NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [ID1485]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [ID1485]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Clovis Oncology

2. **Clarification questions and company responses**
   a. Additional clarification questions and response

3. **Patient group, professional group and NHS organisation submission** from:
   a. Ovacome
   b. Target Ovarian Cancer

4. **Expert personal perspectives** from:
   a. Dr Agnieszka Michael, Consultant Medical Oncologist – clinical expert, nominated by British Gynaecological Cancer Society
   b. Prof. Jonathan Ledermann, Professor of Medical Oncology – clinical expert nominated by Clovis Oncology
   c. Rachel Downing – patient expert, nominated by Target Ovarian Cancer

5. **Evidence Review Group report** prepared by BMJ

6. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

7. **Technical engagement response from company** Clovis Oncology

8. **Technical engagement responses from experts:**
   a. Dr Jonathan Ledermann, clinical expert nominated by Clovis

9. **Evidence Review Group critique of company response to technical engagement** prepared by BMJ

10. **Final Technical Report**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

Document B

Company evidence submission

January 2019

File name	Version	Contains confidential information	Date
1485_Rucaparib_NICE_STA_Document B_Combined v3.0_Redacted	3.0	Yes	15 Feb 2019

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B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication, as summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
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
Intervention	Rucaparib (Rubraca®)	Rucaparib	Not applicable
Comparator (s)	• Routine surveillance For people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy: • Olaparib (Lynparza®) (subject to ongoing appraisal)	• Routine surveillance For people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy: • Olaparib (subject to ongoing appraisal)	Not applicable
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Progression-free survival 2 (that is, progression-free survival on next line of therapy) • Time to next line of therapy	The outcome measures to be considered include: • Overall survival • Progression-free survival • Progression-free survival 2 (that is, progression-free survival on next line of therapy) • Time to next line of therapy	Not applicable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Adverse effects of treatment • Health-related quality of life	• Adverse effects of treatment • Health-related quality of life	
Economic analysis	The reference case stipulates the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. 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.	Incremental cost per QALY gained analysis	Not applicable
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

Key: BRCA, breast cancer gene; CHMP, Committee for Medicinal Products for Human Use; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

B.1.2. Description of the technology being appraised

A summary description of rucaparib is provided in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Rucaparib (Rubraca®)
Mechanism of action	Rucaparib is a potent and selective small molecule inhibitor of PARP1, PARP2 and PARP3. PARP enzymes are instrumental in fixing single strand breaks during cell DNA replication through the BER pathway. When single strand breaks are not fixed, double strand breaks develop. Fixing double strand breaks requires effective activation of the HRR pathway – a complex process involving multiple proteins, including those encoded by breast cancer genes 1 and 2 (BRCA1/2). If either the BER or HRR pathways are non-functional, the other pathway will over compensate; for example, if the HRR pathway is dysfunctional, the BER pathway becomes the primary repair pathway. If both the BER and HRR pathways are non-functional, single strand breaks lead to double strand breaks in cell DNA, which in turn leads to cell death. This concept is known as 'synthetic lethality' and, in the setting of DNA damage, can be achieved by an enzymatic inhibitor of PARP in the context of a mutation in HRR protein genes. HRD is common in ovarian cancer cells, so PARP inhibition can be an effective treatment for people with ovarian cancer – selectively killing cancer cells with HRD while sparing normal cells.
Marketing authorisation status	On 6 June 2018, Clovis Oncology submitted a regulatory application to the EMA to expand the current licence for rucaparib to include maintenance treatment. On 13 December 2018, the CHMP adopted a positive opinion recommending this change. European Commission marketing authorisation was granted on 23 January 2019.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication of interest to this appraisal is: 'Rubraca as monotherapy for the maintenance treatment of 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.'

