# Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy

STA REPORT

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**Title:** Rucaparib for maintenance treatment of recurrent platinum sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum base chemotherapy.

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

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

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| Abbreviation | In full |
|---|---|
| AE | Adverse event |
| AIC | Akaike information criterion |
| ASCO | American Society of Clinical Oncology |
| BIC | Bayesian information criterion |
| BICR | Blinded independent central review |
| BNF | British National Formulary |
| BRCA | breast cancer susceptibility gene |
| BRCAm | breast cancer susceptibility gene mutation |
| CA-125 | Cancer antigen 125 |
| CDF | Cancer Drugs Fund |
| CRD | Centre for Reviews and Dissemination |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CS | Company submission |
| DRS-P | Disease-related symptoms–physical |
| DSU | Decision support unit |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| eMIT | Electronic market information tool |
| EQ-5D | EuroQol 5-dimension Questionnaire |
| EQ-5D-3L | 3-level EuroQol 5-dimension Questionnaire |
| EQ-5D-5L | 5-level EuroQol 5-dimension Questionnaire |
| ERG | Evidence Review Group |
| ESMO | European Society for Medical Oncology |
| FIGO | International Federation of Gynaecology and Obstetrics |
| FOSI | FACT/NCCN Ovarian Symptom Index |
| HR | hazard ratio |
| HRQoL | Health-related quality of life |
| HSUV | Health state utility value |
| HTA | Health technology appraisal |
| ICER | Incremental cost effectiveness ratio |
| ISOQOL | International Society for Quality of Life Research |
| ISQOLS | International Society for Quality of Life Studies |
| ITT | Intention-to-treat |
| IVRS | Interactive voice response system |
| KM | Kaplan–Meier |
| Mg | Milligrams |
| NCCN | National Comprehensive Cancer Network |
| NICE | National Institute for Health and Care Excellence |
| OS | Overall survival |
| OWSA | One-way sensitivity analyses |
| PARP | poly-ADP-ribose polymerase |
| PAS | Patient access scheme |
| PFS | Progression-free survival |
| PFS2 | Time from randomisation to second progression or death |

| | |
|---|---|
| PH | Proportional hazards |
| PLDH | Pegylated liposomal doxorubicin hydrochloride |
| PR | partial response |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PSR OC | Platinum-sensitive relapsed ovarian cancer |
| QALY | Quality adjusted life year |
| RCT | Randomised controlled trial |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAE | Serious adverse event |
| SAS | Safety Analysis Set |
| SD | Standard deviation |
| SE | Standard error |
| SGO | Society of Gynecologic Oncology |
| SLR | Systematic literature review |
| SmPC | Summary of product characteristics |
| STA | Single Technology Appraisal |
| TFST | Time to first subsequent therapy |
| TOI | Trial Outcome Index |
| TSD | Technical Support Document |
| TTD | Time to treatment discontinuation |

# 1 EXECUTIVE SUMMARY

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

Direct evidence on comparative clinical effectiveness of maintenance treatment with rucaparib versus placebo for people with platinum-sensitive ovarian cancer, irrespective of breast cancer susceptibility gene mutation (BRCA) status, is derived from ARIEL3. Subgroups with or without BRCA mutations were listed in the final scope issued by the National Institute for Health and Care Excellence (NICE) as being of interest to the decision problem. ARIEL 3 enrolled those who had received at least two previous platinum-based chemotherapy regimens and achieved a complete or partial response to their last platinum-based regimen for ovarian cancer. Overall, the company's critique of the decision problem aligns with the final scope issued by NICE, with minor deviations in terms of:

- the population enrolled in ARIEL3 is slightly narrower than that specified in the decision problem (limited to high-grade ovarian cancer in ARIEL3 versus no such limitation in the final scope; discussed in Section 2.3.1);
- subgroups relevant to the decision problem and appropriate comparator (routine surveillance or olaparib; Section 2.3.3);
    - the company did not consider the subgroup without a BRCA mutation (non-BRCA) in the CS but provided analyses in response to a clarification request;
    - routine surveillance was presented as the comparator for the full population of ARIEL3 but not for the relevant subgroups of those of non-BRCA status and those with a BRCA mutation and receiving treatment in the second-line setting (BRCA 2L).
- immaturity of data for some outcomes of interest, in particular, overall survival (OS; Section 2.3.4).

## 1.2 Summary of the key issues in the clinical effectiveness evidence

Considering the data from which estimates of effect for rucaparib as a maintenance treatment versus routine surveillance are derived, the Evidence Review Group's (ERG's) key reservations around the evidence are in the areas of:

- estimates of effect in populations of interest to the decision problem (non-BRCA, BRCA 2L and BRCA 3L+) are generated from subgroups of the full trial population of ARIEL3, with accompanying potential weaknesses;

    - imbalances in baseline characteristics between treatment groups and small patient numbers for some subgroups (Section 3.2.1);

    - the BRCA 2L and BRCA 3L+ subgroups were not pre-specified in ARIEL3 and, as such, analyses for these groups are *post hoc* (Section 3.2.3).

- immaturity of data for some outcomes (e.g., OS) and exploratory nature of others (Sections 3.2.2, 3.3.2 and 3.3.3);

- lack of clarity for some aspects of the statistical analysis based on an ordered stepwise multiple comparison (Section 3.2.4), including pre-specification of anticipated direction of effect for quality of life measures.

Direct evidence comparing rucaparib with olaparib for the BRCA 3L+ population is not available, and, therefore, the company carried out various indirect treatment comparisons (ITC), including a network meta-analysis (NMA) and matching-adjusted indirect comparisons (MAIC). Factors that the ERG considers it important to highlight for consideration are:

- comparability of ARIEL3 and identified studies (SOLO2 and Study 19) evaluating olaparib versus routine surveillance and informing the ITCs, including trial design, differences in baseline characteristics and formulation of olaparib used (in particular, Sections 3.4.1, 3.4.2, and 3.4.5);

    - For the primary outcome of PFS, the point estimate for rucaparib versus olaparib was greatly influenced by the data source informing the outcome for patients on olaparib: when using Study 19, PFS favours olaparib over rucaparib, which contrasts with the direction of effect when using SOLO2 to inform the analyses.

    - The ERG considers Study 19 to be a more appropriate source of olaparib data than SOLO2 as Study 19 assesses the efficacy and safety of olaparib capsules, which is the formulation currently recommended for routine commissioning, and reports data that informs the long-term outcomes of PARPi maintenance therapy and of routine surveillance.

- methods underpinning the ITCs:

    - assumption that proportional hazards (PHs) holds for all studies (Section 3.5.1);

        - the ERG agrees with the company that there is limited evidence refuting the PH assumption, but the ERG considers it a strong assumption to assume that PH do hold, especially for relevant *post hoc* subgroups.

    - appropriateness of NMA and MAIC (Sections 3.5.2 and 3.5.3);

        - a MAIC was carried out because of differences in potential treatment effect modifiers within and between ARIEL 3, SOLO2 and Study 19, which could affect the validity of the NMA. NMA and anchored MAIC generate similar results.

        - adjustment for treatment effect modifiers and prognostic factors in MAIC (Section 3.5.3.1). The ERG does not consider that it has been shown that a MAIC adjusting for relevant factors would lead to a less biased estimate than a more standard NMA approach.

## *1.3 Summary of the key issues in the cost effectiveness evidence*

The ERG considers the key issues with the cost-effectiveness analyses are as follows:

- The NICE final scope states that, "If the evidence allows, consideration will be given to subgroups with or without BRCA mutations". At clarification, the company provided subgroup analyses by BRCA status, but maintain the most relevant populations to consider are the ITT and BRCA3L+ populations (Section 4.2.2 and 4.2.5.1). The company argue that BRCA status (except for the case of BRCA3L+ patients) does not guide treatment decisions. However, the ERG considers that:

    - The ARIEL3 ITT population includes BRCA3L+ patients that would receive olaparib in UK clinical practice (and as such routine surveillance is not a relevant comparator),

    - clinical evidence (including evidence provided in the company clarification response) indicates that BRCA patients receiving PARPis experience better clinical outcomes than non-BRCA patients on PARPis and this has an influential effect on the cost-effectiveness of treatments.

    As such, the ERG considers the most relevant populations for the decision problem are the non-BRCA, BRCA2L and BRCA3L+ analyses provided by the company.

- Due to the lack of mature OS data from ARIEL3, the company has used Study 19 OS data for the cost-effectiveness analysis (Section 4.2.5.1). The company has assumed, based on an

interpretation of the ITC analysis, that rucaparib and olaparib can be considered clinically equivalent and have implemented this assumption for the BRCA3L+ subgroup analyses, producing a cost-minimisation analysis. However, the ITC produced inconsistent results, depending on the source data used for olaparib and as such no robust conclusions can be made about the relative efficacy of rucaparib compared with olaparib. However, based on the ERG's preference for Study 19 for the ITC, a cost minimisation analyses is likely to be a best-case scenario for rucaparib compared with olaparib.

- The company's approach to estimating post-progression survival (PPS) is calculating the residual of OS and PFS from Study 19, rather than the residual of Study 19 OS and ARIEL3 PFS, which is preferred by the ERG (Section 4.2.5.1). The company's approach disconnects the PFS (ARIEL3) used to inform the model from PPS. The company's justification for the approach is that, based on what the ERG assumes is a naïve comparison, PFS is longer in ARIEL3 than in Study 19 and as such, PPS is likely to be different, contradicting their earlier claim that outcomes for rucaparib and olaparib would be the same if directly compared in the same trial. The company's approach results in an implied PFS to OS ratio of [redacted]. The committee for the appraisals of niraparib (TA528) and olaparib (GID1296) stated that a ratio of 1:2 is an optimistic assumption. The ERG's preferred approach results in an implied PFS to OS ratio of between 1:1 (considered conservative by the committee for the appraisals of niraparib [TA528] and olaparib [GID1296]) and 1:2.

- Aside from the issues of OS data and the implementation of it in the model, there were several other modelling assumptions the ERG changed when developing the ERG base case, presented in Section 1.4. However, it should be noted that the company's base case and the ERG base case result in ICERs for the ITT, non-BRCA and BRCA2L populations which exceed the NICE cost-effectiveness threshold of £20,000 to £30,000. For the BRCA3L+ population, rucaparib is [redacted] than olaparib, [redacted]. Moreover, until mature OS data are available from ARIEL3, the estimated ICERs are subject to a high degree of uncertainty.

## *1.4 Summary of the ERG's preferred assumptions and resulting ICER*

The ERG's preferred assumptions for the cost-effectiveness analysis of rucaparib compared with routine surveillance (ITT, non-BRCA and BRCA2L populations) and olaparib (BRCA3L+ populations) are outlined in Table 1.

Table 1. ERG preferred assumptions

| Assumption | Population | | | |
|---|---|---|---|---|
| | ITT | Non-BRCA | BRCA2L | BRCA3L+ |
| Using the lognormal distribution for PFS for the non-BRCA population | | X | | |
| Using the Weibull distribution for PFS for the BRCA2L population | | | X | |
| Post-progression survival modelled as the residual of ARIEL3 PFS and Study 19 OS | X | X | X | |
| Use of subsequent therapy proportions from Study 19 | X | X | X | |
| PFS off maintenance costs for routine surveillance | X | X | X | |
| Removal of oral therapy administration costs | X | X | X | X |
| Extension of time horizon to 50 years | X | X | X | |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.

Table 2. ICER resulting from ERG's preferred assumptions

| | Total costs | Total QALYs | Δ costs | Δ QALYs | ICER £/QALY |
|---|---|---|---|---|---|
| **ITT Population** | | | | | |
| Routine surveillance | [redacted] | [redacted] | - | - | - |
| Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | £58,399 |
| **Non-BRCA Population** | | | | | |
| Routine surveillance | [redacted] | [redacted] | - | - | - |
| Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | £50,548 |
| **BRCA2L Population** | | | | | |
| Routine surveillance | [redacted] | [redacted] | - | - | - |
| Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | £58,097 |
| **BRCA3L+ Population** | | | | | |
| Olaparib | [redacted] | [redacted] | - | - | - |
| Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | Rucaparib dominated |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.

## 1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Table 3 to Table 5 presents the ERG's exploratory analyses for the ITT, non-BRCA and BRCA2L populations.

Table 3. Exploratory analyses undertaken by ERG – ITT population

| Scenario | Section in main ERG report | Rucaparib | | Routine surveillance | | ICER £/QALY |
|---|---|---|---|---|---|---|
| | | Costs | QALYs | Costs | QALYs | |
| Corrected company base case | 6.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£53,179** |
| Subsequent therapy proportions from Study 19 | 4.2.8.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£52,979** |

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

Table 4. Exploratory analyses undertaken by ERG – nonBRCA population

| Scenario | Section in main ERG report | Rucaparib | | Routine surveillance | | ICER £/QALY |
|---|---|---|---|---|---|---|
| | | Costs | QALYs | Costs | QALYs | |
| Corrected company base case | 6.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£35,228** |
| Lognormal distribution for PFS | 4.2.5.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£42,614** |
| Subsequent therapy proportions from Study 19 | 4.2.8.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£40,981** |
| Time horizon of 50 years | 4.2.4.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£32,359** |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ICER, incremental cost effectiveness ratio; PFS, progression-free survival; QALYs, quality adjusted life years

Table 5. Exploratory analyses undertaken by ERG – BRCA2L population

| Scenario | Section in main ERG report | Rucaparib | | Routine surveillance | | ICER £/QALY |
|---|---|---|---|---|---|---|
| | | Costs | QALYs | Costs | QALYs | |
| Corrected company base case | 6.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£59,236** |
| Weibull distribution for PFS | 4.2.5.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£53,870** |
| Subsequent therapy proportions from Study 19 | 4.2.8.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£59,929** |
| Time horizon of 50 years | 4.2.4.1 | [redacted] | [redacted] | [redacted] | [redacted] | **£56,269** |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ICER, incremental cost effectiveness ratio; PFS, progression-free survival; QALYs, quality adjusted life years

# 2 INTRODUCTION AND BACKGROUND

## 2.1 Introduction

The company producing rucaparib (Rubraca®; Clovis Oncology) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of rucaparib as a maintenance therapy for recurrent, platinum-sensitive ovarian cancer that has responded to last round of treatment. Specifically, evidence on comparative clinical effectiveness versus placebo is presented for those who have received at least two previous platinum-based chemotherapy regimens and achieved a complete or partial response to their last platinum-based regimen. Herein is a critique of the company's submission (CS) to the Single Technology Appraisal (STA), together with supplementary information, where necessary, provided by the company during the clarification process.

## 2.2 Background

Within Section B.1 of the CS, the company provides an overview of:

- rucaparib, including its mode of action, dose and method of administration (Section B.1.2);
- ovarian cancer, including types of ovarian cancer, prevalence, prognosis and disease management (Section B.1.3).

The ERG considers the CS to present accurate overviews of rucaparib and ovarian cancer that are relevant to the decision problem. Additionally, based on advice from its clinical experts, the ERG considers the CS to provide an accurate description of the current treatment algorithm for the management of people with recurrent ovarian cancer, as depicted in Figure 1.

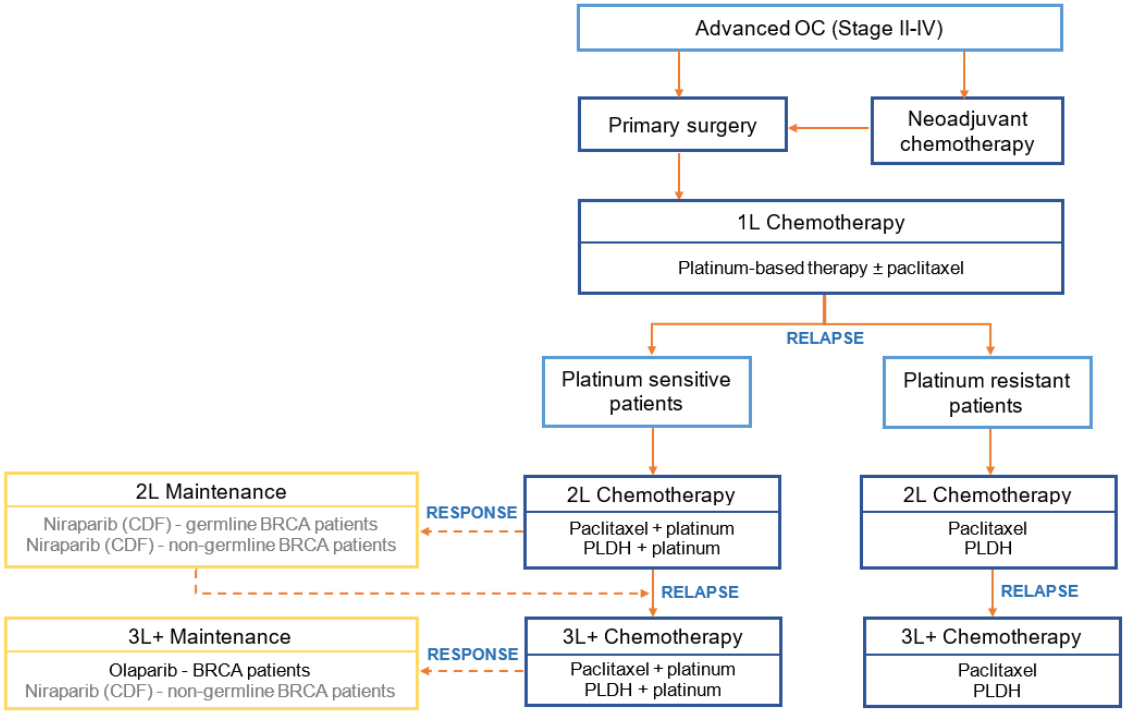
Rucaparib is positioned as an option for maintenance of response to last treatment for people with platinum-sensitive ovarian cancer and who have received two or more prior platinum-based regimens, irrespective of BRCA status. The ERG and its clinical experts consider the proposed position of rucaparib in the treatment pathway to be appropriate. Thus, if recommended by NICE, rucaparib would be placed as a treatment option (Figure 1):

- after two prior lines of platinum-based chemotherapy alongside niraparib, which is currently only available through the cancer drugs fund (CDF) and not through routine commissioning;

and

- after three prior lines of platinum-based chemotherapy alongside niraparib for people without a germline BRCA mutation and alongside olaparib for people with a BRCA mutation.

Figure 1. Clinical pathway of care for advanced ovarian cancer in NHS, England (reproduced from the CS, page 16, Figure 1)




Abbreviations: 1L, first-line; 2L, second-line; 3L+, third- or later-line; BRCA, breast cancer gene; CDF, Cancer Drugs Fund; OC, ovarian cancer; PLDH, pegylated liposomal doxorubicin hydrochloride.
Notes: Bevacizumab-based therapy has also been appraised in the first- and later-line treatment setting but is not recommended within its marketing authorisation for OC indications by NICE.
Source: adapted from the NICE pathway for ovarian cancer.

## *2.3 Critique of company's definition of decision problem*

Table 6. The decision problem (adapted from Table 1, CS pages 8–9)

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | ERG comments |
|---|---|---|---|---|
| **Population** | People with recurrent platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer that is in response (complete or partial) to platinum-based chemotherapy. | People with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. | Aligned to marketing authorisation | Appropriate |
| **Intervention** | •Rucaparib (Rubraca®) | •Rucaparib | Not applicable | Not applicable |
| **Comparator (s)** | •Routine surveillance<br>For people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy:<br>•Olaparib (Lynparza®) (subject to ongoing appraisal) | •Routine surveillance<br>For people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy:<br>•Olaparib (subject to ongoing appraisal) | Not applicable | In the CS routine surveillance was presented as the comparator for the full population but not for the subgroups of people who can't receive olaparib, i.e. non-BRCA and BRCA 2L |
| **Outcomes** | The outcome measures to be considered include:<br>•Overall survival<br>•Progression-free survival<br>•Progression-free survival 2 (that is, progression-free survival on next line of therapy)<br>•Time to next line of therapy<br>•Adverse effects of treatment<br>•Health-related quality of life | The outcome measures to be considered include:<br>•Overall survival<br>•Progression-free survival<br>•Progression-free survival 2 (that is, progression-free survival on next line of therapy)<br>•Time to next line of therapy<br>•Adverse effects of treatment<br>•Health-related quality of life | Not applicable | All relevant outcomes captured and reported although data for OS and PFS2 were immature. The OS in the economic model therefore relies on OS from the trial of olaparib capsules, Study 19. Assuming equivalent OS for rucaparib and olaparib. |
| **Economic analysis** | The reference case stipulates the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>The reference case stipulates the time horizon for estimating clinical and cost effectiveness should be sufficiently long to | Incremental cost per QALY gained analysis | Not applicable | Not applicable |

| | | | | |
|---|---|---|---|---|
| | reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.<br>The economic modelling should include the cost associated with diagnostic testing in people with platinum-sensitive ovarian, fallopian tube, and peritoneal cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. | | | |
| **Subgroups to be considered** | If the evidence allows, consideration will be given to subgroups with or without BRCA mutations. | Consideration is given to subgroups with or without BRCA mutation, as relevant to the decision problem. | Not applicable | The company did not consider the subgroup without a BRCA mutation (non-BRCA) in the CS but addressed it in response to a clarification request |
| Abbreviations: BRCA, breast cancer gene; CHMP, Committee for Medicinal Products for Human Use; CS, company submission; NHS, National Health Service; NICE, National Institute for Health and Care Excellence. | | | | |

### 2.3.1 Population

Clinical effectiveness data for rucaparib are derived from the ARIEL3 trial, which enrolled adults with platinum sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer.[1] Patients had to have received at least two prior platinum-based therapies and to be in response (complete or partial) to the most recent platinum-based chemotherapy. The trial population of ARIEL3, which is limited to high-grade ovarian cancer, is consistent with the population as specified in the marketing authorisation of rucaparib but narrower than that set out in the NICE final scope (not limited to high-grade ovarian cancer).[2] The ERG considers this appropriate as people with high-grade ovarian cancer are more likely to harbour a BRCA mutation or homologous recombination repair deficiency (HRD) and therefore likely to respond better to PARPi.

A relatively small proportion of the ARIEL3 trial population ([redacted]) were enrolled and treated in the UK, although the ERG's clinical experts consider the full trial population largely representative of people in England eligible for rucaparib maintenance treatment. However, as is often the case in clinical trials, patients were slightly younger and had a better performance status in ARIEL3 than can be expected in UK clinical practice. In addition, the proportion of patients in ARIEL3 who had received prior bevacizumab was higher and a larger proportion of patients had a BRCA mutation than would be seen in the equivalent patient group in England.

BRCA status was specified as a subgroup of interest in the NICE final scope. The company presented data for the BRCA subgroup, HRD cohort and ITT population of ARIEL3, as well as the BRCA 3L+ subgroup. In response to a clarification request the company also presented data for the non-BRCA and BRCA 2L subgroups, which are of relevance to this appraisal. The ERG highlights that the BRCA and non-BRCA subgroups were stratified but that BRCA 2L and BRCA 3L+ were non-stratified, *post-hoc* subgroups.

### 2.3.2 Intervention

Rucaparib, brand name Rubraca©, is a poly-ADP (adenosine diphosphate) ribose polymerase inhibitor (PARPi). The mechanism of action for PARPi involves blocking DNA repair in which PARP enzymes identify and repair single strand DNA damage. Inhibiting the PARP pathway allows DNA damage to accumulate and limits the options for DNA repair, ultimately resulting in tumour cell death.[3] This mechanism is particularly effective when other DNA repair mechanism deficiencies are present, such as in patients with high grade serous ovarian cancer in whom HRD and BRCA mutations are more common.

The company first received marketing authorisation for rucaparib treatment from the European Medicines Agency (EMA) in May 2018. The marketing authorisation for rucaparib was expanded in January 2019 to include maintenance therapy.

### 2.3.3 Comparators

Currently, the only maintenance treatment for ovarian cancer recommended for routine commissioning by NICE is the capsule formulation of olaparib, which is limited to patients with a BRCA mutation and who have had at least three prior platinum-based therapies. Niraparib, another PARP inhibitor, is available via the CDF, as an option for maintenance treatment of patients with platinum-sensitive relapsed high-grade serous ovarian cancer, with a germline BRCA mutation who have received two courses of platinum-based chemotherapy, and in patients without a germline BRCA mutation who have received two or more courses of platinum-based chemotherapy. As niraparib is not available for routine commissioning, and is not currently considered standard care in clinical practice, it is not a comparator of interest for this appraisal. Thus, olaparib is the only relevant active comparator and then only for the BRCA 3L+ subgroup. For patients without a BRCA mutation (non-BRCA) or with a BRCA mutation and two prior platinum-based therapies (BRCA 2L) the comparator of interest is routine surveillance.

The comparator in ARIEL3 was rucaparib-matched placebo, which is considered comparable to routine surveillance in clinical practice. The company initially presented data for rucaparib versus routine surveillance (placebo) in the trial ITT population; however, at the clarification stage the company also provided data for this comparison in the non-BRCA and BRCA 2L populations. For the comparison with olaparib in the BRCA 3L+ population, the company carried out several different indirect treatment comparisons with ARIEL3 and the olaparib trials Study 19[4, 5] and SOLO2.[6]

### 2.3.4 Outcomes

All the outcomes listed in the NICE final scope were captured and reported in ARIEL3, although data for OS and PFS2 were immature. OS in the economic model therefore relies on OS from the olaparib trial Study 19, assuming a class effect with equivalent OS for rucaparib and olaparib. Time to next line of therapy was captured as time to first and second subsequent therapy (TFST and TSST) and health-related quality of life (HRQoL) captured as Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18 (FOSI-18) and European Profile of Quality of Life 5 dimensions (EQ-5D).

# 3 CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of rucaparib as a maintenance therapy for recurrent, platinum-sensitive ovarian cancer that has responded to last round of treatment. The Evidence Review Group (ERG) has critiqued the details provided on:

- methods implemented to identify, screen and data extract relevant evidence;
- clinical efficacy of rucaparib;
- safety profile of rucaparib;
- assessment of comparative clinical effectiveness of rucaparib against relevant comparators.

A detailed description of an aspect of the company submission (CS) is provided only when the ERG disagrees with the company's assessment or proposal, or where the ERG has identified a potential area of concern that the ERG considers necessary to highlight for the Committee.

## *3.1 Critique of the methods of review(s)*

The company undertook a broad systematic review with the objective of identifying randomised controlled trials (RCTs) assessing the clinical effectiveness of rucaparib and comparator interventions as maintenance treatments in people with locally advanced or metastatic ovarian cancer or fallopian tube or primary peritoneal carcinomas who had received two or more prior lines of chemotherapy. One study providing direct evidence on the clinical effectiveness of rucaparib versus placebo (considered equivalent to routine surveillance) and relevant to the decision problem was identified (ARIEL3).[1] Overall, the ERG found the company's systematic literature review to be of reasonable quality and likely to have identified all relevant studies, despite limiting inclusion to English-language publications: a summary of the ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem is presented in Table 7.

Table 7. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

| Systematic review step | Section of CS in which methods are reported | ERG assessment of robustness of methods |
|---|---|---|
| Searches | Appendix D.1 (page 4) | Appropriate |
| Inclusion criteria | Appendix D.1, Table 4 (pages 9–10) | Broader than required for the decision problem: clear explanation in CS of rationale for broad scope, and details provided of studies included in the literature review and |

| | | |
|---|---|---|
| | | subsequently excluded due to non-relevance to the decision problem<br>Limited to English-language publications |
| Screening | Appendix D.1 (page 10) | Appropriate |
| Data extraction | Appendix D.1 (page 11) | Appropriate |
| Tool for quality assessment of included study or studies | Section B.2.5 (page 45) and Appendix D.3, Table 22 (pages 65–66) | Appropriate |
| Abbreviations: CS, company submission; ERG, Evidence Review Group. | | |

## *3.2 Critique of trials of the technology of interest*

The ERG agrees with the company's assessment of ARIEL3[1] as being at overall low risk of bias for analysis of PFS, based on the full trial population. However, the ERG considers it important to note that the populations relevant to the decision problem are subgroups of the trial population, and, for reasons outlined in greater detail below, results for the subgroups are at a higher risk of bias than those reported for the full population. The ERG's critique of the design and conduct, and internal and external validity, of ARIEL3 is summarised in Table 8. A summary of the company's and the ERG's quality assessment of ARIEL3 can be found in Appendix 9.1.

