional life years predicted by the company's model.

3.3.3 Partitioned survival model

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 (see Supplementary Appendix). This is markedly lower than the company's modelled estimate of 0.90 QALYs. Assuming that the company's estimated incremental costs of olaparib are reasonable, this implies that the ICER for olaparib versus routine surveillance is likely to be in excess of £92,214 per QALY gained, but may be considerably higher. Undiscounted OS in the placebo group was consistently greater than 2-years irrespective of the selected survivor function.

3.4 Conclusion of the ERG report

The ERG considered the evidence for olaparib for the maintenance treatment of *BRCA1/2m* PSR OC to be relatively weak and at relatively high risk of bias. The ERG did not consider the company's ICERs to be credible. Additional work undertaken by the ERG suggested that the ICER for olaparib versus routine surveillance is likely to be greater than £92,214 per QALY gained. On the basis of the ERG's exploratory analyses and the company's model-predicted OS for the routine surveillance group (approximately 30 months), olaparib does not appear to satisfy NICE's EoL criteria.

4. KEY METHODOLOGICAL ISSUES

Study 19 was subject to several methodological issues. The hypothesis that olaparib has superior efficacy in *BRCAm* patients compared with other patients had not, in the ERG's view, been robustly tested or proved and no Phase III trial was available to confirm results. Whilst the HR for PFS suggested a considerable treatment effect, administration of olaparib was not in accordance with its licence or with clinical practice in England, and outcomes were at risk of internal and external bias. The immaturity of OS data made it difficult to conclude whether PFS advantages would translate into improved survival. The ERG considered that the company's model did not handle competing risks of events or treatment crossover in an unbiased manner. The model appears to over-predict OS for olaparib and under-predict OS for routine surveillance. Directly modelling crossover-adjusted OS data from Study 19 indicated a markedly smaller incremental survival gain compared with the company's modelled predictions. Consequently, the ICER for olaparib is likely to be considerably higher than that suggested by the company's model.

5. NICE GUIDANCE

The Appraisal Committee reviewed the data available on the clinical and cost-effectiveness of olaparib, having considered evidence on the nature of recurrent OC and the value placed on the benefits of olaparib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources. The first ACD (published June 2015) did not recommend olaparib for the treatment of *BRCAm* PSR OC [22]. The Committee noted that substantial disagreement between the results from Study 19 and the model predictions undermined confidence in the company's model, that the model over-predicted the survival gains associated with olaparib, and that olaparib did not satisfy NICE's EoL criteria. The Committee considered that the company's secondary analysis did not produce a valid cost-effectiveness estimate.

Following the first ACD, the company submitted additional analyses, including further survival modelling using CSE-adjusted OS data [38]. Despite being based on similar data, the company's new survival models did not reflect those produced in the ERG's exploratory analyses; in one example, the company's OS estimate was almost double that estimated by the ERG. The ERG was concerned that the company's new survival models had been implemented incorrectly [4]. At the second ACD, the Committee was minded not to recommend olaparib for patients who have had 3 or more courses of platinum-based chemotherapy; within this subgroup, the Committee requested from the company a robust estimate of the cost-effectiveness of olaparib taking account of the cost of somatic testing and taking into account the Committee's concerns about its previous models. The company subsequently produced additional analyses for this subgroup, including the lower price for olaparib and a reduction in the number of cycles from which olaparib would be provided free of charge (15 rather than 18 cycles) [39]. The ERG remained concerned that the company's new modelled OS predictions in the third- and subsequent-line subgroup still did not reflect the observed Study 19 OS data [5]. However, the Committee concluded that within this subgroup, the most plausible ICER was approximately £46,600 to £46,800 per QALY gained and that there was sufficient evidence to suggest that olaparib satisfied NICE's EoL criteria [40].

In December 2015, NICE published its FAD which states that "olaparib is recommended within its marketing authorisation as an option for treating adults with PSR ovarian, fallopian tube or peritoneal cancer who have *BRCA1* or *BRCA2* mutations and whose disease has responded to platinum-based chemotherapy only if: they have had 3 or more courses of platinum-based chemotherapy, and; the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company" [40].