Method of administration and dosage	Rucaparib is provided as a film-coated tablet. The recommended dose of rucaparib is 600mg (two 300mg tablets) taken orally twice daily with or without food (1,200mg total daily dose). Interruption of treatment or dose reduction (600mg to 500mg [two 250mg tablets] to 400mg [two 200mg tablets] to 300mg [one 300mg tablet]) can be considered for adverse event management.
Additional tests or investigations	No additional tests or investigations are needed to prescribe rucaparib, but monthly monitoring of blood counts is a feature of PARP inhibitor treatment.
List price and average cost of a course of treatment	The list price for rucaparib is £3562.00 per pack of 60 300mg, 250mg or 200mg tablets. Estimated average cost of a course of treatment of £110,897from list-price deterministic base case economic analysis, no time-preference discounting ([redacted]inclusive of PAS discount).
Patient access scheme (if applicable)	There is a commercial discount to the list price of rucaparib which has been submitted to the Department of Health that is applicable to this appraisal, subject to approval.
Key: BER, base excision repair; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; HRD, homologous recombination deficiency; HRR, homologous recombination repair; PARP, poly(ADP ribose) polymerase; SmPC, summary of product characteristics. **Source:** Rucaparib SmPC.[1]	

B.1.3. Health condition and position of the technology in the treatment pathway

Disease overview

Brief overview of disease

Ovarian cancer (OC) is a relatively rare disease. Approximately 7,400 people are diagnosed each year in the UK[2] (there were 6,407 cases of OC diagnosed in England in 2016[3]), but it is the most common gynaecological malignancy and the leading cause of death attributed to gynaecological cancer in the UK.[4]

There are different types of OC; epithelial OC (EOC) is the most common type, which can be further classified into different subtypes: serous carcinoma, endometrioid carcinoma, clear-cell carcinoma, mucinous carcinoma, and undifferentiated or unclassified carcinoma.[5] Other types of OC include fallopian tube cancer (FTC) and primary peritoneal cancer (PPC).[6] EOC accounts for approximately 90% of all cases of OC in the UK, and 'serous' is the most common

subtype of EOC, accounting for approximately two-thirds of all cases of EOC.[5] The incidence of PPC (<1%) and fallopian tube cancer (1%) are low in the UK.[6]

Similar to other cancer types, staging of OC assesses how far the cancer has grown and if it has spread. Grading of OC assesses how differentiated the cancer cells are, that is, how different they look to normal cells. The International Federation of Gynecology and Obstetrics (FIGO) system is most commonly used to stage OC. Stage I represents cancer that has not spread from the ovaries, Stage II represents cancer that has spread to the pelvis and is starting to reach the abdomen, Stage III represents cancer that has spread outside of the pelvis but is still local to the ovaries, and Stage IV represents cancer that has spread to distant organs.[7] The grading of OC is characterised on a scale of 1–3, where Grade 1 represents well differentiated cells and Grade 3 represents poorly differentiated cells. Grade 2 and 3 OC are classed as 'high-grade', meaning the tumour(s) is aggressive and likely to grow and spread quickly. The majority of people diagnosed in the UK (55–58%) have advanced stage disease (Stages III and IV)[8] and most cases are high-grade.[9]

Such aggressive disease has a poor prognosis and fewer than 20% of people diagnosed with advanced stage OC in the UK are expected to survive for 5 years or more after their diagnosis (compared to 90% of people diagnosed with Stage I disease).[10] Survival expectations are below the European average, with the UK reporting one of the worst 5-year survival rates in OC. A recent publication of the CONCORD programme showed that the UK had the fourth lowest age-standardised 5-year net survival rate across European countries (n=27) during a 15-year period (2000–2014), and the lowest age-standardised 5-year net survival rate in the EU5 (36.2% in 2010–2014 compared to 43.5% for the same period in France).[11]

Aetiology of ovarian cancer

OC can affect people of any age but is most common in older postmenopausal women. Of the cases diagnosed in the UK, 86% are in people aged 50 years or older, and the median age at presentation is 55–60 years.[4] The majority of OC cases are sporadic and in addition to age, lifestyle and environmental factors can increase the risk of its development. These include smoking, being overweight, exposure to asbestos and radiation, and suffering from medical conditions such as endometriosis or diabetes.[12]