Table 8. Summary of ERG's critique of the design and conduct of ARIEL3, the trial evaluating the technology of interest to the decision problem

| Aspect of trial design or conduct | Section of CS in which characteristic is reported | ERG's critique |
|---|---|---|
| Randomisation | Section B.2.3 (page 22)<br>Appendix D.3, Table 22 (pages 65–66) | Appropriate<br>People randomised 2:1 to rucaparib:placebo<br>Randomisation stratified by: HRD classification, platinum-free interval, and response to prior therapy. |
| Concealment of treatment allocation | Section B.2.3 (page 22) | Appropriate |
| Baseline characteristics | Section B.2.3, Table 6 (pages 35–37) | Baseline characteristics in the ITT population were well balanced between the two groups.<br>Minor imbalances between groups were noted for the BRCA 2L and BRCA 3L+ subgroups (Section 3.2.1). |
| Masking appropriate | Appendix D.3, Table 22 (pages 65–66) | Appropriate<br>Patients and investigators masked to treatment allocation throughout the study. |
| No difference between groups in treatments given, other than rucaparib and placebo | Section B.2.3, Table 5 (pages 25–32) | No evidence to suggest that standard of care differed across countries or between groups.<br>However, as noted by the company, a proportion of patients primarily in the placebo group went on to receive PARPi treatment post-progression, which potentially confounds analysis of long-term outcomes such as overall survival (Section 3.2.2). |
| Dropouts (high drop out and any unexpected imbalance between groups) | Appendix D.3, Table 22 (pages 65–66) | Low rate of withdrawal from study (3 people withdrew from the rucaparib group). |
| Outcomes assessed | Section B.2.3, Table 5 (pages 25–32)<br>Appendix D.3, Table 22 (pages 65–66) | All clinically relevant outcomes assessed. No evidence to suggest that additional outcomes were assessed and not reported.<br>Primary outcome PFS as assessed by the investigator. Analysis of PFS by BICR reported as a secondary outcome.<br>HRQoL was assessed by FOSI-18, a symptom questionnaire specific to ovarian cancer.<br>Several outcomes of the specified in the NICE final scope were exploratory outcomes in ARIEL3.<br>Additional information regarding outcome assessment and the ERG's preferred analysis are discussed below (Section 3.2.2). |
| ITT analysis carried out | Section B.2.6 (page 46) | ITT analysis were reported for all efficacy outcomes, however, the main population of interest to this appraisal are the non-BRCA subgroup and the *post-hoc* subgroups, BRCA 2L and BRCA 3L+. |

| | | |
|---|---|---|
| Subgroup analyses | Section B.2.3, Table 5 (pages 25–32) | Pre-planned subgroup analyses were carried out based on stratification factors and baseline demographic characteristics.<br>Relevance of HRD cohort and ERG's concerns around relevant subgroup analyses discussed in greater detail in the main body of the report (Section 3.2.3). |
| Statistical analysis plan | | |
| • Sample size | Section B.2.4, Table 7 (pages 43–44) | Based on assumptions of treatment effect on PFS in the three patient cohorts forming the stepdown multiple comparison, including a pre-specified range of patients with a BRCA mutation. |
| • Power | Section B.2.4, Table 7 (pages 43–44) | Sample size gives study 90% power to detect a statistically significant difference between rucaparib and placebo at a one-sided α of 0.025. |
| • Analysis for estimate of effect | Section B.2.4, Table 7 (pages 43–44) | PFS was assessed among the BRCA cohort, HRD cohort, and ITT population using an ordered stepdown multiple comparison procedure. Other outcomes assessed in the three cohorts and forming part of the multiple comparison were FOSI-18 DRS-P, FOSI-18 total score, and OS (Section 3.2.4). |
| Evidence synthesis: standard pair-wise meta-analysis | Not applicable | Not applicable. |

Abbreviations: BICR, blinded independent central radiology review; CS, company submission; DRS-P, disease-related symptoms–physical; ERG, Evidence Review Group; FOSI-18, Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18; HRD, homologous recombination deficiency; ITT, intention to treat; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival; OS, overall survival.

### 3.2.1 Baseline characteristics

The baseline characteristics of patients in the ITT population, and the three relevant subgroups (BRCA 2L, BRCA 3L+, and non-BRCA) of ARIEL3, as well as for patients in the trial enrolled in the UK, are presented in Appendix 9.2.

Patient characteristics of the ITT population and the non-BRCA subgroup were well balanced within ARIEL3. For the BRCA 2L and BRCA 3L+ subgroups, there were some imbalances between the treatment arms in the baseline characteristics reflecting their *post hoc* nature, as well as the small sample sizes. There was no consistent direction in terms of the potential bias due to these differences.

The baseline characteristics of the UK cohort of ARIEL3 are similar to the ITT population, with the exception of "best response to prior therapy", defined as best response (partial or complete response) to platinum-based regimen received immediately prior to initiation of maintenance therapy. The UK cohort has a smaller proportion of patients with a complete response compared with the full trial population. This may reflect worse outcomes seen in ovarian cancer patients in the UK compared with other European countries.[7]

Enrolment in ARIEL3 was limited to ensure that any observed treatment benefits were not driven by patients in whom the largest effect size was expected, such that:

- No less than 33% and no more than 37% of patients enrolled were to harbour BRCA mutations;
- No more than 28% of patients enrolled were to harbour germline BRCA mutations.

This is why the proportion of patients with a BRCA mutation is higher in the trial than would be expected in clinical practice (~20% in clinical practice).[8] Additionally, as mentioned in Section 2.3.1, the population in the study is younger and with a better performance status than people typically presenting with advanced ovarian cancer in UK clinical practice.

### 3.2.2 Outcomes assessment

The primary outcome in ARIEL3 was investigator-assessed PFS (PFS-INV). Patients were assessed for disease progression according to RECIST v1.1 every 12 weeks, until disease progression or death. Measurement of CA-125 was performed every third cycle, at discontinuation of treatment, and as clinically indicated. PFS was also assessed by blinded independent central review (PFS-BICR) and analysed as a sensitivity analysis. Although BICR in general has a lower risk of bias than investigator assessment, it was done retrospectively in ARIEL3, whereas investigator assessment was done continuously and the decision to discontinue treatment was made by the investigators. BICR is therefore likely to be confounded by informative censoring, which may bias the PFS-BICR result. The ERG

therefore considers investigator assessed progression to be less confounded and more reflective of clinical practice.

Health-related quality of life (HRQoL) was captured using FOSI-18, which is composed of 18 items covering four sub-scales: emotional and functional wellbeing, symptoms and treatment-related side effects. It is a subset of items in the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire, which is a validated quality of life assessment for people with ovarian cancer.[9] Time to worsening in the disease-related symptoms-physical (DRS-P) subscale and in the total score of the FOSI-18 were predefined as secondary endpoints in ARIEL3. Worsening was defined as at least a 4 unit decrease on the DRS-P subscale and an 8 unit or greater decrease on the total score.

PFS2, TFST, TSST and HRQoL as assessed by EQ-5D are all exploratory rather than secondary outcomes in ARIEL3. The ERG highlights that the results of the exploratory outcomes should be hypothesis generating rather than hypothesis testing.[10] The ERG also notes a discrepancy in the definition of PFS2 between the CS (time from initial disease progression to the next event of disease progression or death) and the CSR (time from randomisation to the second event of disease progression or death). The ERG considers it most likely that the CSR definition of PFS2 is correct.

At the date of the primary analysis database lock (15 April 2017) data maturity had reached 50% for PFS and TFST but not for PFS2, TSST and OS. In the CS, there is no mention of whether crossover from placebo to rucaparib was allowed within the trial; however, a large proportion of patients, primarily in the placebo group ([redacted]), received subsequent treatment with a PARPi outside of the trial. As highlighted by the company, unplanned crossover could confound data for the long-term outcomes PFS2, TSST and OS. The ERG notes that this would likely lead to an underestimate of the relative efficacy of rucaparib compared with placebo. However, in clinical practice subsequent PARPi therapy with olaparib is available through routine commissioning for the subgroup of patients with a BRCA mutation and the trial data may therefore provide a reasonable estimate of the efficacy of rucaparib relative to routine surveillance as used in clinical practice for this subgroup. Although data for these outcomes are currently immature, the substantial crossover needs to be considered when mature data do become available.

### 3.2.3 Subgroup analyses

Patients enrolled in ARIEL3 were stratified at the time of randomisation by HRD status (mutation in BRCA1 or BRCA2, mutation in a non-BRCA gene associated with homologous recombination, or no mutation in BRCA or a homologous recombination gene) using a clinical trial assay (CTA): CTA determines HRD status by identifying mutations in 30 genes involved in HRD. The subgroup of patients with a BRCA mutation included people with germline, somatic, and BRCA status unknown. BRCA wild-type patients included people without a BRCA mutation but with or without HRD. The results of

the CTA in the intention-to treat (ITT) population, were used to categorise patients into pre-specified nested cohorts for the efficacy analysis (Figure 2):

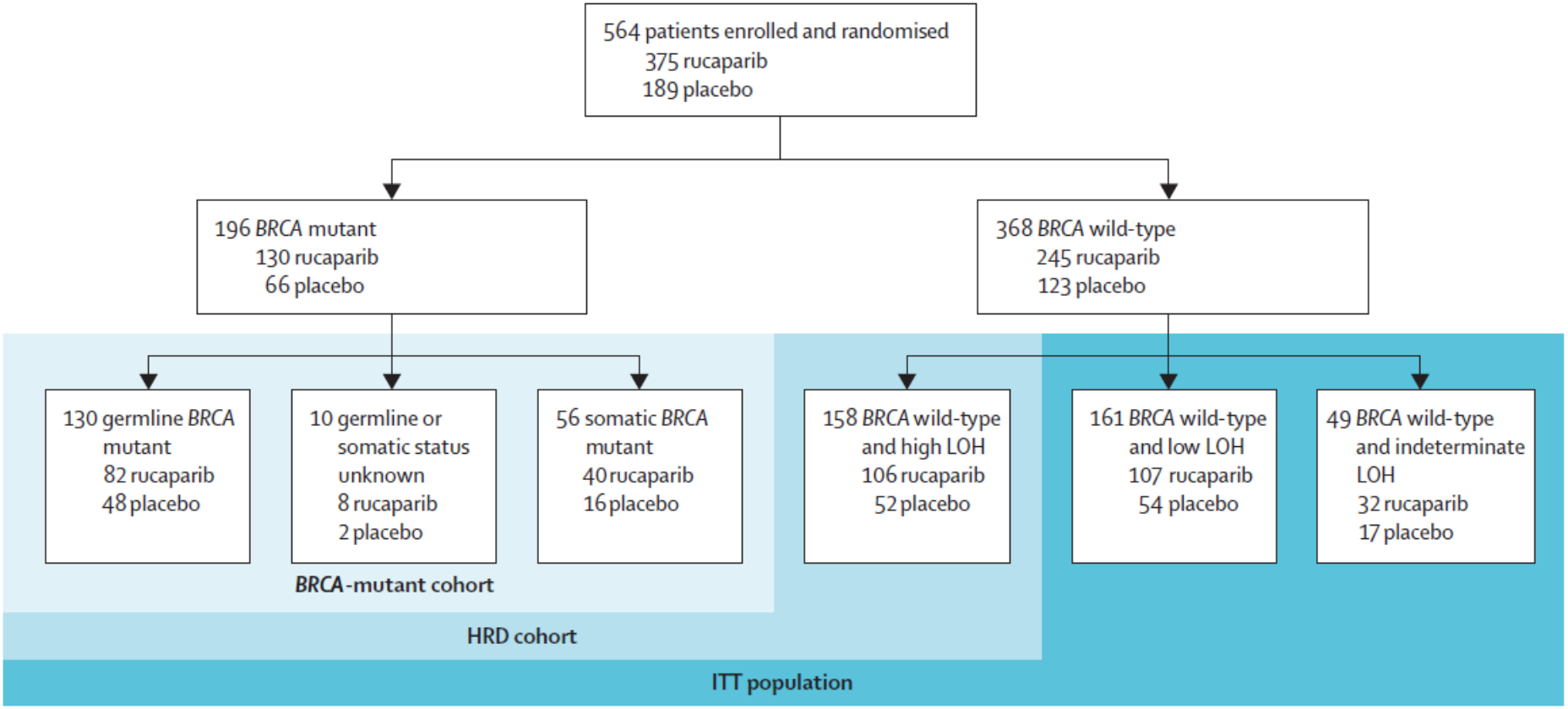
- ITT: all randomised patients;
- HRD cohort: all BRCA mutant patients (germline, somatic, germline/somatic status unknown) and BRCA wild-type with a high loss of heterozygosity (LOH), which is a proposed marker of HRD;
- BRCA mutant cohort: all BRCA mutant patients (germline, somatic, germline/somatic status unknown).

The primary and key secondary outcomes were analysed in the BRCA cohort, HRD cohort, and ITT population, using an ordered stepdown multiple comparisons procedure, described in Section 3.2.4.

As the company highlights, genetic testing for germline BRCA is widely established in England, the outcome of which has an impact on prognosis as well as treatment options available. At the moment, only patients with a confirmed BRCA mutation can receive olaparib maintenance treatment if they have had three prior lines of platinum-based therapy. However, somatic BRCA testing is not widely available in England and therefore the non-BRCA subgroup of ARIEL3, which includes no somatic or germline BRCA, is slightly different from non-BRCA in clinical practice, which includes BRCA wildtype as well as somatic BRCA.

As mentioned in Section 2.3.1, a high proportion of people with high-grade serous ovarian cancer carry genetic mutations such as HRD, which includes mutations of BRCA, and are therefore likely to respond better to PARPi. Genetic testing of HRD status is currently not routinely used in UK clinical practice as the accuracy of currently available tests has not been validated. The HRD cohort is therefore of limited interest to this appraisal. However, as outlined in Sections 2.3.1 and 2.3.3, due to the availability of olaparib depending on BRCA status and number of lines of prior therapies, subgroups of relevance to this appraisal are non-BRCA, BRCA 2L and BRCA 3L+. Although no analysis was pre-planned for the non-BRCA (BRCA wild-type) cohort in ARIEL3, it is a stratified subgroup because BRCA, as part of HRD status, was a stratification factor at randomisation. The BRCA 2L and BRCA 3L+ subgroups on the other hand are non-stratified, *post hoc* subgroups.

Figure 2. Efficacy analysis cohorts (reproduced from CS Figure 2)




**Key:** BRCA, breast cancer gene; HRD, homologous recombination deficiency; ITT, intention-to treat; LOH, loss of heterozygosity.
**Source:** Coleman *et al*. 2017.[1]

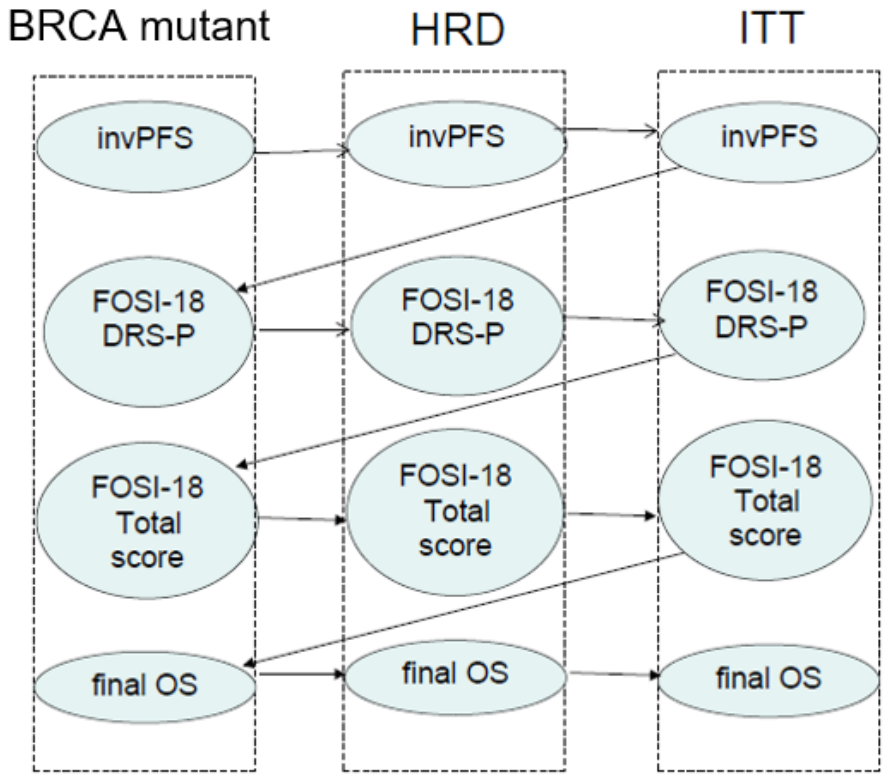
### 3.2.4 Ordered stepdown multiple comparison

The primary and key secondary outcomes were analysed using an ordered stepdown multiple comparisons procedure, as illustrated in Figure 3. The first outcome to be analysed was PFS-INV in the BRCA cohort, followed by the same outcome in the HRD cohort and, lastly, the ITT population. The analysis was then repeated in the three populations in the same order for FOSI-18 DRS-P, FOSI-18 total score and OS. All analyses were tested at a one-sided 0.025 significance level. If the result of the PFS-INV in the BRCA cohort was statistically significant, then significance would be tested in the next outcome and population in the sequence. Once statistical significance was not achieved for one test, statistical significance was not declared for all subsequent analyses in the ordered stepdown procedure.

The ERG considers it appropriate that there was a pre-specified adjustment for the multiple analyses in ARIEL3 and is broadly happy with the approach taken but notes that the approach was stepwise rather than stepdown (as described in the CS) as the one-sided alpha was set to 0.025 for all analyses rather than decreasing. There was also a lack of rationale for the ordering in which the cohorts and outcomes were analysed and the ERG notes that the direction of effect was not specified for these one-sided analyses in the CS. It is unclear, primarily for the patient reported outcomes, if the company expected an improvement or a deterioration in HRQoL and symptoms for patients on rucaparib compared with placebo. This has an impact on the interpretation of any statistically significant findings for these outcomes.

Due to the stepdown multiple comparison used for analysis of the primary and key secondary outcomes, the results in Section 3.3 are presented in the order of the stepdown comparison.

Figure 3. Ordered stepdown procedure (reproduced from CS Figure 3)




Abbreviations: BRCA, breast cancer gene; DRS-P, disease-related symptoms-physical subscale; FOSI-18, Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18; HRD, homologous recombination deficiency; invPFS, investigator-assessed progression-free survival; ITT, intention-to-treat; OS, overall survival.
Source: ARIEL3 CSR.[11]

## *3.3 Clinical effectiveness results*

As discussed in Section 3.2.4, data for ARIEL3 were analysed in a multiple comparison stepdown approach. The results of the outcomes presented in this section are therefore presented in the order specified in the analysis plan as once statistical significance was not achieved for one test, statistical significance was not declared for all subsequent analyses.

### 3.3.1 PFS-INV and PFS-BICR

The primary outcome in ARIEL3 was PFS-INV. At 24 months' follow up, 26% of patients were progression free in the rucaparib group and 2.6% in the placebo group in the ITT population, based on investigator assessment. The Kaplan–Meier curves for PFS show a clear benefit with rucaparib treatment over placebo in the BRCA, HRD and ITT populations (Figure 4). In the BRCA cohort, median PFS was 16.6 months on rucaparib and 5.4 months on placebo, corresponding to a HR of 0.23 (95% CI: 0.16 to 0.34) and a statistically significant difference between groups ($p < 0.0001$, Table 9). The results were statistically significant also in the HRD and ITT populations but the benefit of rucaparib treatment, in terms of point estimate, was slightly lower in the HRD cohort (HR 0.32, 95% CI: 0.24 to 0.42) and even less in the ITT population (HR 0.36, 95% CI: 0.30 to 0.45, Table 9, Figure 4). The secondary

analysis of PFS as assessed by BICR showed similar results to the primary analysis with slightly longer median PFS primarily in the rucaparib group (Table 9).

Table 9. Summary of progression-free survival as assessed by the investigator (adapted from CS Table 8)

| | ITT population | | HRD cohort | | BRCA mutant cohort | |
|---|---|---|---|---|---|---|
| | Rucaparib (n=375) | PBO (n=189) | Rucaparib (n=236) | PBO (n=118) | Rucaparib (n=130) | PBO (n=66) |
| PFS-INV – primary outcome | | | | | | |
| Median PFS, months (95% CI) | 10.8 (8.3 to 11.4) | 5.4 (5.3 to 5.5) | 13.6 (10.9 to 16.2) | 5.4 (5.1 to 5.6) | 16.6 (13.4 to 22.9) | 5.4 (3.4 to 6.7) |
| HR (95% CI) p-value | 0.36 (0.30 to 0.45) <0.0001 | | 0.32 (0.24 to 0.42) <0.0001 | | 0.23 (0.16 to 0.34) <0.0001 | |
| PFS-BICR – secondary outcome | | | | | | |
| Median PFS, months (95% CI) | 13.7 (11.0 to 19.1) | 5.4 (5.1 to 5.5) | 22.9 (16.2 to NR) | 5.5 (5.1 to 7.4) | 26.8 (19.2 to NR) | 5.4 (4.9 to 8.1) |
| HR (95% CI) p-value | 0.35 (0.28 to 0.45) <0·0001 | | 0.34 (0.24 to 0.47) <0·0001 | | 0.20 (0.13 to 0.32) <0·0001 | |

Abbreviations: BICR, blinded independent central radiology review; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; INV, investigator assessed; ITT, intention-to-treat; NR, not reached; PBO, placebo; PFS, progression-free survival.
Notes: Data presented are from the primary endpoint analysis database lock of 15 April 2017.
Source: Coleman *et al*. 2017;[1] ARIEL3 CSR.[11]

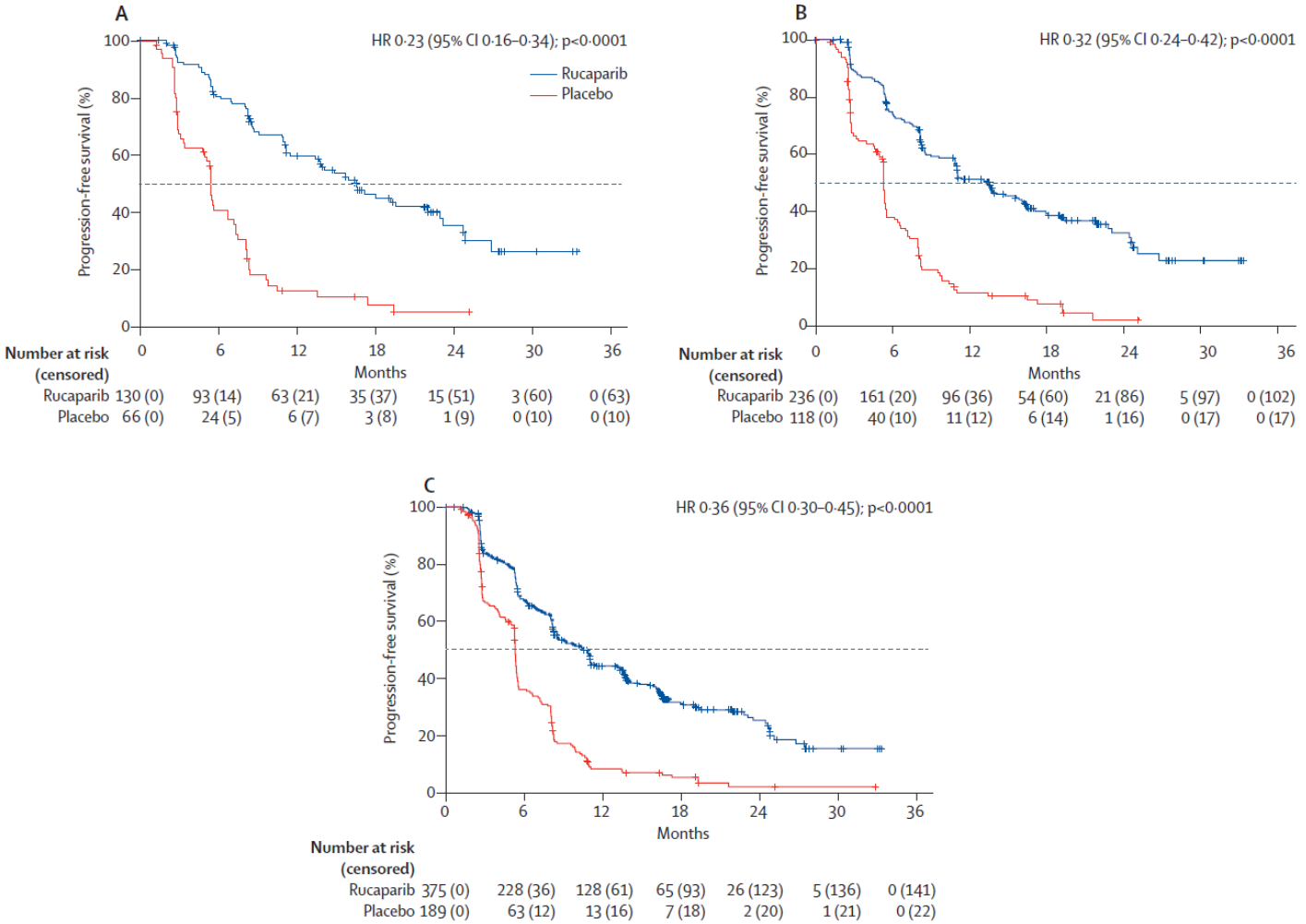
To address the decision problem, as outlined in the NICE final scope, the company also presented data for the BRCA 3L+ subgroup, and, at the clarification stage, also for the BRCA 2L and non-BRCA subgroups. The ERG acknowledges and agrees with the company that some of the groups are *post hoc* subgroups with imbalances in baseline characteristics (BRCA 2L) and small patient numbers (BRCA 2L and BRCA 3L+). Median PFS in the rucaparib arm of the non-BRCA subgroup was [redacted] and the relative difference between the treatment groups was [redacted] than in the ITT population. Inversely, median PFS in the rucaparib arm of the BRCA 2L was [redacted] than in the ITT population. The relative difference between treatments was [redacted] for BRCA 2L [redacted] and BRCA 3L+ [redacted].

Table 10. Summary of PFS INV – post-hoc analyses (adapted from clarification response A1, Table 1)

| Progression-free survival | Non-BRCA | | BRCA 2L | | BRCA 3L+ | |
|---|---|---|---|---|---|---|
| | Rucaparib (n=245) | Placebo (n=123) | Rucaparib (n=77) | Placebo (n=41) | Rucaparib (n=53) | Placebo (n=25) |
| Events, n (%) | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Median PFS, months (95% CI) | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| HR (95% CI) | [redacted] | | [redacted] | | [redacted] | |

Abbreviations: 2L, second line; 3L+, third line or later; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; INV, investigator; NR, not reported; PFS, progression-free survival; SE, standard error.

Figure 4. Kaplan–Meier estimates of progression-free survival as assessed by the investigator (reproduced from CS Figure 4)




Key: A, BRCA mutant cohort; B, HRD cohort; C, ITT population.
Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention to treat.
Source: Coleman *et al*. 2017.[1]

Figure 5. Kaplan–Meier estimates of PFS INV – *post hoc* analysis (adapted from CS Figure 6 and clarification response A1, Figure 1 and Figure 3)

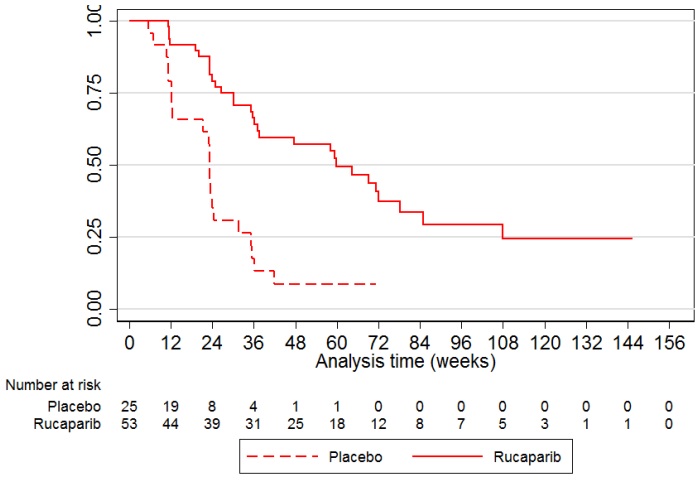
A) non-BRCA

[redacted]

B) BRCA 2L

[redacted]

C) BRCA 3L+




Abbreviations: 2L, second line; 3L+, third line onwards; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

### 3.3.2 Secondary outcomes

The outcome next in line after PFS-INV in the multiple comparison stepdown analysis was time to worsening of the disease-related symptoms-physical (DRS-P) subscale of FOSI-18 (defined as ≥4 point decrease), followed by time to worsening of total score of FOSI-18 (defined as ≥8 point decrease), and finally OS in each of the three populations: BRCA, HRD and ITT.