5.1 Consideration of clinical and cost-effectiveness issues

This section discusses the key issues considered by the Appraisal Committee. The full list can be found in the FAD [40].

5.1.1. Uncertainty surrounding validity of the *BRCA1/2* subgroup

The Committee noted that the key clinical effectiveness evidence was derived the Study 19 *BRCAm* subgroup. It also heard from the company that most of the trial population had been tested for *BRCAm* retrospectively. The Committee noted comments from the ERG that interaction tests between the *BRCAm* subgroup and the whole population were inconclusive, hence it was not possible to be certain that the treatment effect was different in the *BRCAm* subgroup. The Committee heard that there is a biologically plausible reason why people with *BRCAm* disease would benefit more from olaparib than the whole trial population, which could be explained by the relationship between malfunctioning *BRCA* genes and the development of HRD, and the subsequent effect on DNA repair. The Committee concluded that olaparib was clinically effective in the treatment of PSR OC and accepted that there is a biologically plausible reason for olaparib being particularly effective in the *BRCAm* subgroup.

5.1.2 Uncertainty surrounding the size of the treatment effect estimates

The Committee noted that olaparib was associated with statistically significant improvements in median PFS, TFST/D and TSST/D compared with placebo in the *BRCAm* subgroup and the whole trial population. The Committee concluded that whilst relevant, TFST/D and TSST/D had been identified *post hoc* and should be viewed with caution. It also noted that the OS data were immature and may have been confounded by crossover. The Committee noted that without adjustment, the difference between treatment groups in median OS in the *BRCAm* subgroup was 3 months (not statistically significant) but if crossover sites were excluded, this resulted in a statistically significant difference in median OS of 8.3 months. It concluded that there remained uncertainty about the extent to which olaparib increases OS compared with placebo in patients with *BRCAm* OC.

The Committee considered the company's further evidence relating to *BRCAm* patients in Study 19 who had received 3 or more lines of platinum-containing therapy. The Committee noted that this subgroup contained fewer patients than the total *BRCAm* subgroup and that there were imbalances in baseline characteristics, some of which potentially favoured placebo and others which potentially favoured olaparib. Nevertheless, the PFS benefit in this subgroup was 6.9 months (HR=0.11), and the median CSE-adjusted OS benefit was 12.3 months (HR=0.56). The Committee noted clinical experts' comments that a difference of this magnitude had never previously been seen in OC treatment. The Committee concluded that there was evidence of benefit for olaparib in patients who had received three or more lines of platinum-based chemotherapy.

5.1.3 Uncertainties relating to the cost-effectiveness of olaparib in the *BRCAm* subgroup

The Committee considered the company's model structure to be unconventional and very different to those used in previous appraisals. The Committee expressed concern that PFS data from Study 19 had

not been included, despite this being the primary outcome in Study 19. In addition, OS data had not been directly incorporated into the model. The Committee was concerned that intermediate outcomes had been used to make assumptions about longer-term OS, and considered that it would have been more conventional to fit a curve directly to the OS data, with adjustment for placebo group crossover. The Committee concluded that the company's model was a novel design that lacked external validity, and that the use of sequential intermediate outcomes to model OS relied on numerous assumptions that may not all be reasonable. It also noted that graphical plots of survival probabilities from the model showed that the difference between the curves for olaparib and placebo increased at later time points, implying OS benefits for olaparib increase over time. The Committee noted that no data were provided to support this and that greater separation of the curves over time would not be expected during treatment for cancer. The Committee also noted that the substantial disagreement between the results from Study 19 and the model predictions undermined confidence in the company's model. The Committee concluded that the company's modelling of benefit for the *BRCAM* subgroup overestimated the benefit of olaparib and therefore underestimated the ICER for olaparib.