OC can also be caused by inherited faulty genes; the risk of OC is 2.7–3.5 times greater in people with a first degree relative with OC, compared with people with no such family history. This risk increases with a higher number of affected relatives.[13] Inherited genes that increase the risk of OC include faulty versions of homologous recombination genes; an analysis of The Cancer Genome Atlas estimated that approximately 50% of patients with high-grade serous OC have homologous recombination deficiency (HRD).[14] Specific drivers of HRD in OC include:

- Germline mutations in breast cancer gene (BRCA) 1 or BRCA2, estimated to account for up to 15% of all cases of OC[15, 16]
- Somatic mutations in the BRCA1 or BRCA2 genes, estimated to account for between 6% and 8% of cases of high-grade serous OC[14, 17]
- Mutation in a homologous recombination gene other than BRCA1 or BRCA2 (see Appendix L.1 for further details of these), estimated to account for approximately 16% of cases of high-grade serous OC[14]
- Functional silencing of homologous recombination genes, such as through BRCA promoter methylation or other mechanisms, estimated to account for approximately 10% of cases of high-grade serous OC[14]

Symptoms of ovarian cancer

People with OC may experience bloating, loss of appetite, abdominal pain, pelvic pain, more frequent passing of urine, changes in bowel habits, tiredness and weight loss.[18] Only when these symptoms are experienced relatively frequently (12 or more times per month according to NICE Clinical Guideline 122), and as such start to impact daily living, would investigation into the possibility of OC be triggered in UK practice.[19] People with metastatic disease may experience further symptoms relating to the site of metastases (although these are rarer than primary cancer symptoms), which can include shortness of breath and chest pain (lung metastases), sickness and jaundice (liver metastases), or headaches and seizures (brain metastases).[20]

Such changes in physical and physiological functioning can significantly impact health-related quality of life (HRQL) which can be further exacerbated in those patients experiencing side effects of treatment for their disease.[21, 22] Chemotherapy-associated toxicities can particularly reduce a patient's perception of health and in patients with relapsed and progressive disease, median utility values according to

the EQ-5D® visual analogue scale can be as low as 0.17 in patients experiencing Grade 3–4 toxicity.[23] There is also a psychological impact associated with a diagnosis of OC; distress caused by fear and anxiety of recurrence is likely to worsen in patients who have relapsed following initial lines of treatment.[22]

Of note, Target Ovarian Cancer is working to raise awareness of the symptoms of ovarian cancer and campaigning for diagnostic pathways to be shortened in the UK to allow treatment to be initiated at the earliest point, increasing the chance of survival.[24]

Clinical pathway of care

The current clinical pathway of care for advanced OC in NHS England, according to the NICE pathway for the management of OC, is depicted in Figure 1.[25] This pathway of care is applied to all types of OC, including high-grade EOC, PPC and FTC.

Primary surgery is usually the first intervention used to treat advanced OC (with or without neoadjuvant chemotherapy) with an objective of complete resection of all macroscopic disease. Despite this objective, in most cases it is not possible to remove the tumour completely and surgery is therefore typically followed up with first-line (1L) chemotherapy with a platinum-based compound (cisplatin or carboplatin).[26]

Platinum-based chemotherapy has been the established standard of care for many years, with most people with advanced OC responding to 1L chemotherapy treatment with a platinum-based compound.[26] However, responses are often short-lived and around 70–80% of patients relapse following an initial response.[27, 28] The risk of relapse is higher in patients with a suboptimal response to initial treatment: for patients with residual disease <1cm, the risk for recurrence is estimated at 60–70% but for patients with large-volume residual disease, the risk is estimated at 80–85%.[29]