In the BRCA, HRD and ITT populations the completion rates of the FOSI-18 were above [redacted] at baseline but dropped to between [redacted] in the placebo groups and [redacted] in the rucaparib group by cycle 8. The median time to worsening in DRS-P subscale was shorter for patient in the rucaparib group ([redacted]) compared with the placebo group ([redacted]) in the BRCA cohort, although the difference did not reach statistical significance (Table 11). In accordance with the pre-specified

hierarchical stepdown procedure used for adjusting for multiplicity testing in ARIEL3, the lack of statistical significance observed for this outcome in this population means significance could not be established for the remaining secondary analyses (p-values are presented descriptively).

It is unclear from the CS and CSR what the company's hypothesis was around the patient reported outcomes of time to worsening of the DRS-P subscale and FOSI-18 total score, as the analyses are based on a one-sided test but the direction of the effect has not been specified. If the company's hypothesis was that rucaparib prolongs time to worsening of patients' symptoms and QoL, then it is unclear how to interpret the p-values for the FOSI-18 outcomes for any population as mean time to worsening was consistently longer for patients in the placebo group than for patients on rucaparib.

OS data were very immature at the primary analysis (15 April 2017) with only around 22% of people having died in the ITT population and [redacted] in the BRCA subgroup. Median OS was not reached in either treatment arm in the BRCA, HRD or ITT population. At this timepoint there was no statistically significant difference between the treatment arms in any of the three populations.

Table 11. Summary of FOSI-18 outcomes (adapted from CS Table 10)

| | ITT population | | HRD cohort | | BRCA mutant cohort | |
|---|---|---|---|---|---|---|
| | Rucaparib (n=375) | PBO (n=189) | Rucaparib (n=236) | PBO (n=118) | Rucaparib (n=130) | PBO (n=66) |
| FOSI-18 | | | | | | |
| Median TTW in DRS-P subscale* months (95% CI) | [redacted] | | | | | |
| p-value | [redacted] | | | | | |
| Median TTW in total score ‡ months (95% CI) | [redacted] | | | | | |
| p-value | [redacted] | | | | | |
| OS | | | | | | |
| Events (deaths), n (%) | 81 (21.6) | 42 (22.2) | [redacted] | | | |
| Median OS | NE | NE | [redacted] | | | |
| HR (95% CI) p-value | [redacted] | | | | | |

Abbreviations: BRCA, breast cancer gene; CI, confidence interval; DRS-P, Disease-Related Symptoms Subscale-Physical; FOSI-18, Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PBO, placebo; TTW, time to worsening.
Notes: Data are presented from the primary endpoint analysis database lock of 15 April 2017.
*, defined as ≥4 point decrease; †, p-values are presented descriptively but are not representative of significance; ‡, defined as ≥8 point decrease.
Source: Coleman *et al*. 2017;[1] ARIEL3 CSR.[11]

### 3.3.3 Exploratory outcomes

Several exploratory outcomes were captured in ARIEL3, however, only outcomes relevant to the scope of this appraisal are described in this report. Other outcomes presented in the CS but not repeated here

include: CA-125, chemotherapy-free interval (CFI), response in patients with measurable disease at baseline, quality-adjusted PFS and quality-adjusted time without symptoms or toxicity, the results of which are reported in the CS, Section B.2.6. Below are presented results for the exploratory outcomes of ARIEL3 which were specified in the NICE final scope: TFST, TSST, PFS2 and EQ-5D.

At the date of the primary analysis (15 April 2017), patients randomised to rucaparib had a statistically significant improvement in TFST, TSST and PFS2 compared with patients on placebo for all three populations: BRCA, HRD and ITT (Table 12). As for the primary outcome (PFS), the difference between the rucaparib and placebo arms was consistently larger in the BRCA cohort followed by the HRD cohort and the ITT population. At the later data cut off (31 December 2017), the differences in PFS2 between the treatment arms in each of the populations and the difference between the populations were of similar magnitude to the earlier data cut (Table 12). HRQoL as assessed by EQ-5D showed no statistically significant difference between rucaparib and placebo in patients' self-rated health from baseline to end of treatment for either of the three populations.

Table 12. Summary of exploratory outcome results (adapted from CS Table 12)

| | **ITT population** | | **HRD cohort** | | **BRCA mutant cohort** | |
|---|---|---|---|---|---|---|
| | **Rucaparib (n=375)** | **PBO (n=189)** | **Rucaparib (n=236)** | **PBO (n=118)** | **Rucaparib (n=130)** | **PBO (n=66)** |
| Visit cut-off date: 15 April 2017 | | | | | | |
| TFST, median months (95% CI) | [redacted] | | | | | |
| HR (95% CI)<br>p-value | [redacted] | | | | | |
| Visit cut-off date: 15 April 2017 | | | | | | |
| TSST, median months (95% CI) | [redacted] | | | | | |
| HR (95% CI)<br>p-value | [redacted] | | | | | |
| Visit cut-off date: 15 April 2017 | | | | | | |
| PFS2, median months (95% CI) | [redacted] | | | | | |
| HR (95% CI)<br>p-value | [redacted] | | | | | |
| Visit cut-off date: 31 December 2017 | | | | | | |
| PFS2, median months (95% CI) | [redacted] | | | | | |
| HR<br>p-value | [redacted] | | | | | |
| EQ-5D | | | | | | |
| Baseline mean, (SD) | [redacted] | | | | | |
| End of treatment mean (SD) | [redacted] | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Percentage change from baseline, mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| LS mean difference versus placebo<br>(95% CI)<br>p-value | [redacted] | | [redacted] | | [redacted] | |

Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; LS, least squares; NR, not reached; OS, overall survival; PBO, placebo; SD, standard deviation; TFST, time to first subsequent anti-cancer treatment.
Notes: Data are presented from the primary endpoint analysis database lock of 15 April 2017.
Source: ARIEL3 CSR;[11] Summary of clinical efficacy[12]

At the clarification stage, the company provided data on the proportion of patients who received subsequent therapy and how many of these received a platinum-based chemotherapy (Table 13). [redacted] patients in the rucaparib group than in the placebo group had received a subsequent therapy at the time of analysis, as [redacted] patients in the rucaparib group had progressed. However, of the patients who went on to receive a subsequent therapy, [redacted] of rucaparib patients had a platinum-based therapy compared with patients originally randomised to placebo. The difference between rucaparib and placebo was [redacted] in the BRCA 2L and BRCA 3L+ subgroups (Table 13).

Table 13. Subsequent therapy data from ARIEL 3 – post-hoc analyses (adapted from clarification response A7, Table 6)

| | **Patients with any subsequent therapy, n/N (%)** | | | **Patients with a platinum-based therapy as their first subsequent therapy* n/N (%)** | | |
|---|---|---|---|---|---|---|
| | **Rucaparib** | **Placebo** | **Total** | **Rucaparib** | **Placebo** | **Total** |
| Non-BRCA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BRCA 2L | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| BRCA 3L+ | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ITT | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: 2L, second line; 3L+, third line plus; BRCA, breast cancer gene; ITT, intention-to-treat.
*expressed as proportion of patients receiving any subsequent therapy rather than the full trial population.

### 3.3.4 Subgroup analyses

The results of the subgroups of particular interest to this appraisal, that is, non-BRCA, BRCA 2L and BRCA3L+, are reported in the main results for PFS in Section 3.3.1. Pre-specified subgroup analyses of ARIEL3 consistently showed a benefit in favour of rucaparib in reducing the risk of disease progression or death. The results are summarised in the CS, Appendix E, and only for subgroups judged to have adequate numbers of patients.

### 3.3.5 Safety

Safety data were analysed based on the primary analysis data cut of 15 April 2017, but an additional data base lock for an updated safety data analysis occurred on 31 December 2017. Only data from the updated data base lock are presented in the following sections. For safety data from the primary analysis

point, please see the CS Section B.2.10 and CS Appendix L.8. The safety population in ARIEL3 comprised 372 patients in the rucaparib group and 189 patients in the placebo group, who initiated treatment with rucaparib or placebo.

The recommended dose of rucaparib is 600 mg (two 300 mg tablets) taken twice daily, equivalent to a total daily dose of 1200 mg. Patients should start maintenance treatment with rucaparib within eight weeks of completion of their last dose of platinum-based chemotherapy and it is recommended that treatment be continued until progression or unacceptable toxicity. Treatment interruption or dose reduction should be considered for managing adverse reactions such as neutropenia, anaemia and thrombocytopenia. The recommended dose reduction is to 500 mg (two 250 mg tablets) twice daily. If further dose reductions are required, then reduction to 400 mg (two 200 mg tablets) twice daily and eventually to 300 mg (one 300 mg tablets) twice daily is recommended.

Haematological toxicity, including anaemia, and elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are mentioned in the Summary of Product Characteristics (SmPC) as adverse reactions associated with rucaparib therapy. Anaemia and elevations of ALT/AST should be managed with dose adjustments. Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), a serious, but uncommon, adverse event, has been reported in patients who receive rucaparib. Other select adverse events associated with rucaparib therapy are photosensitivity, nausea and vomiting.

#### *3.3.5.1 Treatment exposure*

Rucaparib was administered at the recommended dose in ARIEL3 (600 mg twice a day) until disease progression or intolerable toxicities. The mean duration of treatment was longer in the rucaparib group ([redacted]) compared with the placebo group ([redacted], Table 14). In ARIEL3, a [redacted] proportion of patients had dose reductions in the rucaparib group ([redacted]) compared with the placebo group ([redacted], Table 14).

Table 14. Treatment exposure data, safety population, updated data cut 31 December 2017 (adapted from Table 49, CS Appendix L8)

| | **Rucaparib (n=372)** | **Placebo (n=189)** |
|---|---|---|
| Duration of treatment (months) | | |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Min, Max | [redacted] | [redacted] |
| Dose reductions, n (%)*^ | | |
| Only 1 dose reduction | [redacted] | [redacted] |
| ≥ 2 dose reductions | [redacted] | [redacted] |

Abbreviations: BID, twice a day; min, minimum; max, maximum; SD, standard deviation.
Notes: *, based on the dispensation log; ^, dose reductions may not have necessarily been conducted in a sequential manner.
Source: ARIEL3 CSR;[11] Summary of clinical safety - 18 May 2018.[13]

### *3.3.5.2 Adverse events*

Most patients in ARIEL3 experienced at least one adverse event (100% rucaparib, 96.3% placebo, Table 15). A greater proportion of patients in the rucaparib group reported an adverse event of grade ≥3, a serious adverse event (SAE), or an adverse event leading to discontinuation of study drug, in comparison to the placebo group (Table 15). The majority of dose reductions in ARIEL3 were due to adverse events; [redacted] of patients in the rucaparib group and [redacted] in the placebo group had an adverse event which led to a dose reduction (Table 15). There were also [redacted] people on rucaparib ([redacted]) than on placebo ([redacted]) who had a dose interruption due to an AE. However, although more people in the rucaparib group than in the placebo group discontinued study therapy due to an adverse event, the numbers were relatively low in both treatment groups (rucaparib [redacted] and placebo [redacted]). This indicates that, although a substantial proportion of patients on rucaparib experienced a grade 3 or above adverse event, the majority of these could be managed with dose reductions or dose interruptions.

There were seven fatal adverse events in the rucaparib group and two in the placebo group. Two of the patients in the rucaparib group with a fatal adverse event developed AML or MDS evolving into AML. For these two cases, a relationship to the study drug could not be ruled out.

Table 15. Overall summary of treatment-emergent adverse events, updated data cut 31 December 2017, safety population (adapted from CS Table 26)

| TEAE, n (%) | Rucaparib (n=372) | Placebo (n=189) |
|---|---|---|
| One or more TEAEs | 372 (100.0) | 182 (96.3) |
| One or more serious TEAEs | 83 (22.3) | 20 (10.6) |
| One or more TEAEs of Grade 3 or higher | 222 (59.7) | 30 (15.9) |
| One or more TEAEs leading to death | 7 (1.9) | 2 (1.1) |
| One or more TEAEs leading to study drug discontinuation | 61 (16.4) | 4 (2.1) |
| One or more TEAEs leading to study drug interruption | 243 (65.3) | 19 (10.1) |
| One or more TEAEs leading to study drug dose reduction | 206 (55.4) | 8 (4.2) |
| One or more TEAEs leading to dose reduction or interruption | 267 (71.8) | 20 (10.6) |

Abbreviation: TEAE, treatment emergent adverse event.
Source: Coleman *et al*. 2017;[1] ARIEL3 CSR;[11] Summary of clinical safety - May 2018.[13]

In ARIEL3, adverse events of grade 3 or higher were reported in 59.7% of patients in the rucaparib group, versus 15.9% of those in the placebo group (Table 15). Table 16 summarises AEs of grade 3 or higher reported in more than 5% of patients in either treatment group at the updated safety analysis (31 December 2017). Adverse events of grade 3 or higher reported in more than 10% of patients in either treatment group were combined anaemia/low or decreased haemoglobin (21.5% in the rucaparib group versus 0.5% in the placebo group), anaemia (19.6% versus 0.5%), and combined increased ALT/AST (10.2% versus 0.0%).

Table 16. Grade 3 or higher TEAEs reported in ≥5% of patients in any treatment group (safety population) (CS Table 28)

| AE, n (%) | Updated data cut (31 December 2017) | |
|---|---|---|
| | Rucaparib (n=372) | Placebo (n=189) |
| **At least one Grade 3* or higher TEAE** | 222 (59.7) | 30 (15.9) |
| **Combined preferred terms** | | |
| Combined ALT/AST | 38 (10.2) | 0 (0.0) |
| Combined anaemia and/or low/decreased haemoglobin | 80 (21.5) | 1 (0.5) |
| Combined asthenia/fatigue | 26 (7.0) | 5 (2.6) |
| Combined neutropenia and/or low/decreased ANC | 29 (7.8) | 2 (1.1) |
| Combined Thrombocytopenia and/or low/decreased platelets | 20 (5.4) | 0 (0.0) |
| **System organ class<br>Preferred term** | | |
| **Blood and lymphatic system disorders** | 95 (25.5) | 3 (1.6) |
| Anaemia | 73 (19.6) | 1 (0.5) |
| Neutropenia | 19 (5.1) | 1 (0.5) |
| **Gastrointestinal disorders** | 49 (13.2) | 12 (6.3) |
| **General disorders and administration site conditions** | 31 (8.3) | 6 (3.2) |
| **Investigations** | 77 (20.7) | 1 (0.5) |
| ALT increased | 37 (9.9) | 0 (0.0) |
| **Metabolism and nutrition disorders** | 19 (5.1) | 1 (0.5) |

Abbreviations: AE, adverse events; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; TEAE, treatment emergent adverse event.
Notes: *, NCI-CTCAE grade.
Source: Coleman *et al*. 2017;[1] ARIEL3 CSR;[11] Summary of clinical safety - May 2018.[13]

### 3.3.6 Summary

The primary outcome in ARIEL3 was PFS-INV in the BRCA, HRD and ITT population. The outcome next in line in the multiple comparison stepdown analysis was time to worsening of the DRS-P subscale of FOSI-18 followed by time to worsening of total score of FOSI-18, and finally OS, in each of the three populations: BRCA, HRD and ITT. In accordance with the stepwise analysis plan, when a lack of statistical significance was observed for an outcome significance could not be established for the remaining secondary analyses.

Of the pre-specified populations in the trial analysis plan, the BRCA cohort is of particular interest to this appraisal. In addition, the non-BRCA cohort and data for the BRCA cohort divided by number of lines of prior therapy (BRCA 2L and BRCA3L+) is of interest as this aligns previous NICE guidance (TA381) and how decisions about patients is made in clinical practice. The results of the ITT population and the relevant subgroups are summarised below:

- In the ITT population, median PFS in patients treated with rucaparib (10.8 months) was double that of patients on placebo (5.4 months, HR 0.36, 95% CI: 0.30 to 0.45). The secondary analysis of PFS as assessed by BICR showed similar results to the primary analysis with slightly longer median PFS primarily in the rucaparib group. In the BRCA cohort, median PFS in the rucaparib group was longer than in the ITT population (16.6 months) but similar for the placebo group, which corresponds to a larger relative difference between the treatments (HR 0.23, 95% CI: 0.16 to 0.34). The results of the *post hoc* analyses of the BRCA subgroup by line of therapy were in line with those of the full BRCA subgroup. Median PFS in the rucaparib arm of the non-BRCA subgroup was shorter than in the ITT population and the relative difference between the treatment groups was smaller ([redacted]).

- HRQoL was measured using FOSI-18 and EQ-5D. There was no statistically significant difference in median time to worsening in the DRS-P FOSI-18 subscale between the rucaparib and placebo groups in the BRCA cohort. The difference in time to worsening in DRS-P subscale and for the FOSI-18 total score was larger, in favour of placebo, in the ITT and HRD populations, compared with the difference in the BRCA cohort. However, because of the stepdown analysis approach statistical significance was not declared for these analyses. HRQoL as assessed by EQ-5D showed only small differences and no statistically significant differences between rucaparib and placebo in HRQoL from baseline to end of treatment for any of the three populations.

- The OS data for ARIEL3 were very immature at the primary analysis (event rate around 22% in the ITT population); median OS was not reached in either treatment group and at this timepoint there was no statistically significant difference between the treatment arms.

- Patients randomised to rucaparib had a statistically significant improvement in TFST and PFS2 compared with patients on placebo for all three populations: BRCA, HRD and ITT. The difference between the rucaparib and placebo arms were larger in the BRCA cohort followed by the HRD cohort and the ITT population for both outcomes.

- Of the patients who went on to receive subsequent therapy, in the BRCA subgroup, the proportion of patients who received a platinum-based therapy as their first subsequent therapy was [redacted] in the rucaparib group than in the placebo group. There was [redacted] between treatment arms in the non-BRCA subgroup in the proportion of patients who received subsequent platinum-based therapy.

- Patients on rucaparib were on treatment for longer than patients on placebo but a substantial proportion of patients, primarily in the rucaparib group, had dose reductions or dose

interruptions to manage AEs. A greater proportion of patients in the rucaparib group reported an adverse event of grade ≥3 (59.7% versus 15.9%), a SAE (22.3% versus 10.6%), or an adverse event leading to treatment discontinuation (16.4% versus 2.1%), in comparison to the placebo group.

- The most common AEs of grade 3 or higher were combined anaemia/low or decreased haemoglobin (21.5% in the rucaparib group versus 0.5% in the placebo group), anaemia (19.6% versus 0.5%), and combined increased ALT/AST (10.2% versus 0.0%).

- There were seven fatal adverse events in the rucaparib group and two in the placebo group. Two of the patients in the rucaparib group with a fatal adverse event developed AML or MDS evolving into AML. For these two cases a relationship to the study drug could not be ruled out.

## *3.4 Critique of trials identified and included in indirect comparisons and to inform longterm data in economic modelling*

Due to the absence of head-to-head trials comparing rucaparib with olaparib for the BRCA 3L+ population, the company explored and conducted several indirect treatment comparisons (ITC). In addition, OS data from ARIEL3 are currently not mature enough to inform the comparison of rucaparib and olaparib in the BRCA 3L+ population or the comparison of rucaparib and placebo for the other populations, non-BRCA and BRCA 2L. There is therefore a need to look at the comparability of ARIEL3 and Study 19, the only PARPi trial with mature survival data, to explore the option of relying on an assumption of similar OS for rucaparib and olaparib in the health economic model for all three populations (Section 4.2.5).

In the CS, the company has provided a feasibility study of ITCs of the ITT and BRCA 3L+ populations of ARIEL3 and the two olaparib trials SOLO2 and Study 19 (CS, Section B.2.9. and CS Appendix D.1.), and in response to a clarification request, the company provided baseline characteristics for the non-BRCA and BRCA 2L subgroups of the same trials, to evaluate their comparability across trials. The sections below include a description of the olaparib trials SOLO2 and Study 19 (ARIEL3 is described in Section 3.2), and specifically covers the comparability of the non-BRCA, BRCA 2L and BRCA 3L+ subgroups of ARIEL3 and the two olaparib trials.

### 3.4.1 Study 19

Study 19 is a randomised, double-blind, multicentre placebo-controlled, phase II trial evaluating the efficacy and safety of maintenance treatment with olaparib capsules in patients with platinum-sensitive, high-grade serous ovarian, fallopian or primary peritoneal cancer.[4, 5] Patients were eligible for enrolment in the trial if they had received at least two previous platinum-based therapies, and were in partial or complete response following their last platinum-containing regimen.

Patients were randomised in a 1:1 ratio to olaparib capsules (the formulation currently with a NICE recommendation) 800 mg per day (n=136) or placebo (n=129) with randomisation stratified by platinum-free interval (PFI) (6–12 months or >12 months), response to last platinum-based chemotherapy (CR or PR), and ancestry (Jewish or non-Jewish, as BRCA mutations reportedly occur more frequently in people with Ashkenazi Jewish ancestry), as a proxy of BRCA status. Known BRCA status was not required for inclusion in Study 19; it was instead tested retrospectively for the majority of patients in the study (96%). Thus, the BRCA and the BRCA 3L+ subgroups of Study 19 were *post hoc*, non-stratified subgroups.

The primary outcome in Study 19 was investigator assessed PFS, which was assessed according to RECIST, but only captured up to the primary analysis, at which point 44.1% of patients had progressed in the olaparib group and 72.1% in the placebo group. Median follow-up of survival was 6.5 years (78 months) and, thus, Study 19 provides relatively mature data for OS.

Crossover from placebo to olaparib was not allowed within the trial, but some patients in the placebo group received subsequent treatment with a PARPi outside of the trial, similar to ARIEL3. This is likely to lead to an under estimate of the relative efficacy of olaparib compared with placebo for survival, but potentially provides a reasonable estimate of the efficacy of olaparib relative to routine surveillance as used in clinical practice.

### 3.4.2 SOLO2

SOLO2 is a randomised, double-blind, placebo-controlled, multi-centre, phase III trial evaluating the efficacy and safety of olaparib tablets as maintenance therapy in patients with a BRCA mutation and platinum-sensitive, high-grade serous ovarian, fallopian tube, or peritoneal cancer.[6] Eligibility criteria for enrolment in SOLO2 were similar to Study 19; patients were eligible if they had received two or more previous platinum-based therapies, and were in partial or complete response following their last platinum-containing regimen. The most prominent difference in enrolment criteria is that SOLO2 was limited to patients with a confirmed BRCA mutation. Similar to ARIEL3 and Study 19, the BRCA 3L+ subgroup of SOLO2 was defined *post hoc* for this appraisal.

Patients were randomised in a 2:1 ratio to receive olaparib tablets, 600 mg per day, (n=196) or placebo (n=99) with randomisation stratified by PFI (6–12 months or >12 months) and response to last platinum chemotherapy (CR or PR). The primary outcome in SOLO2 was investigator assessed PFS, similar to Study 19. Median follow-up in SOLO2 was around 22 months, at which point OS data were immature as only 24% of patients had died.

At the time of writing, assessment by NICE of the tablet formulation of olaparib is ongoing. The conclusions of the initial ACD is that olaparib tablets are effective in extending time to progression,

however, the tablet formulation has not been approved by NICE for routine commissioning.[14] The ERG notes that the tablet and the capsule formulations of olaparib have been compared in an open-label, multi-stage, dose finding study (Study 24[15]). The groups informing the comparison of the tablet and capsule formulation were small, with 10–17 patients in each group. In addition, the efficacy of the two olaparib formulations were assessed in terms of objective response rates and tumour shrinkage in patients with advanced ovarian cancer and a BRCA mutation, which is different from the indication for which olaparib has marketing authorisation, that is, as a maintenance therapy to prolong the progression-free interval for patients with relapsed ovarian cancer, who have already responded, that is, are in response (complete or partial) to platinum-based chemotherapy. Based on the results of Study 24, the two formulations of olaparib cannot be considered bioequivalent on a milligram-to-milligram basis but there is little evidence to support equivalence or a significant difference between the formulations in terms of efficacy or safety.

### 3.4.3 Baseline characteristics

The baseline characteristics of patients across the ITT populations as well as the three relevant subgroups (BRCA 2L, BRCA 3L+, and non-BRCA) of ARIEL3, Study 19 and SOLO2 are presented in Appendix 9.2, where available. Baseline characteristics for the BRCA 2L subgroup were not available for Study 19 and therefore no comparison could be made between the baseline characteristics of patients within this subgroup in Study 19 and ARIEL3.

Patient characteristics of the ITT population were generally well balanced within each of the trials. For the non-BRCA subgroup the baseline characteristics were relatively well balanced within both Study 19 and ARIEL3. Patients in the non-BRCA subgroup of Study 19 were slightly more heavily pre-treated with a larger proportion of patients having had three or more prior lines of platinum-based therapy compared with the non-BRCA subgroup in ARIEL3 (Table 62). However, slightly more patients in Study 19 also had a CR to most recent platinum chemotherapy compared with the same subgroup in ARIEL3.

For the BRCA 3L+ population a limited number of baseline characteristics were reported across all three trials (Table 17). Of the four characteristics for which data were available, there were imbalances noted for all characteristics, both within and between trials, reflecting the *post hoc* nature of these subgroups as well as the small sample sizes. There was a larger proportion of patients with ECOG ≥1 in the placebo arm of all three trials, which may bias in favour of the active treatment. In addition, ECOG status was imbalanced between trials with a higher proportion of patients with ECOG ≥1 in ARIEL3 compared with SOLO2 and Study19, which may bias in favour of olaparib. PFI in SOLO2 was balanced within treatment groups in SOLO2, and similar to the placebo groups of ARIEL3 and Study 19. However, PFI was longer in the olaparib group of Study 19 and shorter in the rucaparib group

of ARIEL3. For PFI, the difference between the trials may potentially bias towards olaparib compared with rucaparib irrespective of olaparib study used, but the biggest difference is between ARIEL3 and Study 19. There were also within study differences for response to prior therapy (CR/PR), favouring the placebo arm in ARIEL3 and Study 19. There was no consistent direction in terms of the potential bias due to these differences.

Table 17. Baseline characteristics for BRCA 3L+ population (adapted from CS Appendix D, Table 8)

| | **ARIEL3** | | **Study 19** | | **SOLO2 (weighted average of 3L and 4L+)** | |
|---|---|---|---|---|---|---|
| | **Rucaparib (n=53)** | **Placebo (n=25)** | **Olaparib (n=47)** | **Placebo (n=34)** | **Olaparib (n=85)** | **Placebo (n=37)** |
| Age ≥65 years, % | [redacted] | [redacted] | 27.7 | 17.6 | NE | NE |
| ECOG ≥1, % | [redacted] | [redacted] | 12.8 | 23.5 | 14.1 | 18.9 |
| Platinum-free interval >12 months, % | [redacted] | [redacted] | 63.8 | 47.1 | 45.9 | 43.2 |
| Response to most recent plt chemotherapy, % | [redacted] | [redacted] | CR: 44.7 | CR: 61.8 | CR: 40.0 | CR: 35.1 |

Abbreviations: BMI, body mass index; BRCA, breast cancer gene; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; NR, not reported; plt, platinum; Ruca, rucaparib.
Source: ARIEL data on file; NICE Committee Papers - ID735[16]; Penson et al. 2017.[17]

### 3.4.4 Quality assessment

The company's quality assessment of Study 19 and SOLO2, together with the ERG's independent validation, is presented in Appendix 9.1. ARIEL3, Study 19 and SOLO2 are all of good quality with a low risk of bias for all domains. However, the critique is based on the ITT population for each of the trials. Because the populations of interest for the ITCs are subgroups (non-BRCA, BRCA 2L, and BRCA 3L+) of which some are *post hoc*, based on factors not stratified for at randomisation and with a small sample size, these subgroups are comparable with non-randomised observational data. This is likely to be a reason for the imbalance in the patient characteristics at baseline (see the previous section, 3.4.3). The company has tried to address these issues in the ITC by conducting MAIC as an alternative to NMA. The pros and cons of these two methods are discussed in Section 3.5.