5.1.4 Cost-effectiveness of olaparib in the third- and subsequent-line subgroup

The Committee considered the additional cost-effectiveness analyses provided by the company following the second ACD, which related to the subgroup of *BRCAM* patients who had received 3 or more lines of platinum-based chemotherapy. The Committee concluded that the company's 3 health-state (partitioned survival) model provided a better basis for decision-making than their original model. It noted that the ICERs in this subgroup varied according to the curve used to model OS and, although it considered that on visual inspection the Gompertz curve might be an option, it heard from the company that the log normal and log logistic curves provided the best fit to the data. The Committee accepted that this was not unreasonable and concluded that the most plausible ICERs were £46,600 to £46,800 per QALY gained. The Committee considered whether the EoL criteria would apply to third- and subsequent-line subgroup. It understood that median CSE-adjusted OS for this subgroup in the placebo arm of Study 19 was 20.6 months. The Committee was persuaded that the life expectancy of people who had received 3 or more lines of platinum-based chemotherapy was likely to be less than 24 months.

6. APPRAISAL COMMITTEE'S KEY CONCLUSION

The Committee concluded that in Study 19, olaparib increased PFS and time to subsequent therapy compared with placebo, in the whole trial population and in the *BRCAM* subgroup. It also concluded that there was uncertainty about whether, and to what extent, olaparib increases OS compared with placebo. The Committee concluded that the ICERs presented by the company for olaparib compared with routine surveillance for the overall population of patients with *BRCAM* PSR OC were considerably above the range normally considered to be a cost-effective use of NHS resources

(£20,000 to £30,000 per QALY gained). The Committee concluded that the EoL criteria did not apply to olaparib when considering the overall *BRCAm* PSR OC population. For the subgroup of patients with *BRCAm* PSR who have received 3 or more previous lines of platinum-based chemotherapy, the Committee accepted that the most plausible ICERs were £46,600 to £46,800 per QALY gained. The Committee concluded that there was sufficient evidence to suggest that olaparib met the EoL criteria for this subgroup.

ACKNOWLEDGEMENTS

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (Project No. 14/57/01). See the HTA programme website for further project information (<http://www.hta.ac.uk>). This summary of the ERG report was compiled after NICE issued the FAD. All authors have commented on the submitted manuscript and have given their approval for the final version to be published. The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

Paul Tappenden, Sue Harman, Shijie Ren, Praveen Thokala, Ruth Wong, Clara Mukuria, Clare Green, Simon Pledge and John Tidy declare no financial conflicts of interest.

Contributions made by each author

Sue Harman 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. Paul Tappenden acts as the guarantor of the manuscript.