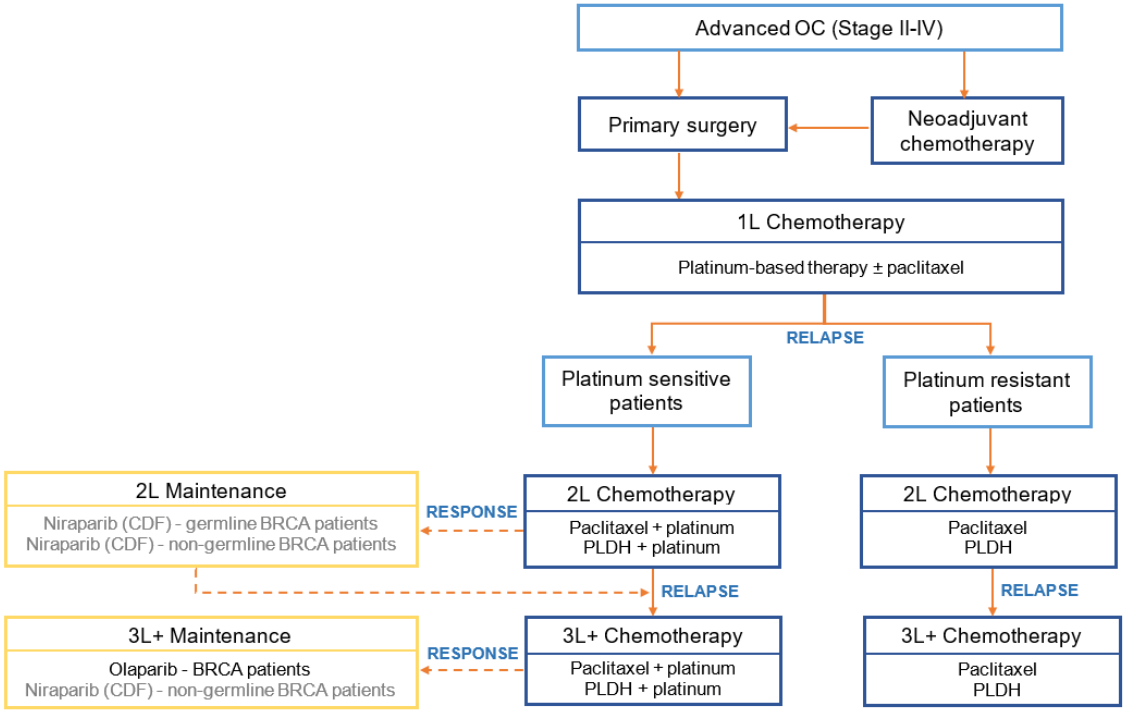
In the relapsed setting, further chemotherapy is recommended, but the exact regimen will depend on the cancer's sensitivity to platinum-based treatment. Historically, platinum sensitivity would have been assessed against recurrence-time based categorisation, but it is generally accepted in modern practice that platinum

sensitivity is a continuum, and that platinum-based chemotherapy is likely the best option for all patients with some level of response to prior platinum in the recurrent setting (as recently discussed and agreed at the ESMO-ESGO Consensus Conference on Ovarian Cancer).[30]

Second-line (2L) or later-line (3L+) platinum-based chemotherapy has the same objective as 1L platinum-based chemotherapy with respect to achieving a response; ideally a complete treatment response, but if not, a partial response. However, with each relapse, platinum-based chemotherapy becomes less effective and eventually patients will become resistant to platinum treatment.[31] Patients with such platinum-resistant or refractory disease will be treated with non-platinum-based chemotherapy in the relapsed setting, typically paclitaxel or pegylated liposomal doxorubicin hydrochloride in NHS England. Such platinum-resistant disease has an extremely poor prognosis and patients are not expected to live beyond 12 months with non-platinum-based chemotherapy.[31]

Maintenance therapies extend the chemotherapy treatment response (increase the length of response) and thus the time to relapse and the need for further chemotherapy treatment (see Section B.2).[32] In the current clinical pathway of care in NHS England, maintenance treatment in the form of olaparib (Lynparza®) is available for patients with BRCA mutations who are responding to 3L+ platinum-based chemotherapy.[33] Maintenance treatment in the form of niraparib (Zejula®) has more recently been made available for patients with germline BRCA mutations who are responding to 2L platinum-based chemotherapy, and patients with non-germline BRCA mutations who are responding to 2L+ chemotherapy through the Cancer Drugs Fund.[34] Maintenance treatments are highlighted in yellow boxes in Figure 1.