### 3.4.5 Comparability of trials for ITC

There is observed clinical and methodological heterogeneity across ARIEL3, SOLO2 and Study 19 with regard to trial design and patient populations. Key differences are discussed below:

- ARIEL3 and SOLO2 are phase III trials whereas Study 19 is phase II.

- ARIEL3 enrolled patients with high-grade serous or endometrioid ovarian cancer, whereas SOLO2 and Study 19 only enrolled patients with high-grade serous ovarian cancer. According

to the ERG's clinical experts, patients with endometrioid ovarian cancer are less likely to have a BRCA mutation than patients with high-grade serous ovarian cancer. Therefore, the difference in type of ovarian cancer may have an impact on the proportion of patients with a BRCA mutation, but this is irrelevant when looking at the BRCA 3L+ subgroup. In addition, proportion of patients with endometrioid ovarian cancer was low in ARIEL3 at around 4%.

- SOLO2 only enrolled patients with BRCA mutation, whereas ARIEL3 and Study 19 enrolled patients with or without a BRCA mutation. Specific subgroups based on BRCA status are assessed in this appraisal and therefore the differences in the proportions of patients with a BRCA mutation in the full trial populations are irrelevant. However, ARIEL3 used BRCA status as a stratification factor in the randomisation process whereas Study 19 used ancestry (Jewish vs non-Jewish) as a proxy of BRCA status, and BRCA status was only confirmed retrospectively. Therefore, the BRCA subgroup in Study 19 is *post hoc*.

- The BRCA 3L+ subgroup is *post hoc* in all three trials, which is reflected in the imbalances seen in the baseline characteristics for all three trials. In addition, data for the BRCA 3L+ subgroup of SOLO2 was taken from a poster presented at the ESMO 2017 conference, which presented data for the BRCA 3L and BRCA 4L+ populations. These groups were combined by the company for the matching adjusted indirect comparison (MAIC), but only the BRCA 3L data was used for the network meta-analysis (NMA).

- Some patients, primarily in the placebo group of Study 19 and ARIEL3 received subsequent treatment with a PARPi. This is likely to lead to an under estimate of the relative efficacy of each PARPi compared with placebo for survival, but for patients with a BRCA mutation it potentially provides a reasonable estimate of the efficacy of PARPi relative to routine surveillance as used in clinical practice, where therapy with olaparib is available through routine commissioning for this subgroup (TA381).

- In Study 19, olaparib was administered in the capsule formulation, which is the formulation recommended for routine commissioning for ovarian cancer patients with a BRCA mutation and at least three prior therapies by NICE in TA381. SOLO2 evaluated the tablet formulation of olaparib. It has been established that the two formulations are not equivalent on a milligram-to-milligram basis, and although they have similar pharmacokinetic properties, how they compare to each other in terms of efficacy and safety has yet to be established.

- Study 19 provides mature OS data with over 6 years of follow-up whereas ARIEL3 and SOLO2 provide immature data with no more than 2 years of follow-up. Study 19 is therefore the only source of long-term survival data for patients with or without a BRCA mutation, whether on a

PARPi or not. However, relying on OS data from Study 19 to inform OS of any PARPi other than olaparib capsules is dependent on a strong assumption of equivalence in efficacy.

- Baseline characteristics were generally well balanced within the ITT populations and the non-BRCA subgroups of the trials, as well as between trials. Baseline characteristics of the BRCA 2L population of Study 19 were not available and therefore could not be compared with the equivalent ARIEL3 population. For the BRCA 3L+ subgroups there were imbalances both within and between trials in reported baseline characteristics, reflecting the *post hoc* nature of these subgroups as well as the small sample size. There was no consistent direction in terms of the potential biases due to these differences.

### 3.4.6 Summary

OS data from ARIEL3 are currently not mature enough to inform the comparison of rucaparib and olaparib in the BRCA 3L+ population or the comparison of rucaparib and placebo for the non-BRCA and BRCA 2L populations. Study 19 is the only trial available to inform the long-term outcomes of PARPi maintenance therapy and of routine surveillance. There are several differences between ARIEL3 and Study 19 in terms of trial design and trial populations, as highlighted in the sections above. However, due to the immature OS data for rucaparib compared with olaparib or routine surveillance, the ERG considers Study 19 to provide the most robust data available but acknowledges that there is limited evidence to show that the assumption of equivalence between rucaparib and olaparib in terms of OS, is conservative or optimistic. There is also limited evidence to show what effect the naïve use of Study 19 data for OS compared with PFS data from ARIEL3 will have for the three different populations. For the non-BRCA and BRCA 3L+ subgroups, for which some baseline characteristics were available to compare between trials, there was no consistent direction in terms of the potential biases due to differences between or within trials.

In the BRCA 3L+ population, for which the relevant comparator to rucaparib is olaparib, both SOLO2 and Study 19 can provide data for an ITC. The clinical outcomes of relevance to the economic model are PFS and OS, and, as there are no mature OS data available for SOLO2, only PFS data is of potential relevance from this study, whereas Study 19 can inform both PFS and OS. The company concludes that SOLO2 provides an overall more robust dataset and more comparable dataset for the BRCA 3L+ group compared with Study 19, as indicated by the larger effective sample size in MAIC synthesis using SOLO2. This is discussed in Section 3.5.3. Despite this, the company combines the data for SOLO2 and Study 19 in the NMA. Although combining PFS data for SOLO2 and Study 19 provides a larger data set and potentially better precision, the ERG cautions against combining the two studies. There is currently little available data to support or refute equivalence between the formulations in terms of clinical efficacy or safety and as Study 19 provides data on the capsule formulation, which is the one

currently with a recommendation from NICE for the BRCA 3L+ population, the ERG considers it more appropriate to only use Study 19 in the ITC. In addition, as there is an intrinsic, although poorly defined, link between PFS and OS it is preferential to use the same dataset to inform both outcomes. The ERG therefore does not consider it appropriate to use both SOLO2 and Study 19 to inform the data for PFS but only Study 19 to inform OS, but rather that only Study 19 is used to inform both outcomes. The ERG acknowledges that one of the main limitations of any ITC of rucaparib and olaparib in the BRCA 3L+ subgroup is that it is based on small, *post hoc* subgroups irrespective of which trials are used.

## *3.5 Critique of the indirect treatment comparison*

The company used two different methods for the indirect treatment comparison (ITC) of rucaparib and olaparib for the BRCA 3L+ population, network meta-analysis (NMA) and matching adjusted indirect comparison (MAIC), which will be discussed in the sections below.

The company has run ITCs for several outcomes including overall survival (OS), time to first subsequent treatment (TFST), PFS2 and time to second subsequent treatment (TSST), although the outcomes of direct relevance to the health economic model are PFS and OS. However, OS data are very immature for ARIEL3 with only [redacted] and [redacted] deaths in the rucaparib and placebo groups, respectively, within the BRCA subgroup, and even fewer in the BRCA 3L+ subgroup. The ERG therefore considers an ITC of rucaparib and olaparib for OS to be of limited value. The results of the company's ITC for TFST, TSST, OS and issues relating to these are therefore not discussed further in this report. The following sections give a description and discussion of methods and results relevant to PFS. The company's analysis and results for OS and other outcomes can be found in CS Section B.2.9. and Appendix D.

### 3.5.1 Proportional hazards

The company assessed the proportional hazards (PH) assumption for each trial, population and outcome, to determine if a hazard ratio (HR) is an appropriate summary measure for the ITCs. The company created virtual patient level data (VPLD) from KM curves for SOLO2 and Study 19. Using the VPLD for SOLO2 and Study 19, and IPD for ARIEL3, the company created log-cumulative hazard plots (log-log plots). The company also investigated the PH assumption by plotting the scaled Schoenfeld residuals against time and by a global test of the slope of the scaled Schoenfeld residuals when plotted against time. The company presented log-log and Schoenfeld plots in the CS for the data originally used in the economic model (CS Section B.3.3). Additional results from the company's assessment of the PH assumption were provided at the clarification stage (clarification question A4).

The company concludes that there was not sufficient evidence to refute the PH assumption between active treatments and placebo for OS and PFS-INV across the investigated populations (Table 18).

There were some signals that indicate PH may not hold for OS in the non-BRCA population of Study 19. However, the company considers these to be inconclusive as the KM curves are based on relatively small sample sizes and that assuming non-PH and implementing, for example, a fractional polynomial approach, would involve other assumptions that would be harder to validate. It is unclear what assumptions the company is referring to and, although the ERG agrees that evidence refuting the PH assumption may be limited, the ERG considers it a strong assumption to assume that PH do hold, especially for *post hoc* subgroups such as non-BRCA in Study 19. However, the potential lack of PH for OS between olaparib and placebo in the non-BRCA subgroup is of limited importance as the immature survival data for rucaparib would make any ITC between olaparib and rucaparib highly uncertain and likely to be unreliable. Therefore, no ITC results for OS are used in the economic model.

Table 18. Proportional hazards test (adapted from CS Appendix D, Table 9)

| Trial | Outcome | ITT | BRCA 2L | BRCA 3L+ | Non-BRCA |
|---|---|---|---|---|---|
| ARIEL3 | PFS (INV) | ✓ | ✓ | ✓ | ✓ |
| Study 19 | OS | ✓ | NA | ✓ | ✓ |
| Study 19 | PFS (INV) | ✓ | NA | ✓ | ✓ |
| SOLO2 | PFS (INV) | NA | NA | ✓ | NA |

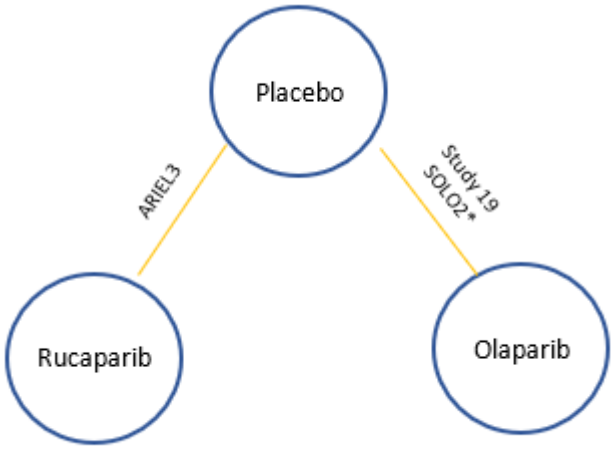
Abbreviations: 2L, two prior lines of therapy; 3L+, three or more prior lines of therapy; BIRC, blinded independent review committee; BRCA, breast cancer gene; INV, investigator-reported; ITT, intention-to-treat; NA, not applicable; OS, overall survival; PFS, progression-free survival.

### 3.5.2 Network meta-analysis

NMAs were conducted in OpenBUGS. The network included ARIEL3, Study 19, and SOLO2 (Figure 6). The company seems to have followed standard procedure for the NMA. Fixed effect models were used for all outcomes. The company states that this was due to the limited evidence base. The ERG notes that considering the potential for significant clinical heterogeneity between the two olaparib trials for PFS, where both trials are included in the network, random effects models should have been explored as well.

Data for the BRCA 3L+ group of SOLO2 were taken from a poster presented at ESMO 2017 that provided PFS data for the BRCA 3L and BRCA 4L+ populations separately. Data for the BRCA 3L group of SOLO2 were used as a proxy for the BRCA 3L+ group. It is unclear why the company only included the BRCA 3L group rather than including the BRCA 3L and BRCA 4L+ groups of SOLO2 separately in the NMA. Instead the company did a pairwise meta-analysis of the results of the BRCA 3L and BRCA 4L+ groups for SOLO2, the results of which the company states support the approach taken. At the clarification stage the company supplied the results of NMA based on Study 19 and SOLO2 individually, which the ERG considers more appropriate as discussed in Section 3.4.

Figure 6. Network diagram (reproduced from CS Figure 6)




Abbreviations: 3L+, third and later line; BRCA, breast cancer gene; INV, investigator assessed; PFS, progression-free survival.
Notes: *PFS-INV only – data for the BRCA 3L group used as a proxy for the BRCA 3L+ group.

The NMAs of PFS-INV showed no statistically significant difference between rucaparib and olaparib, irrespective of which study was informing the data for olaparib but the point estimate varied substantially, with a difference in direction of effect. PFS estimates for the BRCA 3L+ group favoured rucaparib when using SOLO2 data for olaparib ([redacted]), but olaparib was favoured when using Study 19 data ([redacted]). Including both olaparib studies gave a HR of [redacted] ([redacted]).

Table 19. NMA outcomes, BRCA 3L+ group (adapted from CS Table 23)

| | **Rucaparib versus placebo** | **Olaparib versus placebo** | **Rucaparib versus olaparib** |
|---|---|---|---|
| | **HR (95% CrI)** | **HR (95% CrI)** | **HR (95% CrI)** |
| PFS-INV SOLO2 | NR | NR | [redacted] |
| PFS-INV Study 19 | NR | NR | [redacted] |
| PFS-INV SOLO2 and Study 19 | [redacted] | [redacted] | [redacted] |

Abbreviations: CrI, credible intervals; HR, hazard ratio; INV, investigator assessed; NMA, network meta-analysis; NR, not reported; OS, overall survival; PFS, progression-free survival.

NMAs of safety outcomes were conducted on the ITT population for each trial as safety profiles are expected to be the same across patient cohorts, and ITT populations provide the greatest dataset. Similar to the original NMAs for all other outcomes analysed, safety was analysed by combining SOLO2 and Study 19 data for olaparib. The ERG notes that there is limited evidence to show that the safety profile of the tablet and capsule formulations of olaparib are different or the same.

Differences in safety profiles of rucaparib and olaparib were observed. The results of the NMA of discontinuations due to AEs favours olaparib over rucaparib, although the result was not statistically significant. The odds of having a grade ≥3 TEAE were statistically significantly higher for patients on rucaparib compared with olaparib ([redacted]). There were also differences in

individual TEAE, although these results did not reach statistical significance: more patients on rucaparib than on olaparib suffered from grade ≥3 anaemia, neutropenia and thrombocytopenia, and slightly fewer patients suffered from grade ≥3 fatigue on rucaparib than on olaparib. However, the event rates were low across all three rucaparib and olaparib trials.

Table 20. Safety NMA outcomes, ITT population (adapted from CS Table 24)

| | Rucaparib versus placebo | Olaparib versus placebo | Rucaparib versus olaparib |
|---|---|---|---|
| | OR (95% CrI) | OR (95% CrI) | OR (95% CrI) |
| DAE | [redacted] | [redacted] | [redacted] |
| Grade ≥3 TEAE | [redacted] | [redacted] | [redacted] |
| Grade ≥3 anaemia | [redacted] | [redacted] | [redacted] |
| Grade ≥3 fatigue | [redacted] | [redacted] | [redacted] |
| Grade ≥3 Neutropenia | [redacted] | [redacted] | [redacted] |
| Grade ≥3 Thrombocytopenia | [redacted] | [redacted] | [redacted] |

Abbreviations: CrI, credible intervals; DAE, discontinuation due to adverse event; ITT, intention-to-treat; NMA, network meta-analysis; OR, odds ratio; TEAE, treatment emergent adverse event.

### 3.5.3 Matching adjusted indirect comparison

The key assumption of NMA is that any effect modifiers are balanced across trials. While there were broad similarities across the patients enrolled in ARIEL3, SOLO2 and Study 19, there were important differences that according to the company, questioning the validity of NMA. Therefore, the company conducted several MAICs in addition to the NMA:

- Anchored MAIC adjusting for clinically validated effect modifiers (informing the base-case analysis);
- Anchored MAIC adjusting for all available matching factors (sensitivity analysis);
- Unanchored MAIC adjusting for clinically validated effect modifiers and prognostic factors for OS.

An "anchored" indirect comparison is possible where there is a common comparator for the trials and an "unanchored" indirect comparison is used when there is not. The NICE DSU Technical Support Document (TSD) 18 recommends that anchored MAICs should only be adjusted for treatment effect modifiers and not for purely prognostic factors.[18] Therefore, the results of the sensitivity analysis adjusting for both effect modifiers and prognostic factors has not been reported or discussed in this report, but can be found in the CS Appendix D.1. The company also performed an unanchored MAIC for OS because of the differences in 'switching' to PARPi treatment in the placebo arms of ARIEL3 and Study 19. However, as mentioned previously, any ITC of OS will not be described or discussed because of the immaturity of the OS data from ARIEL3.

The anchored MAIC analyses were conducted in accordance to the NICE DSU TSD 18[18] following the methodology described by Signorovitch *et al.*[19] All analyses were conducted using Stata (version 14.2) and R (version 3.4.1) software.

The company conducted the MAICs of rucaparib and olaparib in the ITT population, BRCA subgroup and BRCA 3L+ subgroup of ARIEL3 and Study 19. The ERG is unsure of the company's rationale for conducting MAICs in the ITT population and the BRCA subgroup not limited to 3L+.

In short, individual patient-level data (IPD) from ARIEL3 were matched to aggregate data from SOLO2 and Study 19 by assigning weights to patients in ARIEL3 to balance differences in baseline characteristics from the target population in the comparator trials. The weights were also used to calculate the effective sample size (ESS) achieved after weighting patients. A comparative effect estimate for rucaparib versus olaparib was then derived using the Bucher method:

$$\ln(HR_{rucaparib\ vs\ comparator}) = \ln(HR_{\substack{rucaparib\ vs\ placebo \\ in\ reweighted\ ARIEL\ 3\ patients}}) - \ln(HR_{\substack{comparator\ vs\ placebo \\ in\ comparator\ trial}})$$

In the MAIC informing the base case, the IPD were matched with respect to effect modifiers, conditional on data availability. The identification and validation of potential treatment effect modifiers are described in the following section (Section 3.5.3.1).

For SOLO2, for which PFS data for the BRCA 3L and BRCA 4L+ populations were reported separately, outcome data for the BRCA 3L group and the BRCA 4L+ group were meta-analysed by standard pairwise meta-analysis. Baseline characteristics for the two groups were pooled using a weighted average and utilised for baseline characteristic matching and treatment effect estimates.

Data for the BRCA 3L+ group of SOLO2 were taken from a poster presented at ESMO 2017 that provided PFS data for the BRCA 3L and BRCA 4L+ populations separately.

#### *3.5.3.1 Exploration of prognostic factors and treatment effect modifiers*

The company used a Cox PH regression analyses to investigate the presence of treatment effect modifiers and prognostic factors for OS, PFS-INV and PFS-BICR in the ARIEL3 trial data. According to the company the set of variables considered in the investigation was obtained by considering:

- Factors used as stratification factors in the randomisation of the ARIEL3, SOLO2 and Study 19 trials;

- Factors identified as potential effect modifiers in previous NICE submissions;

- Factors for which baseline characteristics were available in both ARIEL3 and at least one comparator trial (i.e. SOLO2, Study 19);
- Factors for which subgroup analyses were planned in the ARIEL3, SOLO2 and Study 19 trials;
- Clinical experts were asked to supplement the list of potential treatment effect modifiers.

The Cox PH regression models were fitted adjusting for the levels of the potential effect modifiers, treatment and their interaction (separate models for each factor and each outcome). Matching factors with a p-value <0.2 were considered statistically significant. Treatment effect modifiers and prognostic factors were investigated in the ITT population and BRCA mutation cohort. The BRCA 3L+ population could not be analysed separately due to small number of patients. The resulting list of treatment effect modifiers was validated by a clinical expert in the UK who considered some statistically significant results to be clinically implausible and that other factors, which were not found to act as treatment effect modifiers in the ARIEL3 data, are known treatment effect modifiers in the treatment of ovarian cancer.

The factors concluded to be potential treatment effect modifiers and therefore attempts made to adjusted for in the anchored MAIC were:

- BRCA mutation status;
- Prior lines of platinum therapy;
- Platinum-free interval;
- Response to prior platinum therapy;
- BMI.

Although BMI was identified as a treatment effect modifier by the company, this could not be adjusted for as data on BMI were not reported in Study 19 or SOLO2. In addition, for the BRCA 3L+ population, which is the one relevant to the ITC of rucaparib and olaparib, ARIEL3 data were only adjusted for platinum-free interval and response to platinum therapy, but not BRCA status and number of prior lines of therapies as these are already accounted for by limiting the analysis to a subgroup. A potential benefit of using the results of the MAIC over the NMA for PFS is that the data for ARIEL3 have been adjusted to match that of Study 19, which is providing data for OS for both rucaparib and olaparib, thus, keeping the consistency between PFS and OS. According to the ERG's clinical experts all five factors are prognostic factors for patients with ovarian cancer, but the ERG notes that it is only for BRCA mutation status that there is a clear biological rationale for how it can modify the treatment effect of maintenance therapy with a PARPi. The ERG does not consider that it has been shown that an MAIC adjusting for

these factors would lead to a less biased estimate than a more standard NMA approach. In fact, comparing the results of the NMA and anchored MAIC adjusting for these factors, provides very similar results (Section 3.5.2).

Similar to the NMAs, the result of the anchored MAIC of PFS-INV differed substantially depending on the source of olaparib data. PFS estimates for the BRCA 3L+ group favoured rucaparib when using SOLO2 data for olaparib ([redacted]), but olaparib was favoured when using Study 19 data ([redacted]). Synthesising these results gave a HR of [redacted] ([redacted]), similar to the pooled result from the unadjusted NMA ([redacted]). The ERG notes that it is unclear how the company pooled the results of the MAIC with Study 19 and SOLO2.

The difference in results based on the olaparib data used is likely due to differences between the two trials (as discussed in Section 3.4), one of the key differences being the different formulations of olaparib. This is in keeping with the ERG's view that there is insufficient evidence to support the assumption that the capsule and tablet formulations of olaparib can be considered equivalent in terms of efficacy and the ERG therefore considers it inappropriate to combine the two sources of data, and that careful consideration needs to be taken to which data source is deemed to be the most reliable and applicable. In the ERG's view, Study 19 is the more appropriate resource, for the reasons discussed in Section 3.4.6. As mentioned previously, the company considers SOLO2 to provide a more robust and comparable dataset for the BRCA 3L+ population as represented by the larger effective sample size in MAIC synthesis using ARIEL3 and SOLO2 compared to MAIC synthesis using ARIEL3 and Study 19 (Table 21).

In support of using the data from SOLO2 for olaparib, the company also states that survival rates in Study 19 are high and have not been replicated in more recent trials. The ERG notes that the survival rates of patients in Study 19 cannot be compared with those reported in other PARPi maintenance trials as the follow-up time in the other studies is currently short and the data are very immature. Therefore, it is not possible to judge if the survival rates in Study 19 are unusually high. The ERG notes that for PFS SOLO2 provides a more complete data set than Study 19; at the primary analysis of SOLO2 around 60% of patients on olaparib in the BRCA 3L+ subgroup had progressed and more than 95% of patients on placebo. At the primary analysis of Study 19 the equivalent numbers were 34% for BRCA 3L+ on olaparib and 79% for BRCA 3L+ on placebo (Table 22). The company suggests that the substantial difference in results across the analyses justifies the adjustment for imbalances on treatment effect modifiers between trials. The ERG agrees that the BRCA 3L and 4L+ trial populations of SOLO2 have a better overlap in terms of prognostic factors, with the equivalent population of ARIEL3 compared with Study 19. However, the analyses have been adjusted for factors that are prognostic factors, but which have not been shown to necessarily be treatment effect modifiers. Hence, adjusting for them may unnecessarily decrease the effective sample size without the benefit of a more accurate result. In

addition, SOLO2 provides data on the tablet but not the capsule formulation of olaparib and using SOLO2 to inform PFS in the health economic model would introduce a source of dissonance between PFS and OS, which is informed by Study 19.

Table 21. Anchored MAIC outcomes BRCA 3L+ subgroup (adapted from CS Table 25)

| | **Rucaparib versus olaparib** | |
|---|---|---|
| **ARIEL3** | **SOLO2** | **Study 19** |
| Original sample size<br>Rucaparib [redacted]<br>Placebo [redacted] | Effective sample size<br>[redacted] | Effective sample size<br>[redacted] |
| PFS-INV<br>HR (95% CI) | [redacted] | [redacted] |
| Abbreviations: BC, base case; BRCA, breast cancer gene; CI, confidence interval; ESS, estimated sample size; HR, hazard ratio; INV, investigator-assessed; ITT, intention-to-treat; PFS, progression-free survival. | | |

Table 22. Maturity of PFS data - progression event rates at the primary analysis

| | **Olaparib** | **Placebo** |
|---|---|---|
| **SOLO2** | | |
| BRCA 3L | 57% | 95% |
| BRCA 4L+ | 64% | 100% |
| **Study 19** | | |
| BRCA 3L+ | 34% | 79% |
| Abbreviations: 2L, two prior lines of therapy; 3L+, three or more prior lines of therapy; 4L+, four or more prior lines of therapy; BRCA, breast cancer gene. | | |

### 3.5.4 Summary

- There was not sufficient evidence to refute the PH assumption between active treatments and placebo for OS or PFS-INV across the populations of interest in ARIEL3, Study 19 and SOLO2. PH may not hold for OS in the non-BRCA population of Study 19; however, this is of limited importance as no robust ITC is possible for this outcome as Study 19 is the only trial with long term OS data for a PARPi and for routine surveillance.

- The company explored and used two methods for the ITC of rucaparib and olaparib for the BRCA 3L+ population: NMA and MAIC. MAIC was done because of differences in potential effect modifiers within and between trials, which could affect the validity of the NMA. These differences are likely to be, at least partly, due to the *post hoc* and observational nature of the BRCA 3L+ subgroup in the trials. For the anchored MAIC of PFS-INV in the BRCA 3L+ population, data were adjusted for PFI and response to prior platinum therapy, which were identified as potential treatment effect modifiers. The ERG does not consider that it has been shown that an MAIC adjusting for these factors would lead to a less biased estimate than a more standard NMA approach.

- The NMA and anchored MAIC give very similar results. Irrespective of data source or method used, the results do not reach statistically significant differences but with either method the

point estimate was greatly influenced by the data source informing the outcome for patients on olaparib: PFS favours olaparib over rucaparib when using Study 19 to provide the olaparib data and the opposite when using SOLO2. The ERG considers Study 19 to be a more appropriate source of olaparib data than SOLO2, for the reasons outlined in Section 3.4.6. The ERG does not consider the non-statistically significant results justifies the assumption that PFS is equivalent for rucaparib and olaparib. Instead the ITC analyses suggest that the olaparib capsule formulation, currently recommended for routine commissioning, provides longer PFS than rucaparib.

- No conclusions can be drawn about how rucaparib and olaparib compare for OS as OS data are very immature for ARIEL3, and the ITC of rucaparib and olaparib for OS is of limited value.

- Safety analyses (based on ITT population and all three trials) in general favours olaparib over rucaparib, with a statistically significant difference for grade >3 TEAE but no statistically significant difference for individual AEs or discontinuations due to AEs.

## *3.6 Conclusions of the clinical effectiveness section*

The CS, and subsequent clarification response, presents an assessment of rucaparib as a maintenance treatment for patients who have platinum-sensitive, relapsed, high grade ovarian cancer that is in response to platinum-based chemotherapy. One trial, ARIEL3, provides direct comparative evidence on the clinical efficacy and safety of maintenance treatment with rucaparib versus placebo. ARIEL3 is a randomised, double-blind, multicentre placebo-controlled phase III trial evaluating rucaparib in patients irrespective of BRCA mutation status. A relatively small proportion of the study population was recruited in the UK, but the full trial population is representative of patients with recurrent, platinum-sensitive high-grade ovarian cancer eligible for treatment in England.