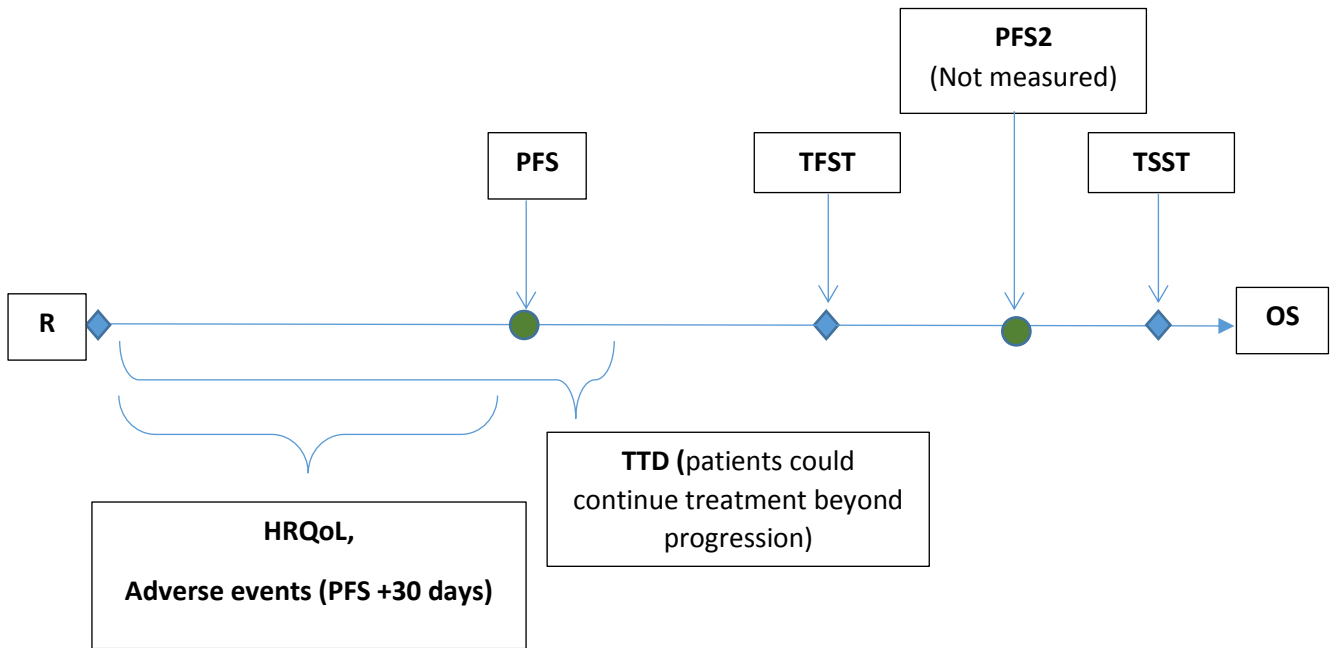
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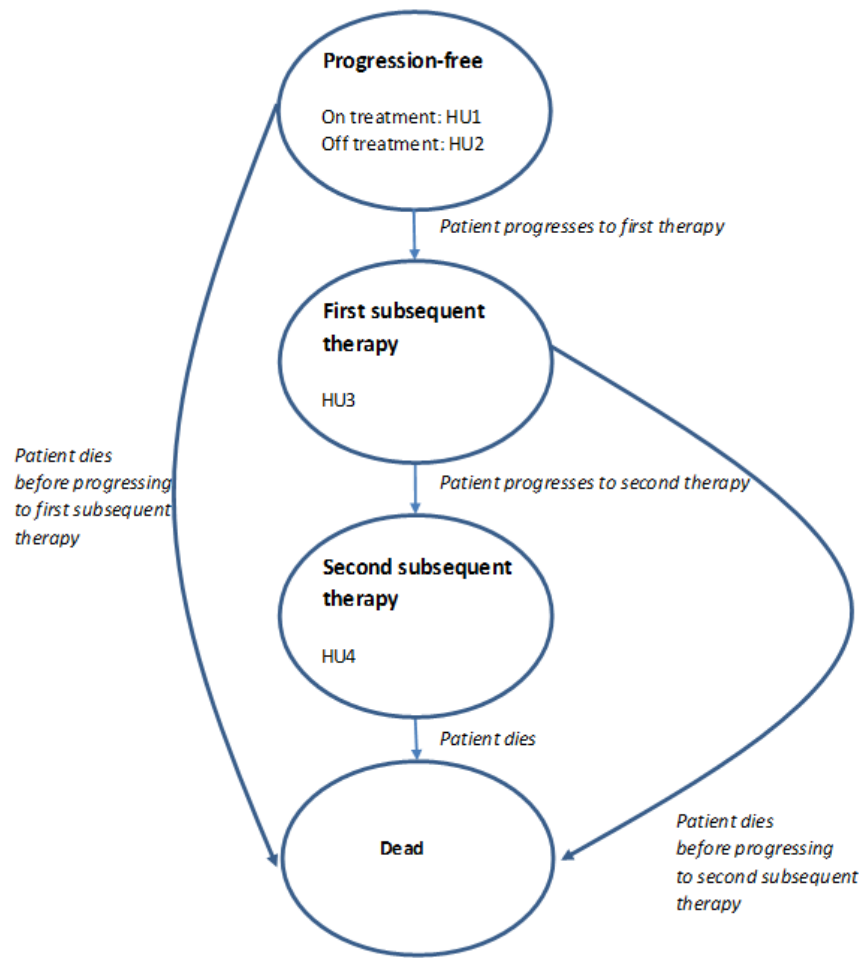
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Figure 1: Outcome measurement in Study 19



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.

Figure 2: Company's model structure



HU – health utility

Supplementary appendix: ERG exploratory analysis results – incremental QALY gains based on ERG’s partitioned survival 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
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

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	
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
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

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	
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