Figure 1: Clinical pathway of care for advanced ovarian cancer in NHS England



Key: 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.[25]

Unmet medical need

Advanced OC is an aggressive disease with a poor prognosis, particularly for patients in the UK where survival expectations are below the European average.[11] Although platinum-based chemotherapy is highly effective in the 1L setting (with most people responding to such treatment), relapse rates are high (70–80%), particularly in patients with a suboptimal response to initial treatment.[27-29] At this point, the disease is considered incurable and while further platinum-based chemotherapy can obtain tumour response, responses become shorter with each relapse until the tumour is considered platinum-resistant and thus fatal, with patients not expected to survive beyond a year.[31]

It is generally accepted that the probability of responding to further platinum-based chemotherapy following relapse depends on the platinum-free interval.[31] Maintenance therapies can extend the treatment response and thus not only prolong disease control (time to relapse) and the time to next-line chemotherapy, but also

potentially increase the subsequent response to further platinum-based chemotherapy.[31, 32] Poly (ADP ribose) polymerase (PARP) inhibitor (PARPi) therapies offer a non-platinum maintenance treatment option in the setting of platinum-sensitive relapsed OC, which may be particularly effective as platinum sensitivity and PARPi sensitivity have been associated with HRD such that sensitivity to platinum and PARPi commonly coexist in advanced OC.[35]

Considering the significant benefits of PARPi maintenance treatment, there is an argument that patients simply monitored through routine surveillance in clinical practice are not receiving optimum care, and that all people with platinum-sensitive relapsed OC should be being prescribed PARPi maintenance treatment. In NHS England, the only maintenance treatment available through routine commissioning and funding (and therefore considered a relevant comparator in accordance with NICE criteria) is olaparib. However, olaparib capsules are only licensed to treat patients with BRCA mutated disease and in NHS England, its use is further restricted to patients who have received three or more previous treatments (due to concerns about its cost effectiveness in the total licensed patient group).[33] Key differences between rucaparib and olaparib are summarised in Table 3.

Rucaparib offers a maintenance treatment with proven clinical effectiveness across a broad range of patients with relapsed OC, irrespective of BRCA mutation status (see Section B.2.6). It also has manageable tolerability but with a safety profile that differs from the safety profile of other PARPi maintenance treatments (see Section B.2.10). By providing a maintenance treatment with universal coverage, and a differing safety profile to other PARPi maintenance treatments, rucaparib addresses an unmet medical need in current clinical practice., and could further advance the incorporation of PARPi maintenance treatment within the standard of care for people with platinum-sensitive relapsed OC.

Table 3: Key differences between rucaparib and olaparib

	Rucaparib - tablets	Olaparib - capsules	Key differences (rucaparib versus olaparib)
Marketing authorisation	Rubraca is indicated as monotherapy for the maintenance treatment of 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.	Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (CR or PR) to platinum-based chemotherapy	• No restriction to BRCA-mutated patients • No restriction to serous EOC
NICE recommendations	Not applicable	Recommend within its marketing authorisation only if patients have had three or more courses of platinum-based chemotherapy and the drug cost for people who remain on treatment after 15 months are met by the company.[33]	• No anticipated restriction to third-line or later setting
Dosing and administration	600mg (two 300mg film-coated tablets) taken orally twice daily with or without food	400mg (eight 50mg hard capsules) taken orally twice daily. Due to the effect of food on olaparib absorption, patients should take olaparib at least 1 hour after food, and refrain from eating preferably for up to 2 hours afterwards.	• Two tablets versus eight capsules need to make up dose • No recommendations on food intake based on treatment
Special warnings and precautions for use	<u>Haematological toxicity</u> During treatment with rucaparib, events of myelosuppression may be observed.	<u>Haematological toxicity</u> Haematological toxicity has been reported in patients treated with olaparib, including mild or moderate	• Photosensitivity and gastrointestinal toxicities observed • Fatal pneumonitis has not been observed