The primary and key secondary outcomes in ARIEL3 were analysed in a multiple comparison stepdown approach. The primary outcome, investigator assessed PFS in the BRCA cohort, showed a statistically significant benefit with rucaparib therapy compared with placebo. The outcomes next in line in the stepdown analysis were PFS in the HRD cohort and ITT population, which were consistent with the primary outcome result favouring rucaparib. Analyses of the non-BRCA subgroup and *post hoc* analyses of the BRCA subgroup by line of therapy (BRCA 2L and BRCA 3L+) support the main analyses, but the efficacy of rucaparib was reduced in the subgroup of patients without a BRCA mutation. Results of the secondary and exploratory outcomes TFST, PFS2 and TSST were also consistent with the primary outcome results favouring rucaparib.

HRQoL, which was measured as time to worsening in the DRS-P FOSI-18 subscale and FOSI-18 total score, generally favoured placebo over rucaparib in the three populations, although because of the

stepdown analysis approach statistical significance was not declared for these analyses. The frequency of grade 3 or more AEs were relatively high in ARIEL3 and a substantial proportion of patients, primarily in the rucaparib group, had dose reductions or dose interruptions to manage AEs; the most common AE in the rucaparib arm was combined anaemia/low or decreased haemoglobin. There were nine fatal adverse events in the trial: two in the placebo group and seven in the rucaparib group, two of which a relationship to the study drug could not be ruled out.

OS data from ARIEL3 are currently not mature enough to inform the comparison of rucaparib and placebo for the ITT, non-BRCA and BRCA 2L populations or of rucaparib and olaparib in the BRCA 3L+ population. Study 19 is the only trial available to inform the long-term outcomes of PARPi maintenance therapy and of routine surveillance. There are several differences between ARIEL3 and Study 19 in terms of trial design and trial populations. However, due to the lack of OS data for rucaparib compared with olaparib or routine surveillance, the ERG considers Study 19 to provide the most robust OS data available but acknowledges that there is limited evidence to support the assumption of equivalence between rucaparib and olaparib in terms of survival. In addition, some patients in the placebo group of Study 19 received post-discontinuation PARPi treatment. This may confound the estimate of the relative efficacy of olaparib versus placebo for OS, as the difference between the treatment groups is reduced by patients in the placebo group benefiting from subsequent PARPi therapy. However, in clinical practice subsequent PARPi therapy with olaparib is available through routine commissioning for the subgroup of patients with a BRCA mutation and the trial data may therefore provide a reasonable estimate of the efficacy of PARPi relative to routine surveillance as used in clinical practice for this subgroup.

For the ITC of rucaparib and olaparib in the BRCA 3L+ population, two olaparib trials were identified, SOLO2 and Study 19. Study 19 assesses the efficacy and safety of olaparib capsules, which is the formulation currently recommended for routine commissioning, whereas SOLO2 assesses olaparib tablets, the appraisal of which is currently ongoing. There are little available data to support or refute equivalence between the formulations in terms of clinical efficacy or safety. However, OS data for SOLO2 are very immature and therefore only PFS data is of potential relevance from this study, whereas Study 19 can inform both PFS and OS. In addition, the ERG has a strong preference, where possible, for a coherent dataset for PFS and OS as opposed to treating them as disconnected outcomes. The ERG therefore considers it more appropriate to focus on Study 19 in the ITC with rucaparib.

The company explored and used two methods for the ITC of rucaparib and olaparib PFS for the BRCA 3L+ population: NMA and MAIC. A MAIC was done because of differences in potential treatment effect modifiers within and between the trials, which could affect the validity of the NMA. With either method, the point estimate was greatly influenced by the data source informing the outcome for patients on olaparib. However, irrespective of data source or method used, the results did not reach statistical

significance. The ERG does not consider the non-statistically significant results justify the assumption that PFS is equivalent for rucaparib and olaparib. Instead the results of the NMA and MAIC are consistent, suggesting that the olaparib capsule formulation provides longer PFS than rucaparib. Safety analyses (based on ITT population and all three trials) in general favours olaparib over rucaparib, with a statistically significant difference for grade >3 TEAE but no statistically significant difference for individual AEs or discontinuations due to AEs.

# 4 COST EFFECTIVENESS

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

The company carried out a systematic literature review (SLR), using a single search strategy, to identify existing cost-effectiveness evidence, health-related quality of life (HRQoL) evidence, and cost and resource use evidence of rucaparib and comparator interventions in women with *de novo* locally advanced or metastatic ovarian cancer, fallopian tube or primary peritoneal carcinomas who have: platinum-sensitive disease; received two or more prior lines of chemotherapy; and responded to platinum-based therapy. A summary of the ERG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 23. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 23. Summary of ERG's critique of the methods implemented by the company to identify health economic evidence

| Systematic review step | Section of CS in which methods are reported | | | ERG assessment of robustness of methods |
|---|---|---|---|---|
| | Cost-effectiveness evidence | HRQoL evidence | Cost and resource use evidence | |
| Searches | Appendix G | Appendix G | Appendix G | Appropriate |
| Inclusion criteria | Appendix G | Appendix G | NR | Restrictions to English-language publications in the last 10 years reasonable.<br>PICOS appropriate for cost-effectiveness evidence and HRQoL evidence.<br>Unclear how cost and resource use evidence was selected for inclusion. |
| Screening | Appendix G | Appendix G | Appendix G | Appropriate |
| Data extraction | Appendix G | Appendix H | Appendix I | Appropriate |
| QA of included studies | Drummond checklist in Appendix G | No QA checklist completed. Report consistency with reference case in Appendix H | Drummond checklist in Appendix G. Report applicability to clinical practice in England in Appendix I | Drummond checklist appropriate.<br>Checklists such as CASP (recommended in DSU TSD 9[20]) would be preferred for HRQoL evidence. |

Abbreviations: CASP, Critical Appraisal Skills Programme; CS, company submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; NR, not reported; PICOS, population, intervention, comparator, outcome, study design; QA, quality assessment

Overall, a total of eight cost-effectiveness studies (across 10 publications), one HRQoL study and two resource and cost use studies were identified. However, the ERG is unclear why the company did not include relevant NICE technology appraisals (TAs) for maintenance therapy in relapsed ovarian cancer

such as TA381[7] and TA528,[8] nor the key sources of utility data identified within those TAs including: NOVA,[21] OVA-301,[22] Study 19;[5] and SOLO2.[6] In response to the ERG's clarification question, the company explained that the SLR focused on indexed databases and key conference proceedings, and therefore, TAs would not be picked up. The company also added that HRQoL data from NOVA, Study 19, and SOLO2 was identified in the clinical SLR and that OVA-301 was excluded during the screening stages, as it did not specifically provide results for patients who were in complete or partial response to their most recent platinum therapy and are undergoing maintenance therapy.

## *4.2 Summary and critique of the company's submitted economic evaluation by the ERG*

### 4.2.1 NICE reference case checklist

Table 24 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.3.[2, 23]

Table 24. NICE reference case checklist

| Element of health technology assessment | Reference case | ERG comment on company's submission |
|---|---|---|
| Perspective on outcomes | All direct health effects, whether for patients or, when relevant, carers | All relevant health effects for patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy have been included. |
| Perspective on costs | NHS and PSS | All relevant costs have been included and are based on the NHS perspective. |
| Type of economic evaluation | Cost–utility analysis with fully incremental analysis | Cost-utility analysis with fully incremental analysis has been provided by the company. |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | Lifetime horizon (30 years). However, to capture costs and benefits for the younger proportion of the cohort, ERG considers a 50 year time horizon is more appropriate. |
| Synthesis of evidence on health effects | Based on systematic review | The company performed an appropriate systematic review. |
| 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. | QALYs calculated using EQ-5D-3L data from ARIEL3. |
| Source of data for measurement of health-related quality of life | Reported directly by patients and/or carers | EQ-5D-3L reported directly from the ITT population of ARIEL3. |
| Source of preference data for valuation of changes in health-related quality of life | Representative sample of the UK population | The ITT population of ARIEL3 is representative of the UK population. |
| Equity considerations | An additional QALY has the same weight regardless of the other | The economic evaluation matches the reference case. |

| | | |
|---|---|---|
| | characteristics of the individuals receiving the health benefit | |
| 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 included in the analysis have been sourced using NHS reference costs[24], the BNF[25] and published literature and are reported in pounds sterling for the price year 2018. |
| Discounting | The same annual rate for both costs and health effects (currently 3.5%) | Discount rate of 3.5% has been used for both costs and health effects. |
| Abbreviations: BNF, British National Formulary; ITT, intention to treat; PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome. | | |

### 4.2.2 Population

The population considered by the company for this single technology appraisal (STA) is based on the proposed marketing authorisation, which includes adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. This population can be split by breast cancer susceptibility gene mutation (BRCA) status and the number of lines of prior platinum-based chemotherapy patients have received.

The company's base-case analyses focus on the intention-to-treat (ITT) population of ARIEL3, which includes all patients, regardless of BRCA status, who have had two lines or more of platinum-based chemotherapy and BRCA patients who have had three or more lines of platinum-based chemotherapy (hereafter, BRCA 3L+ population). However, the NICE final scope states that, "If the evidence allows, consideration will be given to subgroups with or without BRCA mutations".[2] The ERG considers that the company should have presented subgroup analysis for the non-BRCA cohort and the BRCA cohort who have only had two lines of platinum-based chemotherapy (hereafter, BRCA 2L). During the clarification stage, the ERG requested subgroup analyses for the non-BRCA and BRCA2L populations which were provided by the company with the caveat that these are *post-hoc* analyses with small patient numbers and low event rates and as such the results should be interpreted with caution.

### 4.2.3 Interventions and comparators

The intervention and comparators considered in the economic analysis were rucaparib (intervention) and routine surveillance (comparator) for the ITT population and olaparib (comparator) for the BRCA 3L+ population. These are in line with the NICE final scope.[2] However, the ITT population includes BRCA patients who have had 3 or more lines of platinum based chemotherapy and as such would be eligible for olaparib rather than routine surveillance in UK clinical practice. During the clarification stage, the company provided subgroup analysis for the BRCA2L population, which corrects the issue

of appropriate comparator, however the company maintain the ITT population analysis as their base case.

The dosing regimen for rucaparib and olaparib is presented in Table 25. Routine surveillance is assumed to comprise of patient observation, follow-up and general supportive or symptomatic care.

Table 25. Active treatment dosing regimen

| Active treatment | Total Dose | Dose regimen |
|---|---|---|
| Rucaparib | 1200mg | 2 x 300mg tablets, taken orally twice daily |
| Olaparib | 800mg | 8 x 50mg capsules, taken orally twice daily |
| Abbreviations: mg, milligram. | | |

Time to maintenance treatment discontinuation (TTD) for rucaparib for the ITT analyses is based on data from ARIEL3, extrapolated over a lifetime horizon using parametric survival distributions (described further in Section 4.2.5). Early discontinuation of treatment was primarily due to objective disease progression (determined by RECIST) or because of unacceptable toxicity.

For the BRCA3L+ population, in the original company submission, TTD was estimated as a constant discontinuation rate based on discontinuations due to adverse events (AEs) from ARIEL3 (rucaparib) Study 19 (olaparib). However, during the clarification stage the ERG requested the company to estimate TTD using Kaplan Meier (KM) data from ARIEL3 and Study 19 for the BRCA3L population and extrapolate over a lifetime horizon, which the company did for their revised base-case analyses.

It should be noted that the Summary of Product Characteristics (SmPC)[26] states that olaparib should be given until progression of the underlying disease. However, in Study 19, patients could continue to receive olaparib if they were still experiencing clinical benefit and there was no unacceptable toxicity.[26] Please refer to Section 4.2.5 for further detail on the extrapolation of TTD data.

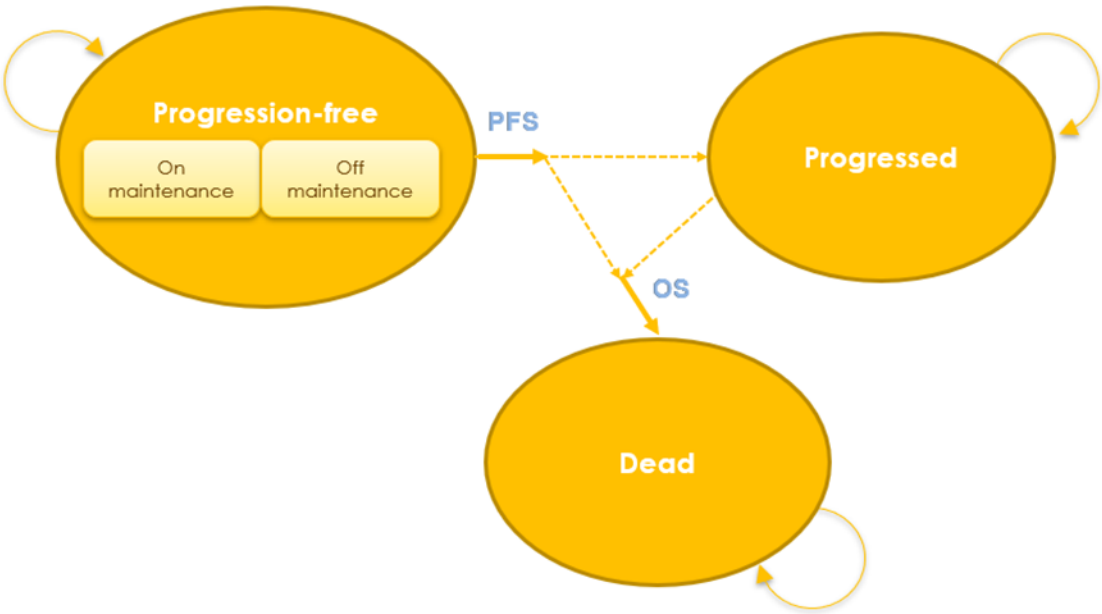
## 4.2.4 Model structure (incl. perspective, time horizon and discounting)

A single *de novo* economic model was developed in Microsoft© Excel to assess the cost-effectiveness of rucaparib compared with routine surveillance (ITT population) and olaparib (BRCA 3L+ population) as maintenance therapy for adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The model structure is based on a partitioned survival analysis structure, with three main health states: progression-free, progressed and dead. The progression-free health state is further sub-divided into progression-free on maintenance and progression-free off maintenance, with proportions determined by TTD data. Figure 7 presents the company model schematic. The company states that the adopted model

structure adopted is in line with previous NICE appraisals for maintenance therapy in relapsed ovarian cancer, including olaparib (TA381 and the ongoing appraisal, GID1296) and TA528.[7, 8, 14]

Figure 7. Model structure (Figure 7 of the CS)




All patients enter the model in the progression-free health state and are assumed to be on rucaparib, routine surveillance (ITT population) or olaparib (BRCA 3L+). For patients in the progression-free health state on active treatment (rucaparib or olaparib), during each model cycle they can be either progression-free and on maintenance treatment or progression-free and off maintenance treatment if they are experiencing unacceptable toxicity. For all patients regardless of treatment strategy, they can remain in the progression free health state until disease progression, at which point they transition to the progressed health state or die (transitioning to the dead health state). When patients transition into the progressed health state, they remain in this health state until death.

The proportion of patients occupying a health state during any given cycle is based on parametric survival curves for the clinical outcomes progression-free survival (PFS) (used to model the progression free health state), overall survival (OS) and TTD (used to estimate the proportion of patients who are progression-free and on maintenance treatment). The proportion of patients occupying the progressed health state for any given cycle is calculated as the difference between OS and PFS per cycle. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 4.2.5.

A cycle length of one month was implemented in the model with half cycle correction applied. The model time horizon was set to 30 years. The perspective of the analysis is based on the UK national

health service (NHS), with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.[23]

#### *4.2.4.1 ERG critique*

The ERG considers the structure of the company's model is appropriate, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other appraised oncology models. The one-month cycle length used in the model is suitable to capture important changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. Half-cycle correction has been appropriately applied in the model to prevent over or under-estimation of costs and quality adjusted life years (QALYs).

The primary issue with the model structure concerns the time horizon of 30 years. When using a 30-year time horizon for the extrapolations of the clinical outcomes for rucaparib for the ITT analysis, a small proportion of patients (~3%) are alive at 30 years. In their clarification response, the company provided subgroup analyses for the non-BRCA and BRCA2L populations and these analyses predict that approximately 6% of patients are alive at 30 years. For the BRCA3L+ population, this is not an issue as OS reaches 0% by 30 years. Due to time constraints, the ERG performed brief analysis looking at whether incorporating background mortality would affect the percentage of patients alive at 30 years. However, background mortality had little impact on OS as the mortality hazard is still higher for patients with ovarian cancer than the general population.

As such, the ERG considers that the time horizon of the model (30 years) may not be long enough to capture outcomes for the younger proportion of the rucaparib cohort and that instead the time horizon should be 50 years. In ARIEL3, the mean age of both the rucaparib and placebo cohorts was 61 years. However, in the rucaparib arm, [redacted] of patients were less than 65 years old and in the placebo arm, this figure was [redacted]. Furthermore, a longer time horizon allows OS to reach 0%. The company performed a scenario where the time horizon of the model is 50 years and results are presented in Section 5.2.3.

More information and critique of the methods used to estimate proportions of patients within each health state is provided in Section 4.2.5.

### 4.2.5 Treatment effectiveness and extrapolation

Treatment effectiveness estimates in the model for rucaparib, routine surveillance and olaparib are calculated using extrapolations of ARIEL3 Kaplan Meier (KM) data for PFS, and Study 19 KM data for OS. Study 19 OS outcomes were used as OS data from ARIEL3 are extremely immature. Time on treatment estimates in the model for ITT patients on rucaparib were based on an extrapolation of TTD KM data from ARIEL3. For the BRCA 3L+ population, the company originally estimated TTD using discontinuation rates due to AEs from ARIEL3 (rucaparib) and Study 19 (olaparib), from which per

cycle probabilities of treatment discontinuation were calculated. However, in their clarification response, the company amended their base-case analysis for the BRCA3L+ population to extrapolate KM TTD data from ARIEL3 (rucaparib) and Study 19 (olaparib). To ensure that TTD cannot be greater than PFS in any given cycle, the company imposed a cap on TTD using PFS; i.e. TTD could never be greater than PFS.

The company first assessed whether the assumption of proportional hazards (PH) held for the outcomes of the ARIEL3 and Study 19 trial data using log-cumulative hazard plots. Extrapolations of the KM data were then performed using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma). In addition to the standard parametric survival distributions, a 1-knot spline distribution was also explored for Study 19 OS outcomes for the ITT population. The company's rationale for the inclusion of the 1-knot spline distribution for OS for the ITT population was to maintain consistency with ERG preferences from the ongoing olaparib appraisal (GID1296).[14] The company states it implemented the process of parametric curve selection recommended in the NICE decision support unit technical support document (DSU TSD) 14 to select an appropriate distribution for the extrapolation of each outcome.[27] The company assessed the fit of each modelled curve against the observed KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility of the extrapolation over the time horizon of the economic model.

Table 26 presents the results of the company's parametric curve selection exercise for PFS, OS and TTD for both the ITT and BRCA 3L+ populations (where applicable). The company chose to model each treatment arm independently. Log-cumulative hazard plots, AIC/ BIC statistics and plots of all the assessed distributions compared with the KM curve can be found in Section B.3.3 of the company submission.

Table 26. Results of the company's parametric curve selection exercise

| Clinical outcome | Data source | Company's preferred survival distribution |
|---|---|---|
| **ITT population** | | |
| PFS | ARIEL3 – investigator assessed | Lognormal |
| OS | Study 19 | 1-knot spline |
| TTD | ARIEL3 | Log-logistic |
| **BRCA 3L+ population** | | |
| PFS | ARIEL3 – investigator assessed | Lognormal |
| OS | Study 19 | Lognormal |
| TTD (rucaparib) | ARIEL3 | Exponential |
| TTD (olaparib) | Study 19 | Log-logistic |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

The company assumed clinical equivalence between rucaparib and olaparib for the BRCA3L+ population. In the model, PFS outcomes for olaparib were assumed to be equal to ARIEL3 PFS outcomes for rucaparib and OS outcomes for rucaparib were assumed to be equal to Study 19 OS outcomes for olaparib.

To calculate the post-progression survival (PPS) for the ITT population analysis, the company extrapolated PFS KM data for olaparib and routine surveillance from Study 19 for the ITT population using a lognormal distribution. The company then calculated the difference between Study 19 PFS and OS to estimate the per cycle progressed health state occupancy, for which costs and utilities associated with the progressed health state are applied.

For the BRCA3L+ population, the company calculated PPS as the difference between the extrapolated ARIEL3 PFS and Study 19 OS. The company's justification for this approach for the BRCA3L+ population is based on the company's assumption of clinical equivalence between rucaparib and olaparib for PFS and OS for this population and thus implying that post-progression outcomes for the two treatments will be equal.

#### *4.2.5.1 ERG critique*

The company's base-case cost-effectiveness analyses focus on the ITT and BRCA3L+ populations. The ERG considers the modelling of treatment effectiveness for these two populations, that is extrapolation of PFS and OS data, to be appropriate. Furthermore, modelling of TTD is also considered by the ERG to be satisfactory. In the original CS, the public PAS for olaparib (free after 15 cycles of treatment) was not included in the base-case analysis for the BRCA3L+ population, however in their clarification response the company corrected this error and provided revised base case results (see Section 5.1).

It should be noted that for the BRCA3L+ population, the assumption of clinical equivalence between rucaparib and olaparib (e.g. PFS and OS are the same for both treatments) was justified by the company based on the results of the indirect treatment comparison (ITC) showing that there is no statistically significant difference for PFS between the two treatments. However, the ERG does not consider the non-statistically significant results justifies the assumption of clinical equivalency for rucaparib and olaparib, as depending on the trial used for the ITC (SOLO2 vs Study 19), the point estimates for the PFS hazard ratio indicate rucaparib is either better (SOLO2) or worse (Study 19) than olaparib for PFS. Furthermore, ITC cannot be performed for OS due to the immature data for both ARIEL3 and SOLO2 (see Section 3.5 for further details).

As mentioned previously, the ERG considers Study 19 to be a more appropriate source of olaparib data than SOLO2, for the reasons outlined in Section 3.4.6. The ITC based on Study 19 demonstrates that the hazard ratio favours olaparib for PFS. Therefore, the company's simplifying assumption of

rucaparib and olaparib having the same PFS and OS is likely to be a favourable assumption for rucaparib. Though, in the absence of comparative analysis of OS for the two treatments, no definitive conclusions can be made. As such, the ERG considers that the company's assumption of PFS and OS being equal for rucaparib and olaparib reduces the analysis down to a cost minimisation analysis, which is the most appropriate way to consider the relative cost differences between the two treatments in lieu of robust relative clinical data.

One of the ERG's main concerns about the company's approach to modelling treatment effectiveness is the lack of subgroup analyses by BRCA status. As mentioned in Section 4.2.2, the NICE final scope states that, "If the evidence allows, consideration will be given to subgroups with or without BRCA mutations".[2] In response to requests from the ERG during the clarification stage, the company performed subgroup cost-effectiveness analyses for the non-BRCA and BRCA2L populations. The company conducted *post-hoc* analysis of ARIEL3 PFS and TTD data by population but caveat the analysis with small patient numbers and heavy censoring.

As with the base case analyses, the company extrapolated the ARIEL3 PFS and TTD for each population using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma). The company selected survival curves based on the lowest AIC/BIC statistics (provided separately to the company's clarification response). However, for the base case ITT and BRCA3L+ analyses, the company stated in the original CS that visual fit and clinical plausibility were considered in addition to lowest AIC/BIC statistics and presentation of all curves were provided.

OS data by BRCA status was obtained from Study 19 and extrapolated using 1-knot spline distributions. Table 27 presents the company's preferred survival distributions for the subgroup analyses.

Table 27. Company and ERG preferred survival distributions for the subgroup analyses.

| Outcome | Company preferred survival distribution | | ERG preferred survival distribution | |
|---|---|---|---|---|
| | non-BRCA | BRCA2L | non-BRCA | BRCA2L |
| PFS | Generalised gamma | Lognormal | Lognormal | Weibull |
| OS | 1-knot spline | 1-knot spline | Same as company | Same as company |
| TTD | Log-logistic | Lognormal | Same as company | Same as company |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation

Table 28 presents the company's deterministic subgroup cost-effectiveness results. At a late stage in the ERG report development, the company provided probabilistic cost-effectiveness results, presented in Table 29. All assumptions used for the company's base case ITT analysis have been maintained for the subgroup analyses. However, the ERG made corrections to the company's model and corrected results can be found in Section 6.1.

Table 28. Company deterministic subgroup cost-effectiveness results (Table 16 and 17, company clarification response)

| Subgroup | Comparators | Total costs | Total QALYs | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|
| Non-BRCA | Routine surveillance | [redacted] | [redacted] | - | - | - |
| | Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | £33,340 |
| BRCA2L | Routine surveillance | [redacted] | [redacted] | - | - | - |
| | Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | £58,054 |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

Table 29. Company probabilistic subgroup cost-effectiveness results (Table 16 and 17, company clarification response)

| Subgroup | Comparators | Total costs | Total QALYs | Incremental costs | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|
| Non-BRCA | Routine surveillance | [redacted] | [redacted] | - | - | - |
| | Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | £32,501 |
| BRCA2L | Routine surveillance | [redacted] | [redacted] | - | - | - |
| | Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | £55,511 |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

The ERG investigated the company's survival distribution selection by comparing all the survival distributions against the KM data for PFS and TTD for each population, assessing clinical validity (for example no clinically implausible tails of the curves) and AIC/BIC statistics. In addition, a comparison of mean modelled PFS and TTD was conducted. Table 27 provides a comparison of the company and ERG preferred curve choices for each subgroup. The ERG considers that the company's curve selections for OS and TTD for both populations is satisfactory.

For the non-BRCA population, the lognormal distribution for modelling PFS provided a superior fit to the KM data compared with the company's preferred choice of the generalised gamma. The lognormal distribution was also the second-best fitting curve when AIC/BIC statistics are considered. Furthermore, the ERG found that the company's preferred curve choices for the non-BRCA population for PFS resulted in the modelled mean [redacted] than modelled mean TTD. The impact of the difference in means, is that treatment costs are [redacted] compared to the benefit obtained. The company did not provide an explanation for why it would be plausible to have such a difference in PFS and TTD. However, according to the SmPC for rucaparib, treatment should be given until disease progression or unacceptable toxicity.[26] While the ERG considers that TTD for this population is modelled appropriately, implementation of the lognormal survival curve for PFS results

in a modelled mean that aligns better with the modelled mean for TTD ([redacted]). Please refer to Section 6 for the results of the alternative curve scenario.

For the BRCA2L subgroup analysis, the ERG considered that Weibull survival curve had a better visual fit to the KM data. In terms of clinical plausibility, [redacted] in comparison to the company's preferred choice of the lognormal survival curve, which estimated that approximately [redacted]. Please refer to Section 6 for the results of the alternative curve scenario.

An additional issue that the ERG is concerned with is the company's approach to modelling PPS for the ITT, non-BRCA and BRCA2L populations. As OS data from ARIEL3 are immature, the company calculated PPS as the residual of extrapolated progression-free survival (PFS) and overall survival (OS) from Study 19 for each population. However, this approach results in an indirect application of a PFS:OS ratio of [redacted], [redacted] 1:2, considered by the committee for the appraisals of niraparib (TA528)[8] and olaparib (GID1296)[14] as being an optimistic assumption.

Moreover, the ERG considers the company's method unconventional as the calculation of PPS is disconnected from the PFS informing the analyses. Therefore, the overall patient population per cycle used to estimate costs and benefits does not sum to one. Thus, depending on the cycle, costs and benefits maybe over or underestimated.

During the clarification stage, the ERG requested the company to calculate PPS as the residual of ARIEL3 PFS and Study 19 OS for the ITT, non-BRCA and BRCA2L populations. The ERG considers that this approach to calculating PPS makes the most of the mature data available. However, the ERG acknowledges that the approach has several limitations, including:

- using different sources of data for PFS and OS,
- the inherent assumption that OS outcomes for rucaparib are at least as good as olaparib,
- patients in the routine surveillance arm for ARIEL3 and Study 19 are similar,
- data for the BRCA2L subgroup from Study 19 includes all BRCA patients regardless of number of lines of platinum-based chemotherapy.

In the company's clarification response, they state that the ERG preferred method for calculating PPS is not appropriate as it assumes that the mortality hazard is higher for patients on rucaparib compared with olaparib, based on what the ERG assumes is a naïve comparison of PFS from ARIEL3, which demonstrates longer PFS than in Study 19. As such, the company state that calculating PPS as the residual of ARIEL3 PFS and Study 19 OS will result in shorter PPS outcomes. The company therefore

maintained their base case assumption for the ITT, non-BRCA and BRCA2L populations. However, the ERG wishes to highlight that for the BRCA3L+ population, the company contradicted their PPS approach used for the ITT, non-BRCA and BRCA2L populations by assuming that PPS outcomes would be the same for both olaparib and rucaparib, as they are considered clinically equivalent and as such calculated PPS as the residual of ARIEL3 PFS and Study 19 OS.

Irrespective of the justification for maintaining their base case approach to PPS, the company did provide scenario analyses of the ERG preferred method in their clarification response. For the non-BRCA and BRCA2L analyses, the ERG preferred PPS approach results in a PFS:OS ratio of greater than 1:1, which the committee for the appraisals of niraparib (TA528) and olaparib (GID1296) considered was too conservative, but less than 1:2. For the ITT population, the ERG preferred approach results in a PFS:OS ratio that is greater than 1:2, but less than the company's resultant ratio of [redacted] (response to clarification question B4). Table 30 presents the results of the company scenarios for PFS:OS ratios of 1:1 and 1:2, as well as the results for the ERG preferred PPS approach for the ITT, non-BRCA and BRCA2L populations.

Table 30. Comparison of company scenarios for PPS (taken from the company's clarification response)

| Scenario | ICERs | | |
|---|---|---|---|
| | ITT | Non-BRCA | BRCA2L |
| Company case [redacted] | £50,681 | £33,340 | £58,054 |
| PFS:OS ratio = 2 | £62,767 | £35,560 | £61,415 |
| PFS:OS ratio = 1 | £108,976 | £57,726 | £105,704 |
| PPS calculated as the residual of ARIEL3 PFS and Study 19 OS (**ERG preferred approach**) | **£59,078** | **£45,217** | **£79,007** |

Abbreviations: BRCA, breast cancer susceptibility gene mutation, ERG. Evidence review group; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; PFS, progression-free survival; PPS, post-progression survival; OS, overall survival

### 4.2.6 Adverse events

For the base-case analysis, the company included grade 3 or higher adverse events (AEs) that were reported by at least 5% of patients in either treatment arm of ARIEL3, presented in Table 31. In addition, the company included nausea and vomiting to reflect clinical expert opinion and thrombocytopenia and hypertension for consistency with TA528.[8]

Based on information provided in the company's clarification response, treatment-emergent adverse events (TEAEs) were used from ARIEL3 and are based on data available at the primary database lock (15 April 2017). For olaparib, treatment-related adverse events (TRAEs), obtained from EMA CHMP assessment report for olaparib, were used.[28]

Table 31. Grade 3 and above adverse event rates from ARIEL3 and Study 19 (obtained from economic model)

| Adverse Event | Rucaparib (ARIEL3) | Routine surveillance (ARIEL3) | Olaparib (Study 19) |
|---|---|---|---|
| Combined ALT/AST | [redacted] | [redacted] | 0.0% |
| Anaemia | [redacted] | [redacted] | 5.1% |
| Fatigue/asthenia | [redacted] | [redacted] | 7.4% |
| Neutropenia | [redacted] | [redacted] | 5.9% |
| Thrombocytopenia | [redacted] | [redacted] | 0.0% |
| Nausea/vomiting | [redacted] | [redacted] | 4.4% |
| Hypertension | [redacted] | [redacted] | 0.0% |
| Abbreviations: ALT, alanine aminotransferase; AST, combined aspartate transaminase. | | | |

Using the values presented in Table 31, the company calculated a per cycle risk of each AE, presented in Table 32. The company assumed the risk of AEs were the same, regardless of BRCA status and line of therapy.

Table 32. Adverse event risk per month (Table 55 of the CS)

| Adverse Event | Rucaparib | Routine surveillance | Olaparib |
|---|---|---|---|
| Combined ALT/AST | [redacted] | [redacted] | 0.00% |
| Anaemia | [redacted] | [redacted] | 0.36% |
| Fatigue/asthenia | [redacted] | [redacted] | 0.52% |
| Neutropenia | [redacted] | [redacted] | 0.41% |
| Thrombocytopenia | [redacted] | [redacted] | 0.00% |
| Nausea/vomiting | [redacted] | [redacted] | 0.31% |
| Hypertension | [redacted] | [redacted] | 0.00% |
| Abbreviations: ALT, alanine aminotransferase; AST, combined aspartate transaminase. | | | |

The impact of AEs on patients' quality of life is considered in the model and is described further in Section 4.2.7, while the costs of managing AEs are discussed in Section 4.2.8.

#### *4.2.6.1 ERG critique*

The ERG considers the company's approach to selecting AEs to be included in the model is reasonable. The ERG's clinical experts confirmed that all AEs expected to be encountered in patients receiving rucaparib and olaparib that have an impact on patients' quality of life, or are associated with substantial costs, have been included in the model. However, the ERG considers the use of both TEAEs and TRAEs are an inconsistency, but that it is unlikely to have a substantial impact on the ICER.

The ERG considers that the company could have taken a simpler approach to incorporating AEs in the model, by assuming that AEs happen in the first cycle of the model and using the rates reported in Table 31 to weight AE specific costs and utilities, rather than apply a continuous risk of each AE over the lifetime horizon of the model. However, the ERG considers that AEs are not a key driver of the model and changing how AEs are implemented in the model is likely to have minimal impact on the ICER.

### 4.2.7 Health-related quality of life

In the company's base-case analysis, health state utility values (HSUVs) were derived from EQ-5D-3L data collected in ARIEL3. During the ARIEL3 trial, all patients in the ITT population completed the EQ-5D-3L questionnaire at screening, on day one of every treatment cycle, at treatment discontinuation and at the 28-day follow-up visit after treatment discontinuation. At cycle one, 525 responses were collected. By the end of treatment and the 28-day follow-up, 245 and 174 responses were collected, respectively. Table 33 presents the mean HSUV for the progression-free and progressed disease health states.

Table 33. ARIEL3 health state utility values used for cost-effectiveness analysis (Table 56 of the CS)

| Health state | Utility value (SE) | 95% confidence interval |
|---|---|---|
| Progression-free | [redacted] | [redacted] |
| Progressed disease | [redacted] | [redacted] |
| Abbreviations: SE, standard error. | | |

For the progressed disease HSUV, the company calculated a utility decrement of [redacted] for progressed disease using a mixed-effects linear regression model, fitted using all available EQ-5D-3L data and applied this to the mean progression-free HSUV.

In the base-case analysis, the company did not include the utility impact of AEs as HSUVs were derived directly from patients in ARIEL3 and as such captured the impact of experiencing AEs. However, the company performed a scenario analysis included the utility impact of AEs, using disutilities derived from the published literature, but this had minimal impact on the ICER.

#### *4.2.7.1 ERG critique*

The ERG considers that the company's approach to estimating HSUVs is reasonable as it measured changes in HRQoL directly from patients in the ARIEL3 trial using a generic preference-based measure (EQ-5D), following the key components of the NICE reference case.[23] The ERG considers that the exclusion of AE disutilities for the base-case analysis is reasonable and that the company's scenario including disutilities demonstrates that AEs are not a key driver of cost-effectiveness for rucaparib.

However, the company assumed utility is the same regardless of BRCA status, or number of platinum-based chemotherapy regimens received prior to maintenance treatment. To explore the validity of this assumption, the ERG sought clinical expert opinion who advised that a patient's quality of life may fall with each line of platinum-based chemotherapy they receive but will not be affected by BRCA status. Following a clarification request from the ERG, the company provided EQ-5D data for patients in ARIEL3 who received two prior lines of platinum-based chemotherapy therapy and three or more prior lines of platinum-based chemotherapy (Table 34). The ERG considers that EQ-5D data obtained from

ARIEL3 is similar regardless of whether a patient received two prior lines or three or more prior lines and thus finds the company's base case utility assumption is reasonable.

Table 34. EQ-5D subgroup analysis for ARIEL3 patients (adapted from Table 49 of the company's clarification responses)

| Health state | Utility value | 95% confidence interval |
|---|---|---|
| **Base case (ITT)** | | |
| Progression-free | [redacted] | [redacted] |
| Coefficient for progression | [redacted] | [redacted] |
| Progressed disease | [redacted] | [redacted] |
| **Two prior lines of platinum-based chemotherapy** | | |
| Progression-free | [redacted] | [redacted] |
| Coefficient for progression | [redacted] | [redacted] |
| Progressed disease | [redacted] | [redacted] |
| **Three or more prior lines of platinum-based chemotherapy** | | |
| Progression-free | [redacted] | [redacted] |
| Coefficient for progression | [redacted] | [redacted] |
| Progressed disease | [redacted] | [redacted] |
| Abbreviations: ITT, intention to treat; NR, not reported | | |

Finally, the ERG would also like to note that the company did not apply age-related utility decrements and assumed utilities were constant over the lifetime time horizon. Although those assumptions were not touched upon in the CS, the ERG considers them to be reasonable given that rucaparib is indicated for patients with a short life expectancy, and consistent with the analysis in TA528, TA381 and GID1296.[7, 8, 14]

## 4.2.8 Resources and costs

Costs in the company's original submission analysis comprised of the intervention and comparators' acquisition and administration costs, the costs associated with subsequent therapies, disease management costs (i.e. health state costs), adverse event costs, BRCA testing costs and end of life costs. At the clarification stage, the company explained that the cost year for unit inputs in the CS varied from 2016-2018 depending on the specific input source. As such, the company inflated all costs to 2018 using the harmonised index of consumer prices (HICP) in the revised base-case.

***Intervention and comparators' acquisition and administration costs***

At the time of writing this report, the company has proposed a simple patient access scheme (PAS) discount of [redacted] to the Department of Health and Social Care. The model and all results reported in the CS include the proposed discount for rucaparib. Following a clarification request from the ERG, the company also included the PAS for olaparib reported in NICE TA381 guidance and provided revised results.[7] Drug acquisition costs used in the model for rucaparib and olaparib are given in Table 35. The company also included monthly administration costs for rucaparib and olaparib, using the cost reported

by NHS Reference Costs 2016-17 to deliver oral chemotherapy, inflated to 2018 prices (£167.91) .[24] Routine surveillance does not involve active treatment and therefore no drug acquisition costs or administration costs are incurred.

Table 35. Intervention and comparator aquisition costs

| Active treatment | Pack size | Cost per pack | Dose | Cost per month, list price | Cost per month, PAS price |
|---|---|---|---|---|---|
| Rucaparib | 60 tablets | £3,652.00 | 2 x 300mg tablets, taken orally twice daily | £7,227.89 | [redacted] |
| Olaparib | 448 capsules | £3,550.00 | 8 x 50mg capsules, taken orally twice daily | £3,859.04 | £3,859.04 up to month 15, then £0.00 thereafter |
| Abbreviations: PAS, patient access scheme | | | | | |

***Costs associated with subsequent therapies***

The cost of subsequent therapy was applied to newly progressed patients per cycle in the model as a one-off cost. The included therapies were determined according to the subsequent therapies received in the ARIEL3 trial, but only therapies used in the UK were considered by the company. The company also adjusted the proportion of treatments received so that patients treated with a poly ADP ribose polymerase inhibitor (PARPi) were not allowed to receive subsequent therapy with a PARPi, and that the only PARPi received after progression was olaparib.

Subsequent therapies were calculated separately for patients that received maintenance with a PARPi (i.e. the rucaparib and olaparib cohorts), and patients with no prior use of PARPis (i.e. the routine surveillance cohort). However, the ERG considers it important to note that the company assumed subsequent therapies were the same regardless of BRCA status, or number of platinum-based chemotherapy regimens received prior to maintenance treatment.

The cost data and administration schedules outlined in Table 36 were used to calculate the average total cost of each subsequent therapy regimen. Monthly acquisition costs and administration costs were then calculated using the number of administrations per treatment cycle and the length of each treatment cycle in days.

In the company's original submission, the method described by Sacco *et al*., 2010 was followed to estimate intravenous (IV) drug costs assuming vial sharing.[29] However, the ERG's clinical experts advised that vial sharing does not routinely occur in the NHS, and therefore, upon request of the ERG, the company removed vial sharing from their base-case analysis.

Table 36. Data used to calculate the total cost of each subsequent therapy regimen

| Subsequent therapy data | Section of CS in which data are reported | Source of data |
|---|---|---|
| Unit price and pack information | Table 58 in Appendix M.2 | eMIT[30] for generic drugs and the BNF[25] for proprietary drugs not listed in eMIT |
| Administration schedule for each therapy | Table 59 in Appendix M.2 | EMC[26] SmPC for each therapy and clinical expert opinion |
| Administration costs | Table 57 in Section 5.3 | NHS Reference Costs 2016-17[24] |
| Abbreviations: CS, company submission; EMC, electronic Medicines Compendium; eMIT, electronic market information tool; SmPC, summary of product characteristics; | | |

The total one-off cost of subsequent therapy was then calculated using the monthly acquisition and administration costs, the proportion of patients receiving therapy, and the mean duration of therapy (Table 37). This led to one-off costs of £6,014.34 for patients that received maintenance with a PARPi (i.e. rucaparib and olaparib) and £17,228.81 for patients with no prior use of PARPis (i.e. routine surveillance).

Table 37. Data used to calculate the total one-off cost of subsequent therapy

| Subsequent therapy | Drug acquisition cost per month [a] | Drug administration cost per month [a] | Total cost per month [a] | Mean months received [b] | % patients who received maintenance PARPi [c] | % patients with no prior use of PARPi [c] |
|---|---|---|---|---|---|---|
| No subsequent therapy | £0.00 | £0.00 | £0.00 | [redacted] | [redacted] | [redacted] |
| Bevacizumab | £3,764.95 | £258.48 | £4,023.43 | [redacted] | [redacted] | [redacted] |
| Carboplatin monotherapy | £50.26 | £258.48 | £308.75 | [redacted] | [redacted] | [redacted] |
| Cisplatin monotherapy | £15.04 | £400.90 | £415.94 | [redacted] | [redacted] | [redacted] |
| Cyclophosphamide | £42.31 | £167.91 | £210.21 | [redacted] | [redacted] | [redacted] |
| Docetaxel | £43.46 | £258.48 | £301.94 | [redacted] | [redacted] | [redacted] |
| Doxorubicin | £12.56 | £258.48 | £271.04 | [redacted] | [redacted] | [redacted] |
| Etoposide | 35.11 | £1,477.22 | £1,512.33 | [redacted] | [redacted] | [redacted] |
| Gemcitabine + carboplatin | £109.07 | £563.17 | £672.23 | [redacted] | [redacted] | [redacted] |
| Gemcitabine + cisplatin | £73.84 | £705.58 | £779.43 | [redacted] | [redacted] | [redacted] |
| Gemcitabine monotherapy | £58.81 | £563.17 | £621.97 | [redacted] | [redacted] | [redacted] |
| Hormonal therapy | £3.01 | £167.91 | £170.91 | [redacted] | [redacted] | [redacted] |
| PARPi therapy (olaparib) | £3,859.04 | £167.91 | £4,026.95 | [redacted] | [redacted] | [redacted] |
| Paclitaxel + carboplatin | £83.01 | £400.90 | £483.91 | [redacted] | [redacted] | [redacted] |
| Paclitaxel + cisplatin | £47.79 | £400.90 | £448.69 | [redacted] | [redacted] | [redacted] |
| Paclitaxel monotherapy | £32.75 | £400.90 | £433.65 | [redacted] | [redacted] | [redacted] |
| PLDH + carboplatin | £1,046.75 | £294.77 | £1,341.52 | [redacted] | [redacted] | [redacted] |
| PLDH + cisplatin | £1,020.34 | £300.68 | £1,321.01 | [redacted] | [redacted] | [redacted] |
| PLDH monotherapy | £1,009.06 | £294.77 | £1,303.83 | [redacted] | [redacted] | [redacted] |
| Topotecan | £196.37 | £1,477.22 | £1,673.59 | [redacted] | [redacted] | [redacted] |
| Trabectedin | £4,009.78 | £ 400.90 | £4,410.68 | [redacted] | [redacted] | [redacted] |

| | | |
|---|---|---|
| **Total weighted one-off cost of subsequent therapy** | **£6,014.34** | **£17,228.81** |
| Abbreviations: NA, not applicable; PARPi, poly ADP ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin hydrochloride<br><br>a Calculated using the data reported in Table 36; b taken from NICE TA381[7] and the ongoing appraisal, ID1926[31] ; c estimated from ARIEL3 with adjustments to reflect UK practice | | |

***Disease management costs***

As described in Appendix M.3 of the CS, the company estimated resource use from three clinicians experienced in treating patients with ovarian cancer in the UK and obtained unit costs from NHS Reference Costs 2016-17 and the PSSRU 2017, and inflated those costs to 2018 prices.[24, 32] In summary, disease management costs comprised of: imaging; laboratory tests; nutritional support; hospital-based appointments with healthcare professionals; and community-based visits with healthcare professionals. Resource use per model cycle (monthly) and unit costs according to the health state of the patient (progression-free on maintenance, progression-free off maintenance and progressed) are given in Table 38. Disease management costs for patients on routine surveillance are calculated using PFS, as such this means that patients accrue the progression-free on maintenance cost until their disease progresses. Table 39 presents the resulting costs for each health state per model cycle.

Table 38 Health state resource use and costs (adapted from Table 61 in Appendix M.3 of the CS)

| Item | Unit cost | Resource use (per model cycle) | | |
|---|---|---|---|---|
| | | Progression-free On maintenance | Progression-free Off maintenance | Progressed |
| CT scan | £123.06 | 0.33 | 0.00 | 0.36 |
| Blood test | £3.14 | 1.00 | 0.04 | 1.07 |
| CA125 blood test | £1.16 | 0.98 | 0.35 | 1.08 |
| Liver function test | £1.16 | 0.78 | 0.15 | 1.08 |
| Renal function test | £8.09 | 0.55 | 0.15 | 1.08 |
| Nutritional support | £832.25 | 0.01 | 0.01 | 0.22 |
| Medical oncologist | £176.98 | 1.00 | 0.33 | 1.08 |
| Clinical nurse specialist | £84.36 | 0.33 | 0.11 | 0.50 |
| GP | £37.92 | 0.17 | 0.00 | 0.17 |
| Nurse | £45.10 | 0.33 | 0.00 | 0.33 |
| Psychologist | £147.94 | 0.00 | 0.00 | 0.08 |
| Palliative care specialist / team visit | £82.08 | 0.00 | 0.00 | 0.37 |
| Abbreviations: CT, computed tomography; CA-125, cancer antigen 125 | | | | |

Table 39. Health state costs (adapted from Table 59 of the CS)

| Health state | Total cost per model cycle (monthly) |
|---|---|
| Progression-free (on maintenance) | £292.02 |
| Progression-free (off maintenance) | £76.22 |
| Progressed disease | £550.07 |

***Other costs***

Adverse event management costs and end-of-life costs were taken from the NICE STA of niraparib for maintenance therapy in relapsed ovarian cancer (TA528) and inflated to 2018 prices at the clarification stage.[8] The cost to manage each AE included in the company's original model is provided in Table 60 of the CS, while the one-off cost of death inflated to 2018 prices is £3,884.25.

The company's original submission included a one-off cost for BRCA testing in each treatment arm. However, given that BRCA testing is done routinely in the NHS, the ERG considers that the cost does not need to be included in the model as it inflates total costs for all comparators. Upon request of the ERG, BRCA testing costs were removed from the company's revised base-case analysis.

#### *4.2.8.1 ERG critique*

The ERG identified two implementation errors in the company's analysis that required correction. Drug acquisition and administration costs were not applied to patients in the first cycle and during the clarification stage, the ERG requested the company to inflate unit costs to the same cost year or use the most recent version of cost sources. Following this, the company inflated unit costs from NHS Reference Costs 2016/17[24] and the PSSRU 2017[32] to 2018 prices, even though the NHS Reference Costs schedule for 2017/18[33] and the PSSRU 2018[34] were published prior to the clarification stage. Please refer to Section 6.1 for the corrected company base-case cost-effectiveness results.

The ERG's main concerns relate to the company's estimation of subsequent therapies, which is a primary driver of cost-effectiveness in the model. Firstly, the ERG is unclear how subsequent treatments received in ARIEL3 were selected for inclusion. For example, the company costed some of the least common therapies such as cisplatin plus paclitaxel and paclitaxel plus cisplatin, and excluded some therapies received by patients in the UK such as radiotherapy and tamoxifen. Moreover, the company did not address the ERG's clarification question on how subsequent therapies received in ARIEL3 were selected for inclusion. Secondly, the ERG notes that OS data from ARIEL3 are immature and as trial data accumulates, there are likely to be more subsequent therapies received by patients, potentially underestimating the cost of subsequent therapies estimated from ARIEL3. Thirdly and most importantly, as OS informing the model is from Study 19, the ERG considers that data on subsequent therapy use should come from the same trial as OS. Upon a clarification request from the ERG, the company provided a scenario using subsequent therapy data from Study 19. However, in doing so, the company omitted one combination therapy (carboplatin + gemcitabine hydrochloride) received in Study 19 and carried over several proportions from ARIEL3, without justification. As a result, the proportion of patients receiving subsequent therapies in the company's scenario analysis is substantially reduced. For completeness, the ERG ran a scenario using all subsequent therapy data from Study 19 and results are presented in Section 6.3.

Table 40. Subsequent therapy data from Study 19

| Subsequent therapy | Company's base-case (ARIEL3) | | Company's response to CQ B6 (Study 19*) | | Study 19* | |
|---|---|---|---|---|---|---|
| | previous PARPi | no prior use of PARPi | previous PARPi | no prior use of PARPi | previous PARPi | no prior use of PARPi |
| No subsequent therapy | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Bevacizumab | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Carboplatin monotherapy | [redacted] | [redacted] | [redacted] | [redacted] | 44.60% | 38.70% |
| Cisplatin monotherapy | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Cyclophosphamide | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Docetaxel | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Doxorubicin | [redacted] | [redacted] | [redacted] | [redacted] | 21.60% | 27.40% |
| Etoposide | [redacted] | [redacted] | [redacted] | [redacted] | 8.10% | 6.50% |
| Gemcitabine + carboplatin | [redacted] | [redacted] | [redacted] | [redacted] | 27.00% | 41.90% |
| Gemcitabine + cisplatin | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Gemcitabine monotherapy | [redacted] | [redacted] | [redacted] | [redacted] | 5.40% | 3.20% |
| Hormonal therapy | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| PARPi therapy (olaparib) | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Paclitaxel + carboplatin | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Paclitaxel + cisplatin | [redacted] | [redacted] | [redacted] | [redacted] | 8.10% | 4.80% |
| Paclitaxel monotherapy | [redacted] | [redacted] | [redacted] | [redacted] | 9.50% | 16.10% |
| PLDH + carboplatin | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| PLDH + cisplatin | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| PLDH monotherapy | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Topotecan | [redacted] | [redacted] | [redacted] | [redacted] | 10.80% | 21.00% |
| Trabectedin | [redacted] | [redacted] | [redacted] | [redacted] | NR | NR |
| Carboplatin + cyclophosphamide | [redacted] | [redacted] | [redacted] | [redacted] | 14.90% | 4.80% |
| Carboplatin + doxorubicin | [redacted] | [redacted] | [redacted] | [redacted] | 20.30% | 24.20% |
| Carboplatin + docetaxel | [redacted] | [redacted] | [redacted] | [redacted] | 14.90% | 3.20% |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cisplatin + cyclophosphamide | [redacted] | [redacted] | [redacted] | [redacted] | 12.20% | 3.20% |
| Carboplatin + gemcitabine hydrochloride | [redacted] | [redacted] | [redacted] | [redacted] | 6.80% | 4.80% |
| Cisplatin + cyclophosphamide + docetaxel | [redacted] | [redacted] | [redacted] | [redacted] | 8.10% | 0% |

Abbreviations: NR, not reported; PARPi, poly ADP ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin hydrochloride

Note: For PARPi therapy, the ERG used proportions presented in Ledermann et al., 2016[5] to inform the cost of subsequent therapies. The proportions are 22.6% for BRCA patients and 27.4% for ITT patients

*Data from Study 19 reported in the committee papers (1) for TA381 (Table 7.22 in 02 - Submission from the technology manufacturer - AstraZeneca)[7]

Aside from issues around subsequent therapy costs, the company did not consider the disease management costs (i.e. health state costs) included in recent NICE appraisals for maintenance therapy in relapsed ovarian cancer such as TA381,[2] TA528,[3] or the ongoing appraisal, GID1296.[7, 8, 31] However, except for disaggregating PFS into on- and off-maintenance treatment, the ERG considers them to be largely similar. In addition, clinical experts advising the ERG agreed with the company's assumption that progression-free patients would be monitored less often when they stop receiving maintenance treatment with a PARPi (Table 38). However, they disagreed that progression-free patients receiving routine surveillance would receive the same management as progression-free patients receiving a PARPi (on-maintenance treatment). In response to a clarification request from the ERG, the company provided a scenario in the ITT population, where off-maintenance costs were applied to the progression-free cohort on routine surveillance. The impact of this analysis on the ICER was noteworthy, increasing from £50,681 to £51,636

Finally, during the clarification stage, the ERG requested a number of scenarios, including: zero administration costs for oral PARPis and oral chemotherapies; reduced doses of PLDL; and, subgroup specific (BRCA 3L+) subsequent therapy data from ARIEL3, but these had a small impact on the ICER.

# 5 COST EFFECTIVENESS RESULTS

In response to the ERG's clarification questions, the company submitted revised results which incorporated the following changes:

- the vial sharing assumption has been removed;
- no costs are applied for breast cancer gene (BRCA) testing;
- and all costs have been inflated to a 2018 cost year.

The company's original and revised base-case results focus on the intention-to-treat (ITT) population of ARIEL3, which includes all patients, regardless of BRCA status, who have had two lines or more of platinum-based chemotherapy and BRCA patients who have had three or more lines of platinum-based chemotherapy (BRCA 3L+ population). Subgroup results for the non-BRCA cohort and the BRCA cohort who have only had two lines of platinum-based chemotherapy (BRCA 2L) were provided by the company following a clarification request by the ERG. However, the company maintained that their base-case analysis is the ITT and BRCA 3L+ analysis. As such, the results and critique of those subgroup analyses are reported in Section 4.2.5.1.

The company's revised base-case results for the ITT population and BRCA 3L+ population are presented in Section 5.1, and the results of revised deterministic and probabilistic sensitivity analyses (PSA) are presented in Section 5.2.1 and Section 5.2.2. All results are inclusive of the proposed discount for rucaparib (a simple patient access scheme [PAS] discount of [redacted]) and the approved PAS for olaparib.

## *5.1 Company's cost effectiveness results*

***ITT population***

The results of the company's base-case analysis for the ITT population are provided in Table 41. According to the company's analysis, rucaparib is expected to extend patients' lives by around 1.859 years compared to routine surveillance. This translates to an incremental quality-adjusted life year (QALY) gain for rucaparib of [redacted] QALYs, and an incremental cost-effectiveness ratio (ICER) of £50,681 per QALY gained.

Table 41. Revised deterministic base-case results for the ITT population (reproduced from Table 8 of the company's clarification responses)

| Therapy | Total costs | Total LYG | Total QALYs | Incremental costs | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| Routine Surveillance | [redacted] | 3.060 | [redacted] | - | - | - | - |
| Rucaparib | [redacted] | 4.919 | [redacted] | [redacted] | 1.859 | [redacted] | £50,681 |
| Abbreviations: BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year. | | | | | | | |

***BRCA 3L+ population***

The results of the company's base-case analysis for the BRCA 3L+ population are provided in Table 42. Due to the equal efficacy assumption adopted by the company, rucaparib is not expected to extend or improve BRCA 3L+ patients' lives compared to olaparib and given that rucaparib is more expensive than olaparib, rucaparib is dominated by olaparib.