	Rucaparib - tablets	Olaparib - capsules	Key differences (rucaparib versus olaparib)
		anaemia, neutropenia, thrombocytopenia and lymphopenia. Myelodysplastic syndrome/acute myeloid leukaemia MDS/AML have been reported in a small number of patients who received olaparib; the majority of cases have been fatal. Pneumonitis Pneumonitis has been reported in a small number of patients receiving olaparib, and some reports have been fatal. Embryofoetal toxicity Olaparib can cause foetal harm when administered to a pregnant woman. Pregnancy/contraception Olaparib should not be used during pregnancy and in women of childbearing potential not using reliable contraception. Interactions	
	Myelodysplastic syndrome/acute myeloid leukaemia MDS/AML, including cases with fatal outcomes, have been reported in patients who received rucaparib. Photosensitivity Photosensitivity has been observed in patients treated with rucaparib. Gastrointestinal toxicities Gastrointestinal toxicities are frequently reported with rucaparib, but are generally low grade. Embryofoetal toxicity Rucaparib can cause foetal harm when administered to a pregnant woman. Pregnancy/contraception		

	Rucaparib - tablets	Olaparib - capsules	Key differences (rucaparib versus olaparib)
	Pregnant women should be informed of the potential risk.	Olaparib co-administration with strong CYP3A inducers or inhibitors should be avoided - see below.	
Interaction with other medicinal products	*In vitro* data and medicinal product interaction study data are available for rucaparib. Caution should be used for concomitant use of: • strong CYP3A4 inhibitors or inducers; • strong inhibitors of P-glycoprotein • UGT1A1 substrates Dose adjustments may be considered when co-administering: • medicinal products metabolised by CYP1A2 • medicinal products that are CYP2C9 substrates • CYP3A substrates Interactions between rucaparib and oral contraceptives have not been studied.	No formal drug interaction studies have been performed. The recommended monotherapy dose is not suitable for combination with other anticancer medicinal products. Olaparib should also not be co-administered with: • strong CYP3A4 inhibitors or inducers • strong CYP3A5 inhibitors or inducers Caution should be used for concomitant use of: • vaccines or immunosuppressive agents • CYP3A4 substrates • CYP2C9 substrates, including statins The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.	• Interaction studies available • No restriction on concomitant use of strong CYP3A4/5 inhibitors or inducers

Key: AML, acute myeloid leukaemia; BRCA, breast cancer gene; CR, complete response; EOC, epithelial ovarian cancer; MDS, myelodysplastic syndrome; PR, partial response; SmPC, summary of product characteristics.
Source: Olaparib SmPC[36]; Rucaparib SmPC.[1]

B.1.4. Equality considerations

Not applicable.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

Full details of the systematic literature review process and methods used to identify and select the clinical evidence relevant to this appraisal are provided in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

The pivotal regulatory evidence to support rucaparib, and the focus of this submission is the ongoing, randomised, double-blind, placebo-controlled, Phase III study ARIEL3; this study provides direct data for the comparison of rucaparib with routine surveillance (represented by placebo).

A summary of ARIEL3 is presented in Table 4, with further details of its design provided in Section B.2.3.

Table 4: Clinical effectiveness evidence

Study	ARIEL3; NCT01968213				
Study design	ARIEL3 is an ongoing, randomised, international, double-blind, placebo-controlled, multicentre, Phase III study evaluating rucaparib versus placebo as maintenance therapy in recurrent, platinum-sensitive ovarian carcinoma.				
Population	Adult patients with platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, who have received at least two previous platinum-based chemotherapy regimens, and had achieved complete or partial response to their last platinum based regimen.				
Intervention(s)	Rucaparib (n=375)				
Comparator(s)	Placebo (n=189)				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	ARIEL3 presents the pivotal regulatory clinical evidence in support of rucaparib in the population directly relevant to the decision problem.				
Reported outcomes specified in the decision problem	• **progression-free survival** • **overall survival** • progression-free survival 2 (i.e. progression-free survival on next line of therapy) • time to next line of therapy • **adverse effects of treatment** • **health-related quality of life.**				
All other reported outcomes	• Response in patients with measurable disease • CA-125 • Chemotherapy-free interval				

Additional studies relevant to this appraisal are those providing clinical evidence for active comparator technologies (olaparib) which are used to inform indirect treatment comparison (ITC) estimates presented in Section B.2.9. Details of these studies are provided in Appendix D.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

ARIEL3 study

Further details of the methodology of the ARIEL3 study are presented in Table 5.