Table 42. Revised deterministic base-case results for the BRCA 3L+ population (reproduced from Table 9 of the company's clarification responses)

| Therapy | Total costs | Total LYG | Total QALYs | Incremental costs | Incremental LYG | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| Olaparib | [redacted] | 3.091 | [redacted] | - | - | - | - |
| Rucaparib | [redacted] | 3.091 | [redacted] | [redacted] | 0.000 | [redacted] | Rucaparib dominated |
| Abbreviations: 3L+, responding to platinum-based chemotherapy in the third- or later-line setting; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year. | | | | | | | |

## *5.2 Company's sensitivity analyses*

### 5.2.1 Probabilistic sensitivity analysis (PSA)

PSA was undertaken using 2,000 iterations. The ERG considers the parameters and respective distributions chosen for PSA, outlined in Table 61 of the CS, to be generally sound.

***ITT population***

In the ITT population, PSA results produced a mean ICER of [redacted] per QALY gained for rucaparib compared to routine surveillance (Table 43), which the ERG considers to be comparable to the deterministic base-case results. Furthermore, the ERG could produce very similar PSA results when replicating the analysis. The scatterplots and cost-effectiveness acceptability curves (CEACs) for the ITT population are presented in Figure 8 and Figure 9, respectively.

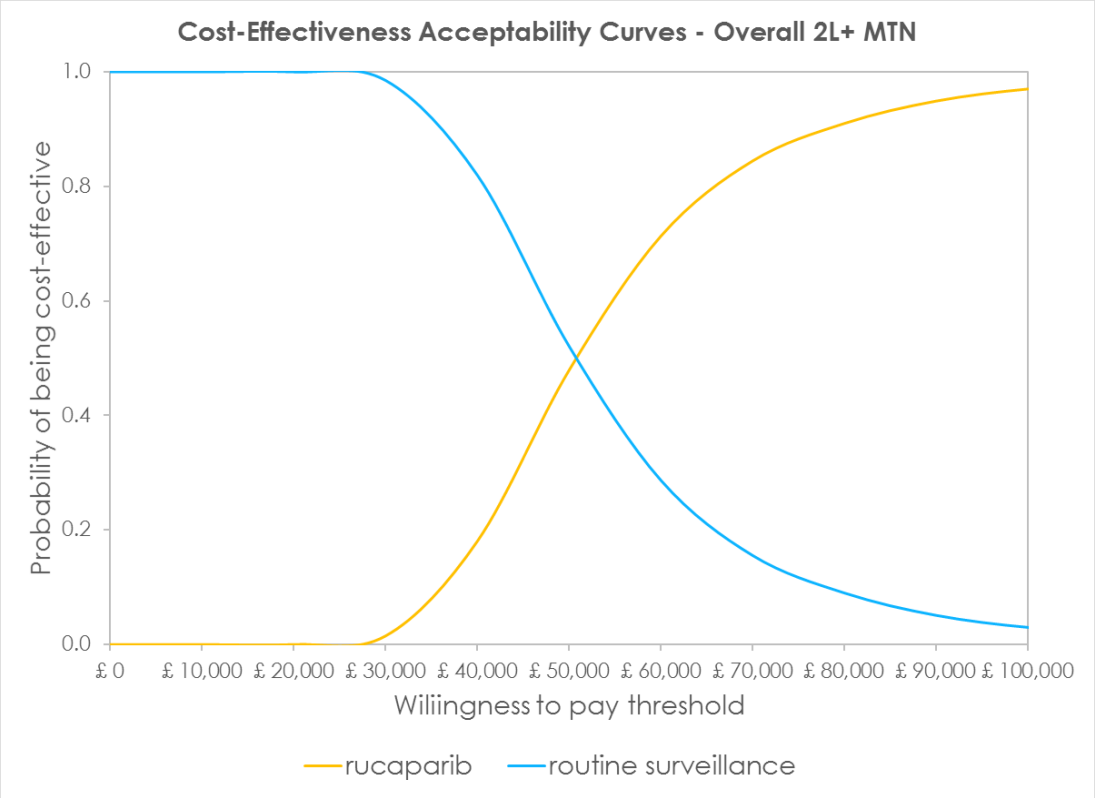
Table 43. Revised probabilistic base-case results for the ITT population (reproduced from Table 10 of the company's clarification responses)

| Technologies | Total costs | Total QALYs | Incremental costs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| Routine Surveillance | [redacted] | [redacted] | - | - | - |
| Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.

Figure 8. Cost-effectiveness plane of 2,000 PSA iterations in the ITT population (taken from the revised economic model)

Figure 9. CEAC of 2,000 PSA iterations in the ITT population (taken from the revised economic model)




***BRCA 3L+ population***

In the BRCA 3L+ population, olaparib dominates rucaparib in PSA, which is consistent with the deterministic analysis. Mean PSA results are provided in Table 62 and the ERG was able to produce very similar results when they replicated the analysis. The scatterplots and CEACs for the BRCA 3L+ population are presented in Figure 10 and Figure 11, respectively.

Table 44. Revised probabilistic base-case results for the BRCA 3L+ population (reproduced from Table 11 of the company's clarification responses)

| Technologies | Total costs | Total QALYs | Incremental costs | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| Olaparib | [redacted] | [redacted] | - | - | - |
| Rucaparib | [redacted] | [redacted] | [redacted] | [redacted] | Rucaparib dominated |
| Abbreviations: 3L+, responding to platinum-based chemotherapy in the third- or later-line setting; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year. | | | | | |

Figure 10. Cost-effectiveness plane of 2,000 PSA iterations in the BRCA 3L+ population (taken from the revised economic model)

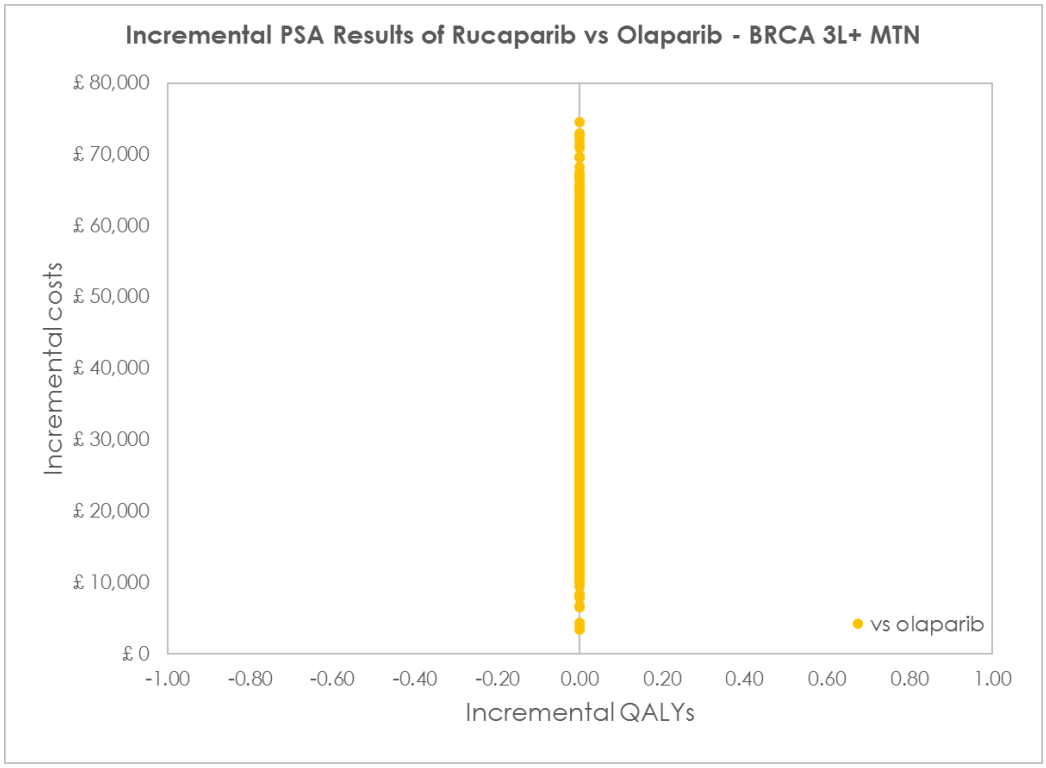



Figure 11. CEAC of 2,000 PSA iterations in the BRCA 3L+ population (taken from the revised economic model)

### 5.2.2 One-way sensitivity analysis (OWSA)

The company carried out OWSAs to assess the impact of varying model parameters according to their associated 95% confidence intervals, or by 20% if no information on the standard error was available. Figure 12 and Figure 13 display tornado diagrams of the 10 most influential parameters from the OWSA in the ITT population and BRCA 3L+ population, in terms of impact on net monetary benefit using a willingness-to-pay threshold of £30,000. During the clarification stage, the company also provided tabulated results of individual parameters on the ICER. Those results are presented in Table 45 for the ITT population. As for the BRCA 3L+ population, rucaparib was dominated by olaparib using the lower and upper bounds of each parameter, and therefore, tabulated results on the ICER are not reported here. In summary, the main drivers of the model in the ITT population and BRCA 3L+ population included the cost of subsequent therapies, relative survival parameters for progression free survival (PFS) and overall survival (OS), and disease management costs (monitoring costs).

Figure 12. Revised tornado diagram for the ITT population (reproduced from Figure 30 of the company's clarification responses)

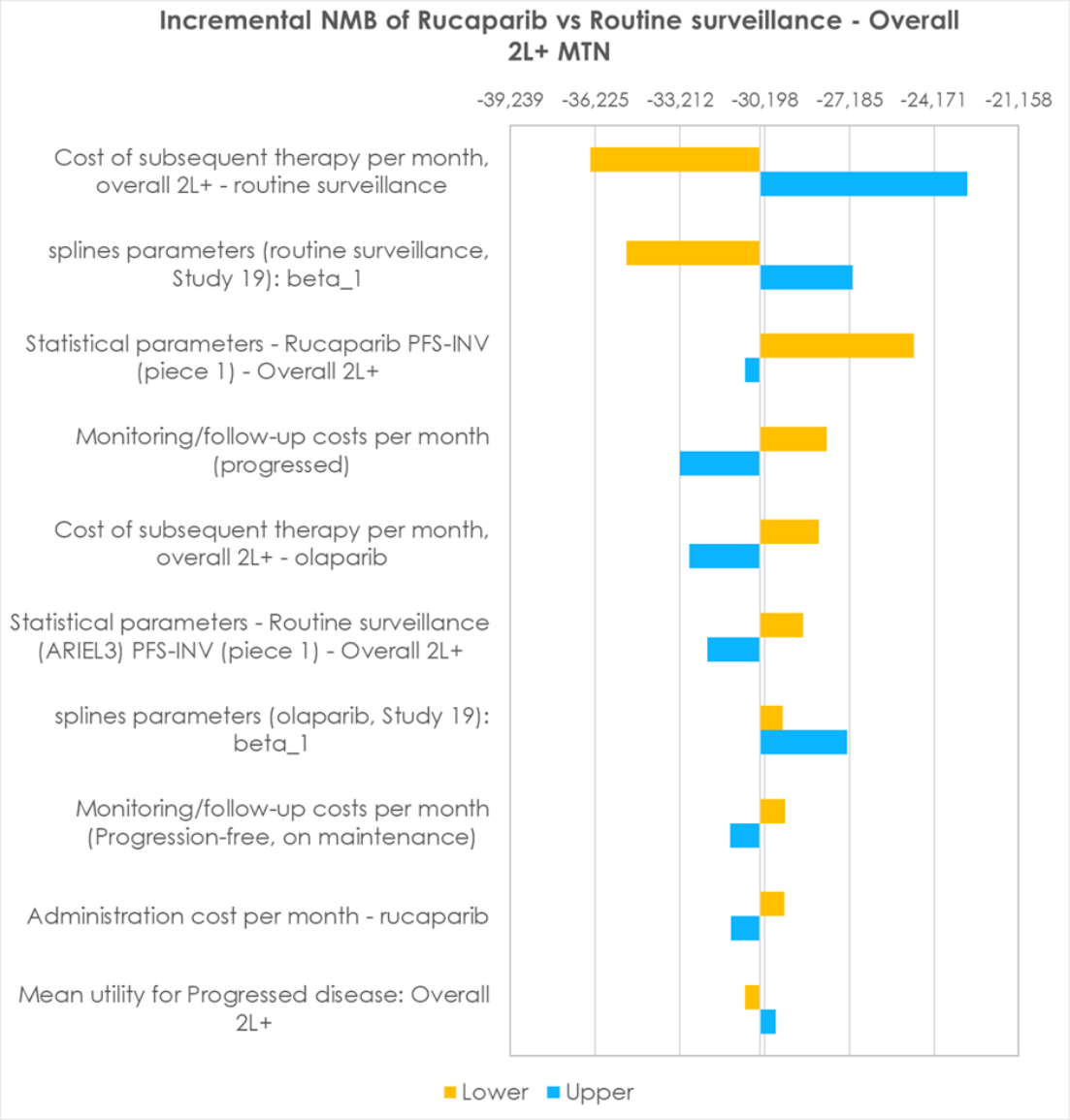


Figure 13. Revised tornado diagram for the BRCA 3L+ population (reproduced from Figure 31 of the company's clarification responses)

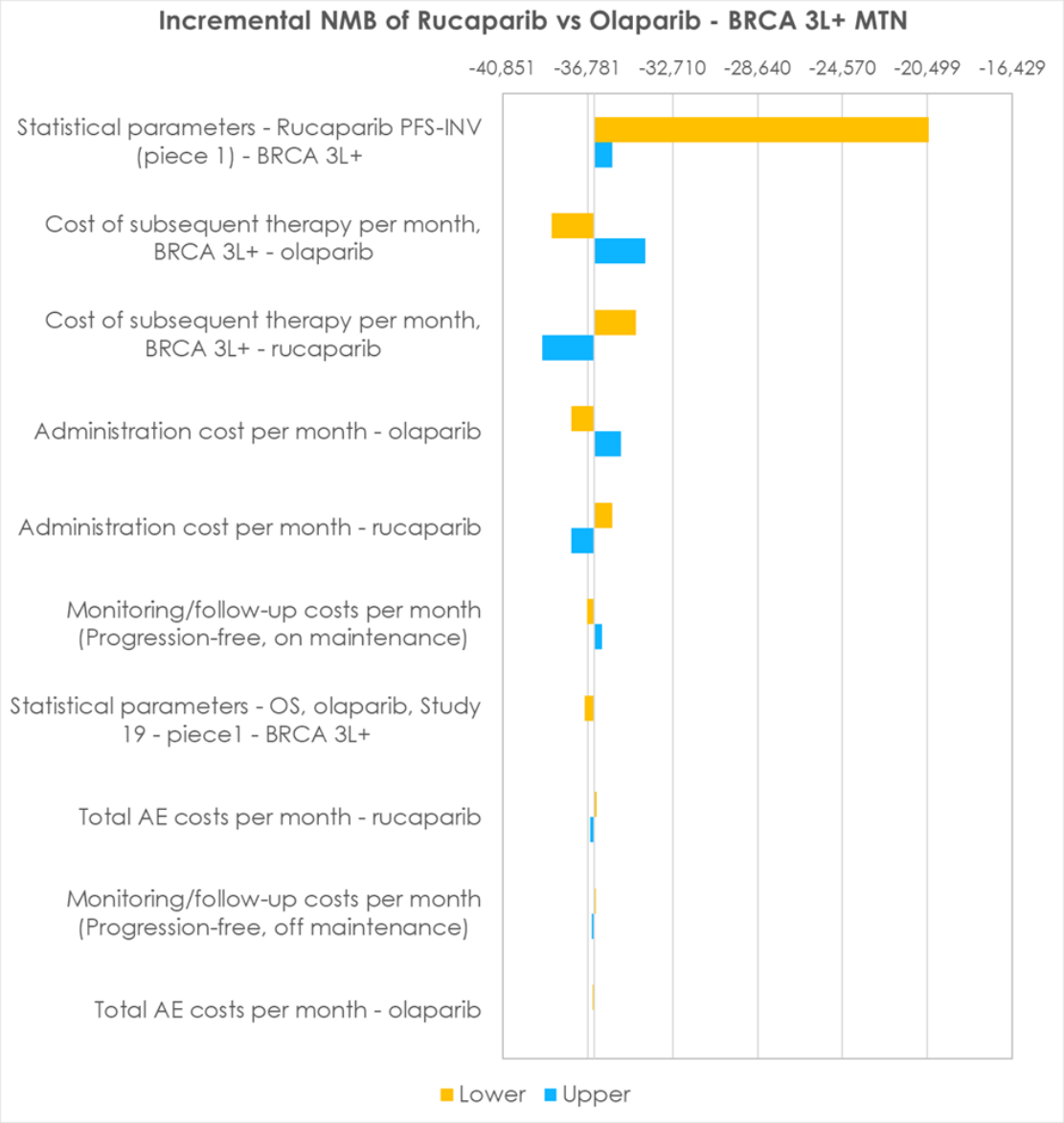



Table 45. OWSA for the revised base-case with ICER as outcome, ITT population (reproduced from Table 52 of the company's clarification responses)

| # | Parameter | Lower bound ICER | Upper bound ICER | Difference ICER |
|---|---|---|---|---|
| 1 | Cost of subsequent therapy per month, overall 2L+ - routine surveillance | £54,809 | £45,669 | £9,140 |
| 2 | Splines parameters (routine surveillance, Study 19): beta_1 | £58,199 | £46,703 | £11,495 |
| 3 | Statistical parameters - Rucaparib PFS-INV (piece 1) - Overall 2L+ | £49,659 | £47,867 | £1,792 |
| 4 | Monitoring/follow-up costs per month (progressed) | £49,067 | £52,640 | £3,573 |
| 5 | Cost of subsequent therapy per month, overall 2L+ - olaparib | £49,264 | £52,401 | £3,137 |

| | | | | |
|---|---|---|---|---|
| 6 | Statistical parameters - Routine surveillance (ARIEL3) PFS-INV (piece 1) - Overall 2L+ | £48,876 | £53,134 | £4,258 |
| 7 | splines parameters (olaparib, Study 19): beta_1 | £49,616 | £46,968 | £2,648 |
| 8 | Monitoring/follow-up costs per month (Progression-free, on maintenance) | £50,079 | £51,411 | £1,332 |
| 9 | Administration cost per month - rucaparib | £50,092 | £51,395 | £1,303 |
| 10 | Mean utility for Progressed disease | £51,309 | £50,067 | £1,242 |
| 11 | Mean utility for Progression-free disease | £51,062 | £50,305 | £757 |
| 12 | Total AE costs per month - rucaparib | £50,592 | £50,789 | £197 |
| 13 | One-off costs: Cost of death cost | £50,741 | £50,607 | £134 |
| 14 | Risk of AEs for Rucaparib: Anaemia | £50,650 | £50,715 | £65 |
| 15 | Monitoring/follow-up costs per month (Progression-free, off maintenance) | £50,653 | £50,715 | £62 |
| 16 | Risk of AEs for Rucaparib: Neutropenia | £50,669 | £50,695 | £25 |
| 17 | Risk of AEs for Rucaparib: Nausea/vomiting | £50,669 | £50,694 | £25 |
| 18 | Risk of AEs for Rucaparib: Thrombocytopenia | £50,670 | £50,694 | £24 |
| 19 | Risk of AEs for Rucaparib: Fatigue/asthenia | £50,672 | £50,691 | £19 |
| 20 | Risk of AEs for Routine surveillance: Anaemia | £50,683 | £50,674 | £9 |
| Abbreviations: 2L+, post second line AE, adverse events; ICER, incremental cost-effectiveness ratio; INV, investigator; ITT, intention-to-treat; OWSA, one-way sensitivity analysis; PFS, progression free survival | | | | |

### 5.2.3 Scenario analysis

A revised list of scenario analyses for the ITT population and BRCA 3L+ population is provided in Table 46. According to the scenario analysis, results in the ITT population were most sensitive to the PFS:OS ratio and the choice of OS curve. The ERG's critique of the PFS:OS ratio can be found in Section 4.2.5.1.

As for the BRCA 3L+ population, results were robust to all scenarios except for the scenario that considered the matching adjusted indirect comparison (MAIC) based on SOLO2 to inform PFS. As outlined in Section 3.4.6 and 4.2.5, PFS favours olaparib over rucaparib when using Study 19 to provide the olaparib data and the opposite when using SOLO2. However, irrespective of data source or method used, the results do not reach statistically significant differences, and this is reflected by the small differences in QALYs between olaparib and rucaparib.

Table 46 Revised list of scenairo analysis (reproduced from Table 12 of the company's clarification responses)

| | **ITT population** | **BRCA 3L+ population** |
|---|---|---|
| **Scenario name** | **ICER vs routine surveillance** | **ICER vs olaparib** |
| Base case | £ 50,681 | Rucaparib dominated |
| Second-best parametric fits for OS: Log-logistic (BRCA 3L+), Lognormal (Overall 2L+) | £ 70,926 | Rucaparib dominated |
| Third-best parametric fits for OS: Weibull (BRCA 3L+), Loglogistic (Overall 2L+) | £ 78,320 | Rucaparib dominated |

| | | |
|---|---|---|
| Second-best parametric fits for PFS: Generalised gamma | £ 41,413 | Rucaparib dominated |
| Third-best parametric fits for PFS: Log-logistic | £ 53,213 | Rucaparib dominated |
| Overall 2L+ MTN: Second-best parametric fits for rucaparib TTDD: Generalised Gamma | £ 49,070 | N/A |
| Discontinuation rule - Constant discontinuation rate for all interventions | £ 43,200 | N/A |
| BRCA 3L+ MTN discontinuation rule: TTDD curves for rucaparib: Exponential | N/A | Rucaparib dominated |
| Discontinuation rule - Treat until progression for all interventions | £ 56,388 | Rucaparib dominated |
| Overall 2L+ MTN: PFS-OS ratio = 1, routine surveillance PFS: Lognormal | £ 108,976 | N/A |
| Overall 2L+ MTN: PFS-OS ratio = 2, routine surveillance PFS: Lognormal | £ 62,767 | N/A |
| PFS-OS ratio = 1, routine surveillance PFS: based on HR | £ 108,637 | Rucaparib dominated |
| PFS-OS ratio = 2, routine surveillance PFS: based on HR | £ 62,590 | Rucaparib dominated |
| (B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by base case NMA estimates for relative efficacy (equivalence in OS only) | N/A | Rucaparib dominated |
| (B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (Study 19) estimates for relative efficacy (equivalence in OS only) | N/A | Rucaparib dominated |
| (B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (SOLO2) estimates for relative efficacy (equivalence in OS only) | N/A | £ 1,639,601 |
| (B3) BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (pooled analysis) estimates for relative efficacy (equivalence in OS only) | N/A | Rucaparib dominated |
| BRCA 3L+ MTN: Equivalence in OS and PFS. PFS based on parametric curves from olaparib in Study 19 | N/A | Rucaparib dominated |
| Alternative AE assumption: Apply AE disutilities but do not accrue AE costs | £ 50,530 | Rucaparib dominated |
| Alternative AE assumption: Do not apply AE disutilities and do not accrue AE costs | £ 50,439 | Rucaparib dominated |
| Alternative AE costs based on feedback from UK clinical expert | £ 50,456 | Rucaparib dominated |
| Alternative frequency of RU based on feedback from UK clinical expert | £ 49,933 | Rucaparib dominated |
| Extend time horizon to 50 years | £ 48,516 | Rucaparib dominated |
| No discounting for costs and health outcomes | £ 39,894 | Rucaparib dominated |
| Do not allow vial sharing (assume wastage) - IV/SC drugs* | £ 50,681 | Rucaparib dominated |
| Exclude one-off cost of BRCA mutation test at the beginning of the time horizon* | £ 50,681 | Rucaparib dominated |
| Do not apply administration cost of maintenance and subsequent therapies | £ 49,184 | Rucaparib dominated |
| PF and PD mean utility values reported in the niraparib NICE submission [TA528]; PF: 0.831, PD: 0.799 | £ 49,198 | Rucaparib dominated |

| | | |
|---|---|---|
| Shares for subsequent therapy costs unadjusted for non-UK treatments (all patients, ARIEL3) | £ 51,795 | Rucaparib dominated |
| Question B2: Overall 2L+ MTN: Calculate PPS as residual of OS and PFS | £ 59,078 | N/A |
| *Note, these scenarios are now included in the revised base case, hence no difference from revised base case ICERs is shown<br>Abbreviations: 2L+, post second line; 3L+, responding to platinum-based chemotherapy in the third- or later-line setting; AE, adverse events; BRCA, breast cancer gene; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INV, investigator; ITT, intention-to-treat; IV, intravenous; MTN, maintenance; N/A, not applicable; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression free survival; PF, progression free; PD, progressed disease; PPS, post-progression survival; RU, resource use | | |

## *5.3 Model validation and face validity check*

The CS reports that an internal peer reviewer not involved in the original implementation of the economic model performed quality assurance of the model by validating the logical structure of the model, mathematical formulas, sequences of calculations, and parameter inputs. The company also sought external validation from UK clinical experts on the following:

- Cost-effectiveness model structure and approach;
- Prognostic factors and treatment effect modifiers;
- Validation of parametric distributions for the parametric survival analyses of PFS and OS;
- Equivalence of PARPi efficacy;
- PARPi dosing and dose interruptions; and
- Resource use inputs.

Where information was publicly available on the cost-effectiveness of other PARPis for the same indication (most notably niraparib and olaparib), the company compared the results for rucaparib against these as a face validity check.

# 6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

## 6.1 Model corrections

The Evidence Review Group (ERG) described two implementation errors in Section 4.2.8.1 of this report related to calculation of costs. These are summarised here, together with the combined impact of the corrections on the final incremental cost-effectiveness ratio (ICER). The ERG made the following corrections:

1. The company did not apply drug acquisition and administration costs in the first model cycle and therefore the ERG amended the model so that those costs were incurred in the first cycle;

2. The ERG disagrees with the company's approach to inflate costs from NHS Reference Costs 2016/17[24] and the PSSRU 2017[32] to 2018 prices given that the NHS Reference Costs schedule for 2017/18[33] and the PSSRU 2018[34] were published prior to the clarification stage.

Deterministic results are provided in Table 47 and

Table 48 for the company's corrected base-case, in the intention-to-treat (ITT) population and the breast cancer susceptibility gene mutation (BRCA) positive cohort who have had three or more lines of platinum-based chemotherapy (BRCA 3L+), respectively. Both analyses include rucaparib's (proposed) and olaparib's patient access scheme (PAS).

Table 47. Deterministic results of company's base-case analysis (ITT) corrected by the ERG

| Therapy | Total costs | Total LYs | Total QALYs | Incremental costs | Incremental LYs | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|
| Routine Surveillance | [redacted] | 3.060 | [redacted] | - | - | - | - |
| Rucaparib | [redacted] | 4.919 | [redacted] | [redacted] | 1.859 | [redacted] | £53,179 |
| Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year. | | | | | | | |

Table 48. Deterministic results of company's base-case analysis (BRCA 3L+) corrected by the ERG

| Therapy | Total costs | Total LYs | Total QALYs | Incremental costs | Incremental LYs | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|
| Olaparib | [redacted] | 3.091 | [redacted] | - | - | - | - |
| Rucaparib | [redacted] | 3.091 | [redacted] | [redacted] | 0.000 | [redacted] | Rucaparib dominated |
| Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year. | | | | | | | |

As explained in Section 5, the company have maintained the ITT analysis is their base-case, but the ERG considers that the subgroup analyses (i.e. the non-BRCA cohort and the BRCA cohort who have only had two lines of platinum-based chemotherapy [BRCA 2L]) are more appropriate than the ITT

analysis. Consequently, the ERG has presented corrected subgroup analyses for the non-BRCA cohort in Table 49 and BRCA 2L cohort in Table 50.

Table 49. Deterministic results of company's non-BRCA subgroup analysis corrected by the ERG

| Therapy | Total costs | Total LYs | Total QALYs | Incremental costs | Incremental LYs | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|
| Routine Surveillance | [redacted] | 2.832 | [redacted] | - | - | - | - |
| Rucaparib | [redacted] | 5.211 | [redacted] | [redacted] | 2.378 | [redacted] | £35,228 |
| Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year. | | | | | | | |

Table 50. Deterministic results of company's BRCA 2L subgroup analysis corrected by the ERG

| Therapy | Total costs | Total LYs | Total QALYs | Incremental costs | Incremental LYs | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|
| Routine Surveillance | [redacted] | 3.513 | [redacted] | - | - | - | - |
| Rucaparib | [redacted] | 6.550 | [redacted] | [redacted] | 3.036 | [redacted] | £59,236 |
| Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year. | | | | | | | |

At a late stage in the report, the company provided functioning probabilistic sensitivity analyses (PSA) for the non-BRCA and BRCA2L models, however, the ERG had already made corrections to the models provided at clarification stage and as such did not have enough time to edit the new models and produce PSA ICERs.

## *6.2 Exploratory and sensitivity analyses undertaken by the ERG*

In Section 4 of this report, the ERG has described several scenarios that warrant further exploration in addition to the company's own sensitivity and scenario analyses to ascertain the impact of these changes on the ICER. The scenarios the ERG have produced are applied to the company's updated and corrected base-case analysis for the ITT population, as well as the BRCA subgroup analyses, provided by the company in their clarification response and corrected by the ERG as mentioned in Section 6.1. The scenarios that the ERG has produced are as follows:

1. Alternative progression-free survival (PFS) survival curves for the non-BRCA and BRCA2L populations (Section 4.2.5.1)
    a. Using the lognormal distribution for PFS for the non-BRCA population;
    b. Using the Weibull distribution for PFS for the BRCA2L population.
2. Using subsequent therapy proportions from Study 19 to estimate subsequent therapy costs (Section 4.2.8.1). Please see Appendix 9.3 for detailed description of analysis.

3. Extension of time horizon to 50 years for the non-BRCA and BRCA2L (Section 4.2.4.1)

## 6.3 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Table 51 to Table 53 presents the results of the ERG exploratory analyses described in Section 6.2. Results reported include the company's proposed patient access scheme (PAS) of [redacted].

Table 51. Results of the ERG's scenario analysis for the ITT population

| | Results per patient | Rucaparib | Routine surveillance | Incremental value |
|---|---|---|---|---|
| **0** | **Corrected company base case** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | | | **£53,179** |
| **2** | **Subsequent therapy proportions from Study 19** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | | | **£52,979** |

Abbreviations: ERG, evidence review group; ICER, incremental cost effectiveness ratio; ITT, intention-to-treat; QALYs, quality adjusted life years.

Table 52. Results of the ERG's scenario analysis for the non-BRCA population

| | Results per patient | Rucaparib | Routine surveillance | Incremental value |
|---|---|---|---|---|
| **0** | **Corrected company base case** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | | | **£35,228** |
| **1a** | **Lognormal distribution for PFS** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | | | **£42,614** |
| **2** | **Subsequent therapy proportions from Study 19** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | | | **£40,981** |
| **3** | **Time horizon of 50 years** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | | | **£32,359** |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ERG, evidence review group; ICER, incremental cost effectiveness ratio; ITT, intention-to-treat; PFS, progression free survival; QALYs, quality adjusted life years.

Table 53. Results of the ERG's scenario analysis for the BRCA2L population

| | Results per patient | Rucaparib | Routine surveillance | Incremental value |
|---|---|---|---|---|
| **0** | **Corrected company base case** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | | | **£59,236** |
| **1b** | **Weibull distribution for PFS** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | | | **£53,870** |
| **2** | **Subsequent therapy proportions from Study 19** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | - | - | **£59,929** |
| **3** | **Time horizon of 50 years** | | | |
| | Total Costs (£) | [redacted] | [redacted] | [redacted] |
| | QALYs | [redacted] | [redacted] | [redacted] |
| | **ICER** | | | **£56,269** |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; ERG, evidence review group; ICER, incremental cost effectiveness ratio; ITT, intention-to-treat; PFS, progression free survival; QALYs, quality adjusted life years.

## *6.4 ERG's preferred assumptions*

In this section, the ERG presents its base case ICERs for the ITT, non-BRCA and BRCA2L populations. For the BRCA3L+ population, as the company's assumes clinical equivalence between rucaparib and olaparib, this reduces the analysis to a cost-minimisation. Many of the company provided scenarios have been included in the ERG base case assumptions as well as the company's proposed PAS discount of [redacted], which are outlined in Table 54 to Table 57 for each population.

Table 54. ERG's preferred model assumptions – ITT population

| Preferred assumption | Section in ERG report | Incremental costs | Incremental QALYs | Cumulative ICER £/QALY |
|---|---|---|---|---|
| Corrected company base-case | *6.1* | [redacted] | [redacted] | **£53,179** |
| Post-progression survival modelled as the residual of ARIEL3 PFS and Study 19 OS | *4.2.5.1* | [redacted] | [redacted] | **£62,331** |
| Use of subsequent therapy proportions from Study 19 | *4.2.8.1, 6.2 & 6.3* | [redacted] | [redacted] | **£62,102** |
| PFS off maintenance costs for routine surveillance | *4.2.8.1* | [redacted] | [redacted] | **£63,220** |
| Removal of oral therapy administration costs | *4.2.8.1* | [redacted] | [redacted] | **£61,725** |
| Extension of time horizon to 50 years | *4.2.4.1* | [redacted] | [redacted] | **£58,399** |

Abbreviations: ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.

Table 55. ERG's preferred model assumptions – non-BRCA population

| Preferred assumption | Section in ERG report | Incremental costs | Incremental QALYs | Cumulative ICER £/QALY |
|---|---|---|---|---|
| Corrected company base-case | *6.1* | [redacted] | [redacted] | **£35,228** |
| Using the lognormal distribution for PFS for the non-BRCA population | *4.2.5.1, 6.2 & 6.3* | [redacted] | [redacted] | **£42,614** |
| Post-progression survival modelled as the residual of ARIEL3 PFS and Study 19 OS | *4.2.5.1* | [redacted] | [redacted] | **£48,161** |
| Use of subsequent therapy proportions from Study 19 | *4.2.8.1, 6.2 & 6.3* | [redacted] | [redacted] | **£57,007** |
| PFS off maintenance costs for routine surveillance | *4.2.8.1* | [redacted] | [redacted] | **£58,092** |
| Removal of oral therapy administration costs | *4.2.8.1* | [redacted] | [redacted] | **£56,673** |
| Extension of time horizon to 50 years | *4.2.4.1* | [redacted] | [redacted] | **£50,548** |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; PFS, progression-free survival; OS, overall survival.

Table 56. ERG's preferred model assumptions – BRCA2L population

| Preferred assumption | Section in ERG report | Incremental costs | Incremental QALYs | Cumulative ICER £/QALY |
|---|---|---|---|---|
| Corrected company base-case | *6.1* | [redacted] | [redacted] | **£59,236** |
| Using the Weibull distribution for PFS for the BRCA2L population | *4.2.5.1, 6.2 & 6.3* | [redacted] | [redacted] | **£53,870** |
| Post-progression survival modelled as the residual of ARIEL3 PFS and Study 19 OS | *4.2.5.1* | [redacted] | [redacted] | **£62,221** |
| Use of subsequent therapy proportions from Study 19 | *4.2.8.1, 6.2 & 6.3* | [redacted] | [redacted] | **£63,236** |
| PFS off maintenance costs for routine surveillance | *4.2.8.1* | [redacted] | [redacted] | **£64,186** |
| Removal of oral therapy administration costs | *4.2.8.1* | [redacted] | [redacted] | **£62,668** |
| Extension of time horizon to 50 years | *4.2.4.1* | [redacted] | [redacted] | **£58,097** |

Abbreviations: BRCA, breast cancer susceptibility gene mutation; PFS, progression-free survival; OS, overall survival.

Table 57. ERG's preferred model assumptions – BRCA3L+ population

| Preferred assumption | Section in ERG report | Total costs Rucaparib | Total costs Olaparib | Incremental costs |
|---|---|---|---|---|
| Corrected company base-case | *6.1* | [redacted] | [redacted] | [redacted] |
| Removal of oral therapy administration costs | *4.2.8.1* | [redacted] | [redacted] | [redacted] |

Abbreviations: BRCA, breast cancer susceptibility gene mutation.

## *6.5 Conclusions of the cost effectiveness section*

Overall, the company's submission and subsequent clarification responses provide estimates of the cost-effectiveness of rucaparib compared with routine surveillance (ITT, non-BRCA and BRCA2L populations) and olaparib (BRCA3L+) that are relevant to the decision problem defined in the National Institute of Health and Care Excellence (NICE) final scope. The company maintain the most relevant populations to consider are the ITT and BRCA3L+ populations as they argue that BRCA status (except for the case of BRCA3L+ patients) does not guide treatment decisions. The company state that both non-BRCA and BRCA2L patients will receive the same routine surveillance. Furthermore, ARIEL3 was not designed to prospectively evaluated PFS by BRCA status and thus subgroup analyses provided in the company clarification response are *post hoc*.

However, the ERG considers that firstly, ARIEL3 ITT population includes BRCA3L+ patients and as such, routine surveillance is not a relevant comparator as these patients would receive olaparib and secondly, clinical evidence (including evidence provided in the company clarification response) indicates that BRCA patients receiving PARPis experience better clinical outcomes than non-BRCA patients on PARPis and this has an influential effect on the cost-effectiveness of treatments.[7, 8, 14] As such, the ERG considers the most relevant populations for the decision problem are the non-BRCA, BRCA2L and BRCA3L+ analyses provided by the company.

One of the key issues with the cost-effectiveness analyses is the lack of mature overall survival (OS) data from ARIEL3 and as such the company's reliance on the assumption that OS and, as such, post-progression outcomes observed in Study 19 for olaparib would be the same as for rucaparib. Currently, Study 19 is the only source of mature OS data for any PARPi for patients with recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy. For the BRCA3L+ analyses, based on the assumption that rucaparib and olaparib are clinically equivalent, the company assumed that PFS (informed by ARIEL3) and OS (informed by Study 19) would be the same for both treatments. Therefore, the cost-effectiveness analysis reduces to a cost minimisation exercise.

However, the indirect treatment comparison (ITC) demonstrated that the relative effectiveness of rucaparib compared with olaparib is inconsistent. When using Study 19 for olaparib PFS data, the ITC

demonstrated that PFS was favourable for olaparib and the reverse was estimated when using SOLO2 PFS data. As such, no conclusions can be made about relative efficacy between the two treatments. However, based on the ERG's preference for Study 19 for the ITC, the cost minimisation analyses are likely to be a best-case scenario for rucaparib compared with olaparib.

For the non-BRCA and BRCA2L analyses, the company's approach to implementing Study 19 data to estimate post-progression survival (PPS), calculated as the residual of OS and PFS from Study 19, has resulted in an implied PFS to OS ratio of [redacted]. The committee for the appraisals of niraparib (TA528)[8] and olaparib (GID1296)[14] stated that a ratio of 1:2 is an optimistic assumption for a PARPi. In addition, the company's approach disconnects the PFS (ARIEL3) used to inform the model from PPS. The company's justification for the approach is that, based on what the ERG assumes is a naïve comparison, PFS is longer in ARIEL3 than in Study 19 and as such, PPS is likely to be different, contradicting their earlier claim that outcomes for rucaparib and olaparib would be the same. Thus, the ERG considers that the calculation of PPS should be as the residual of Study 19 OS and ARIEL3 PFS. The ERG acknowledges there are flaws with this approach, but the change in approach results in an implied PFS to OS ratio of between 1:1 (considered conservation by the committee for the appraisals of niraparib (TA528)[8] and olaparib (GID1296)[14] and 1:2.

Aside from the issues of OS data and the implementation of it in the model, there were several other modelling assumptions the ERG changed when developing the ERG base case, including alternative survival distributions for modelling PFS for the non-BRCA and BRCA2L analyses, use of Study 19 subsequent therapy data to calculate subsequent therapy costs, using PFS off maintenance costs for routine surveillance, removal of oral therapy administration costs and extension of time horizon to 50 years. However, it should be noted that the company's base case and the ERG base case result in ICERs for the ITT, non-BRCA and BRCA2L populations which exceed the NICE cost-effectiveness threshold of £20,000 to £30,000. For the BRCA3L+ population, rucaparib is [redacted] than olaparib, [redacted]. Moreover, until mature OS data are available from ARIEL3, the estimated ICERs are subject to a high degree of uncertainty.

# 7 END OF LIFE

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

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

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

The company have not made a case for end-of-life status and the ERG considers that this is appropriate.

# 8 REFERENCES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# 9 APPENDICES

## 9.1 Quality assessment

Table 58. Summary of quality assessment

| | ARIEL3 | | SOLO2 | | Study 19 | |
|---|---|---|---|---|---|---|
| **Study question** | **Risk of bias** | | | | | |
| Was randomisation carried out appropriately? | Low | Low | Low | Low | Low | Low |
| Was the concealment of treatment allocation adequate? | Low | Low | Low | Low | Low | Low |
| Were the groups similar at the outset of the study in terms of prognostic factors? | Low | Low | Low | Low | Low | Low |
| Were the care providers, participants and outcome assessors blind to treatment allocation? | Low | Low | Low | Low | Low | Low |
| Were there any unexpected imbalances in drop-outs between groups? | Low | Low | Low | Low | Low | Low |
| Is there any evidence to suggest that the authors measured more outcomes than they reported? | Low | Low | Low | Low | Low | Low |
| Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Low | Low | Low | Low | Low | Low |

## 9.2 Baseline characteristics

Table 59. Baseline characteristics of the trial ITT populations (reproduced from CS Table 19)

| | ARIEL3 | | SOLO2 | | Study 19 | |
|---|---|---|---|---|---|---|
| | **Rucaparib (n=375)** | **PBO (n=189)** | **Olaparib (n=196)** | **PBO (n=99)** | **Olaparib (n=136)** | **PBO (n=129)** |
| Age in years, median (range) | 61 ([redacted])* | 62 ([redacted])* | 56 (51–63) | 56 (49–63) | 58 (21–89) | 59 (33–84) |
| Race, white % | 80.5 | 78.8 | 88.3 | 91.9 | 95.6 | 97.7 |
| BMI, mean | 27.9 | 26.6 | NR | NR | NR | NR |
| ECOG ≥1, % | 25.3 | 28.0 | 16.3 | 22.2 | 17.6 | 24.8 |
| FIGO ≥III, % | 88.0 | 86.8 | NR | NR | 88.2 | 89.1 |
| Ovarian tumour site, % | 83.2 | 84.1 | 83.7 | 86.9 | 87.5 | 84.5 |
| Serous histology, % | 95.2 | 94.7 | 100 | 100 | 100 | 100 |
| BRCA mutation, % | 34.7 | 34.9 | 100 | 100 | 54.4 | 48.1 |
| Prior lines of platinum chemotherapy, median (range) | 2 (2-6) | 2 (2–5) | Number, %:<br>2: 56.1<br>3: 30.6<br>4: 9.2<br>≥5: 3.6 | Number, %:<br>2: 62.6<br>3: 20.2<br>4: 12.1<br>≥5: 5.0 | 2 (0-7) | 2 (2-7) |
| Platinum-free interval >12 months, % | 59.2 | 64.0 | 59.7 | 59.6 | 61.0 | 58.1 |
| Response to most recent platinum chemotherapy, % | CR: 34<br>PR: 66 | CR: 34<br>PR: 66 | CR: 46<br>PR: 54 | CR: 47<br>PR: 53 | CR: 42<br>PR: 58 | CR: 49<br>PR: 51 |

**Key**: BRCA, breast cancer gene; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ERG< Evidence Review Group; FIGO, International Federation of Gynecology and Obstetrics; NR, not reported; PBO, placebo; PR, partial response.
* Age range corrected by ERG to match those reported in CSR.
**Source**: Coleman *et al*. 2017[1]; Ledermann *et al*. 2016[35]; Pujade-Lauraine *et al*. 2017.[6]

Table 60. Baseline characteristics for BRCA 2L population ARIEL3 (adapted from clarification response A2, Table 2)

| | **Rucaparib (n=77)** | **Placebo (n=41)** |
|---|---|---|
| Age, median years | [redacted] | [redacted] |
| Race, white % | [redacted] | [redacted] |
| BMI, mean | [redacted] | [redacted] |
| Time since diagnosis, mean years | [redacted] | [redacted] |
| Metastatic sites <3, % | [redacted] | [redacted] |
| ECOG ≥1, % | [redacted] | [redacted] |
| FIGO ≥III, % | [redacted] | [redacted] |
| Ovarian tumour site, % | [redacted] | [redacted] |
| Serous histology, % | [redacted] | [redacted] |
| BRCA mutation, % | [redacted] | [redacted] |
| Jewish ancestry, % | [redacted] | [redacted] |
| Platinum-free interval >12 months, % | [redacted] | [redacted] |
| CR to most recent platinum chemotherapy, % | [redacted] | [redacted] |
| Prior lines of chemotherapy ≥3, % | [redacted] | [redacted] |
| Prior lines of platinum therapy ≥3, % | [redacted] | [redacted] |
| Prior use of bevacizumab, % | [redacted] | [redacted] |

**Key:** 2L, second line; BMI, body mass index; BRCA, breast cancer gene; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics.

Table 61. Baseline characteristics for BRCA 3L+ population (reproduced, CS Appendix D, Table 8)

| | ARIEL3 | | Study 19 | | SOLO2 – BRCA 3L | | SOLO2 – BRCA 4L+ | | SOLO2 (weighted average of 3L and 4L+) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Ruca (n=53) | Placebo (n=25) | Olaparib (n=47) | Placebo (n=34) | Olaparib (n=60) | Placebo (n=20) | Olaparib (n=25) | Placebo (n=17) | Olaparib (n=85) | Placebo (n=37) |
| Age ≥65 years, % | [redacted] | [redacted] | 27.7 | 17.6 | Median (range): 56.5 (37–83) | Median (range): 58.5 (42–70) | Median (range): 57.0 (47–71) | Median (range): 61.0 (43–75) | NE | NE |
| Race, white % | [redacted] | [redacted] | NR | NR | NR | NR | NR | NR | NR | NR |
| BMI, mean | [redacted] | [redacted] | NR | NR | NR | NR | NR | NR | NR | NR |
| ECOG ≥1, % | [redacted] | [redacted] | 12.8 | 23.5 | 15.0 | 25.0 | 12.0 | 12.0 | 14.1 | 18.9 |
| FIGO ≥III, % | [redacted] | [redacted] | NR | NR | NR | NR | NR | NR | NR | NR |
| Ovarian tumour site, % | [redacted] | [redacted] | NR | NR | NR | NR | NR | NR | NR | NR |
| Serous histology, % | [redacted] | [redacted] | NR | NR | NR | NR | NR | NR | NR | NR |
| BRCA mutation, % | [redacted] | [redacted] | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Platinum-free interval >12 months, % | [redacted] | [redacted] | 63.8 | 47.1 | 48.0 | 60.0 | 40.0 | 24.0 | 45.9 | 43.2 |
| Response to most recent plt chemotherapy, % | [redacted] | [redacted] | CR: 44.7 | CR: 61.8 | CR: 37.0 | CR: 35.0 | CR: 48.0 | CR: 35.0 | CR: 40.0 | CR: 35.1 |

**Key:** BMI, body mass index; BRCA, breast cancer gene; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; NR, not reported; plt, platinum; Ruca, rucaparib.
**Source:** ARIEL data on file; NICE Committee Papers - ID735[16]; Penson et al. 2017.[17]

Table 62. Baseline characteristics for non-BRCA population (adapted from clarification response A2, Table 2)

| | ARIEL 3 | | Study 19 | |
|---|---|---|---|---|
| | **Rucaparib (n=245)** | **Placebo (n=123)** | **Olaparib (n=57)** | **Placebo (n=61)** |
| Age, median years | [redacted] | [redacted] | 62 | 63 |
| Race, white % | [redacted] | [redacted] | - | - |
| BMI, mean | [redacted] | [redacted] | - | - |
| Time since diagnosis, mean years | [redacted] | [redacted] | - | - |
| Metastatic sites <3, % | [redacted] | [redacted] | - | - |
| ECOG ≥1, % | [redacted] | [redacted] | 19.3 | 24.6 |
| FIGO ≥III, % | [redacted] | [redacted] | - | - |
| Ovarian tumour site, % | [redacted] | [redacted] | 87.7 | 80.3 |
| Serous histology, % | [redacted] | [redacted] | 100 | 100 |
| BRCA mutation, % | [redacted] | [redacted] | 0 | 0 |
| Jewish ancestry, % | [redacted] | [redacted] | 10.5 | 4.9 |
| Platinum-free interval >12 months, % | [redacted] | [redacted] | 59.6 | 60.7 |
| CR to most recent platinum chemotherapy, % | [redacted] | [redacted] | 35.1 | 41.0 |
| Prior lines of chemotherapy ≥3, % | [redacted] | [redacted] | - | - |
| Prior lines of platinum therapy ≥3, % | [redacted] | [redacted] | 43.9 | 42.6 |
| Prior use of bevacizumab, % | [redacted] | [redacted] | - | - |

**Key:** 2L, second line; BMI, body mass index; BRCA, breast cancer gene; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics.

Table 63. Baseline characteristics of UK patients in ARIEL3 (reproduced from clarification response A9)

| | **Rucaparib (n=41)** | **Placebo (n=26)** | **Total (n=67)** |
|---|---|---|---|
| **Age, median (range) [years]** | [redacted] | [redacted] | [redacted] |
| Age group, n (%) | | | |
| <65 years | [redacted] | [redacted] | [redacted] |
| 65–74 years | [redacted] | [redacted] | [redacted] |
| 75–85 years | [redacted] | [redacted] | [redacted] |
| **Race, n (%)** | | | |
| White | [redacted] | [redacted] | [redacted] |
| Non-white | [redacted] | [redacted] | [redacted] |
| Unknown | [redacted] | [redacted] | [redacted] |
| **ECOG performance status, n (%)** | | | |
| 0 | [redacted] | [redacted] | [redacted] |
| 1 | [redacted] | [redacted] | [redacted] |
| **Type of ovarian cancer, n (%)** | | | |
| Epithelial ovarian cancer | [redacted] | [redacted] | [redacted] |

| | | | |
|---|---|---|---|
| Fallopian tube cancer | [redacted] | [redacted] | [redacted] |
| Primary peritoneal cancer | [redacted] | [redacted] | [redacted] |
| **Histology, n (%)** | | | |
| Serous | [redacted] | [redacted] | [redacted] |
| Endometrioid | [redacted] | [redacted] | [redacted] |
| Mixed | [redacted] | [redacted] | [redacted] |
| **FIGO Stage at diagnosis, n (%)** | | | |
| Stage IA | [redacted] | [redacted] | [redacted] |
| Stage IB | [redacted] | [redacted] | [redacted] |
| Stage IC | [redacted] | [redacted] | [redacted] |
| Stage IIA | [redacted] | [redacted] | [redacted] |
| Stage IIB | [redacted] | [redacted] | [redacted] |
| Stage IIC | [redacted] | [redacted] | [redacted] |
| Stage IIIB | [redacted] | [redacted] | [redacted] |
| Stage IIIC | [redacted] | [redacted] | [redacted] |
| Stage IV | [redacted] | [redacted] | [redacted] |
| Other | [redacted] | [redacted] | [redacted] |
| Missing | [redacted] | [redacted] | [redacted] |
| **BRCA mutant subgroups, n (%)** | [redacted] | [redacted] | [redacted] |
| BRCA1 | [redacted] | [redacted] | [redacted] |
| BRCA2 | [redacted] | [redacted] | [redacted] |
| Germline[a] | [redacted] | [redacted] | [redacted] |
| Somatic[a] | [redacted] | [redacted] | [redacted] |
| Unknown[a] | [redacted] | [redacted] | [redacted] |
| Missing | [redacted] | [redacted] | [redacted] |
| **BRCA wild-type subgroups[b], n (%)** | [redacted] | [redacted] | [redacted] |
| LOH high[c] | [redacted] | [redacted] | [redacted] |
| LOH low[d] | [redacted] | [redacted] | [redacted] |
| LOH indeterminate[e] | [redacted] | [redacted] | [redacted] |
| Time since cancer diagnosis, median (range) [months] | [redacted] | [redacted] | [redacted] |
| **Time since cancer diagnosis group, n (%)** | | | |
| >12-24 months | [redacted] | [redacted] | [redacted] |
| >24 months | [redacted] | [redacted] | [redacted] |
| **Measurable disease at baseline (as per investigator), n (%)** | | | |
| Yes | [redacted] | [redacted] | [redacted] |
| No | [redacted] | [redacted] | [redacted] |
| **Bulky disease (any lesion >2cm) at baseline (as per BICR), n (%)** | | | |
| Yes | [redacted] | [redacted] | [redacted] |
| No | [redacted] | [redacted] | [redacted] |
| **Number of prior previous chemotherapy regimens** | | | |
| Median (range) | [redacted] | [redacted] | [redacted] |
| 2, n (%) | [redacted] | [redacted] | [redacted] |

| | | | |
|---|---|---|---|
| ≥3, n (%) | [redacted] | [redacted] | [redacted] |
| **Number of platinum-based regimens** | | | |
| Median (range) | [redacted] | [redacted] | [redacted] |
| 2, n (%) | [redacted] | [redacted] | [redacted] |
| ≥3, n (%) | [redacted] | [redacted] | [redacted] |
| Penultimate progression-free interval after last dose of platinum, median (range) [months] | [redacted] | [redacted] | [redacted] |
| **Randomisation stratification: penultimate progression-free interval, n (%)** | | | |
| 6–12 months, n (%) | [redacted] | [redacted] | [redacted] |
| >12 months, n (%) | [redacted] | [redacted] | [redacted] |
| **Randomisation stratification: best response from previous platinum therapy, n (%)** | | | |
| RECIST CR | [redacted] | [redacted] | [redacted] |
| RECIST / CA-125 PR | [redacted] | [redacted] | [redacted] |

**Key:** BICR, blinded independent central radiology review; BRCA, breast cancer gene; CA-125, cancer antigen 125; CR, complete response; CTA, clinical trial assay; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; LOH, loss of heterozygosity; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.
**Notes**: [a], combines both CTA and central test to determine type, this is the variable used for analysis; [b], includes non-BRCA HRD and biomarker negative patients; [c], genomic LOH of 16% or greater as detected by next generation sequencing of tumour tissue; [d], genomic LOH of less than 16%; [e], not evaluable for percent of genomic LOH due to low tumour content or low aneuploidy in the biopsy testing.

## *9.3 Subsequent therapy scenario analysis*

In their clarification response, the company updated subsequent therapy proportions to be based on data from Study 19. However, upon further inspection, the ERG found several discrepancies with the data (described further in Section 4.2.8.1). The ERG updated the economic models with subsequent therapy data obtained from the committee papers for TA381 (Table 7.22)[7]. Six new combination therapies, were added, including: carboplatin + cyclophosphamide; carboplatin + doxorubicin; carboplatin + docetaxel; cisplatin + cyclophosphamide; carboplatin + gemcitabine hydrochloride; and, cisplatin + cyclophosphamide + docetaxel. Within the TA381 committee papers, the ERG found that the doses of cyclophosphamide, cisplatin, docetaxel and gemcitabine hydrochloride were maintained when they were received as a monotherapy or a combination therapy while the doses for carboplatin and doxorubicin were similar.

Therefore, the ERG made a simplifying assumption and added the proportion of each individual therapy included in the new combination therapy to the existing monotherapy in the model. For example, to cost carboplatin + cyclophosphamide combination therapy in the model for patients with no prior use of PARPis, the proportion of patients receiving that combination (4.8%) was added to the proportion of patients who received carboplatin as a monotherapy (38.7% + 4.8%) and cyclophosphamide as a monotherapy (0% + 4.8%).

Olaparib (or any PARPi) was not included as a subsequent therapy option in the economic analysis for TA381. However, when the ERG reviewed Ledermann et al. 2016 (the source used to inform OS), the ERG found that 27.4% of the placebo cohort (including 22.6% from the BRCA mutation cohort) received a PARPi after discontinuation. To maintain the assumption that patients with no prior use of PARPis only receive olaparib and not any other PARPi after progression in the UK, the ERG included the PARPi proportions from Study 19 to the subsequent therapy analysis.