Trial design

The ARIEL3 study consists of a 90-day screening phase prior to randomisation to confirm eligibility; a double-blind treatment phase consisting of continuous 28-day maintenance treatment cycles (until disease progression, death, or another reason for discontinuation); and a follow-up phase.

Upon formal closure of the study, individual patients who are continuing to benefit from treatment with rucaparib, and who do not meet any of the criteria for withdrawal, have the option to enter an open-label extension protocol in which they will continue to receive rucaparib.

Randomisation

Eligible patients were randomised in a 2:1 ratio to receive oral rucaparib (600mg twice daily) or matching placebo. The population enrolled was unselected with regard to the molecular characteristics of the tumour. Randomisation was carried out within 8 weeks of completing a course of platinum-based chemotherapy and was conducted through a central randomisation procedure using Interactive Voice Response System/Interactive Web Response System on a block size of six. To ensure that treatment groups were balanced, the following criteria were included as randomisation stratification factors:

- HRD classification by the clinical trial assay (CTA), developed by Foundation Medicine, Incorporated (FMI), which identifies mutations in 30 genes involved in HRD through analysis of tumour tissue (full details provided in Appendix L.1)
  - BRCA mutant (deleterious tumour alteration in BRCA1 or BRCA2 genes)
  - BRCA wild-type
    - non-BRCA HRD (mutations in any of the other 28 identified HRD genes)
    - biomarker negative (no deleterious mutations in the 30 identified HRD genes)
- Interval between completion of the penultimate platinum-based regimen and disease progression by radiological assessment
  - 6 to 12 months
  - >12 months

- Best response to platinum regimen received immediately prior to initiation of maintenance therapy. All responses required that cancer antigen 125 (CA-125) was in the upper limit of normal (ULN)
  - Complete response (CR), defined as complete radiological response by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
  - Partial response (PR), defined as PR by RECIST v1.1 and/or a Gynaecologic Cancer Group (GCIG) CA-125 response.

Enrolment 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.

Table 5: Summary of methodology of ARIEL3

Trial number (acronym)	NCT01968213 (ARIEL3)
Location	This is a global study currently being conducted in 87 centres in 11 countries: Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, the UK, and the US.
Trial design	ARIEL3 is an ongoing, randomised, double-blind, placebo-controlled, multicentre, Phase III study, evaluating the efficacy and safety of rucaparib versus placebo as maintenance therapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer following a response to second line or later platinum-based chemotherapy.
Eligibility criteria for participants	**Inclusion criteria:** • Have signed an IRB/IEC approved ICF prior to any study-specific evaluation • 18 years or older at the time the ICF was signed • Have a histologically confirmed diagnosis of high-grade (Grade 2 or 3) serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer – For mixed histology, >50% of the primary tumour must be confirmed to be high-grade serous or endometrioid – Grade 2 tumours classified under a three tier system should have been re-reviewed by local pathology and confirmed as high-grade under the two tier system • Received prior platinum-based therapy and have platinum-sensitive disease (that is, documented radiological disease progression >6 months following the last dose of the penultimate platinum administered) – Received two or more prior platinum-based treatment regimens, including platinum-based regimen that must have been administered immediately prior to maintenance therapy in this trial. In addition, up to one non-platinum chemotherapy regimen was permitted. Prior hormonal therapy was permitted; this treatment was not counted as a non-platinum regimen – There was no upper limit on the number of prior platinum-based regimens that may have been received, but the patient must have been sensitive to the penultimate platinum-based regimen administered – If both neoadjuvant and adjuvant treatment were administered pre/post any debulking surgery, this was considered one treatment regimen – Prior maintenance therapy following a prior treatment regimen was permitted, with the exception of the regimen received immediately prior to maintenance in this study. No anti-cancer therapy was permitted to

	be administered as maintenance treatment in the interval period between completion of the most recent platinum-based therapy and initiation of study drug in this trial • Achieved best response of either CR or PR to the most recent platinum-based regimen administered and was randomised to study treatment within 8 weeks of the last dose of platinum received – The most recent platinum-based regimen must have been a chemotherapy doublet. The choice of the platinum and the second chemotherapy agent was at the investigators' discretion – A minimum of four cycles of platinum chemotherapy must have been administered. There was no cap on the maximum number of cycles; however, additional cycles of treatment administered following completion of therapy for the specific purpose of enabling patient eligibility and randomisation within 8 weeks of the last platinum dose was not permitted – A CR was defined as a complete radiological response as per RECIST v1.1, that is, absence of any detectable disease and CA-125 <ULN*. – A PR was defined as either a PR as per RECIST v1.1 (if disease was measurable prior to chemotherapy) or a serological response as per GCIG CA-125 response criteria (if disease was not measurable according to RECIST v1.1) ▪ Note: It was acceptable for sites to utilise local and contemporaneous clinical imaging reports to record lesion measurement history and define a burden of disease according to RECIST; it was not a requirement to re-read radiological scans to collect these data – CA-125 must also have been <ULN for all responses classified as a PR – R0 surgery (no visible tumour) or R1 surgery (residual disease <1 cm) as a component of the most recent treatment regimen was not permitted. The response assessment must have been determined solely in relation to the chemotherapy regimen administered. The presence of measurable disease or CA-125 >2 x ULN, immediately prior to the chemotherapy regimen, was required – Responses must have been maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry in the study – All disease assessments performed prior to and during this chemotherapy regimen must have been adequately documented in the patient's medical record • Have had sufficient archival FFPE tumour tissue (1 x 4µm section for haematoxylin and eosin stain and approximately 8 to 12 x 10µm sections, or equivalent) available for planned analyses – The most recently collected tumour tissue sample should have been provided, if available

	– Submission of a tumour block was preferred; if sections were provided, these must all have been from the same tumour sample – Sample must have been received at the central laboratory at least 3 weeks prior to planned start of treatment in order to enable stratification for randomisation • Have had CA-125 measurement that was <ULN • Have had an ECOG performance status of 0 to 1 • Have had adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug: – Bone marrow function ▪ ANC ≥1.5 × 10^9/L ▪ Platelets >100 × 10^9/L ▪ Haemoglobin ≥9g/dL – Hepatic function ▪ AST and ALT ≤3 × ULN; if liver metastases, then ≤5 × ULN ▪ Bilirubin ≤1.5 × ULN (<2 × ULN if hyperbilirubinemia was due to Gilbert's syndrome) – Renal function ▪ Serum creatinine ≤1.5 × ULN or estimated GFR ≥45 mL/min using the Cockcroft Gault formula **Exclusion criteria:** • History of a prior malignancy except: – Curatively treated non-melanoma skin cancer – Breast cancer treated curatively >3 years ago, or other solid tumour treated curatively >5 years ago, without evidence of recurrence – Synchronous endometrioid endometrial cancer (Stage 1A G1/G2) • Prior treatment with any PARPi, including oral or intravenous rucaparib. Patients who previously received iniparib were eligible • Required drainage of ascites during the final two cycles of their last platinum-based regimen and/or during the period between the last dose of chemotherapy of that regimen and randomisation to maintenance treatment in this study

	• Symptomatic and/or untreated CNS metastases. Patients with asymptomatic previously treated CNS metastases were eligible, provided they had been clinically stable for at least 4 weeks. • Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of study drug. • Known HIV or AIDS-related illness, or history of chronic hepatitis B or C. • Pregnant or breast feeding women. Those of childbearing potential must have had a negative serum pregnancy test ≤3 days prior to first dose of study drug. • Received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > NCI CTCAE Grade 1, with the exception of Grade 2 non-haematological toxicity such as alopecia, peripheral neuropathy, and related effects of prior chemotherapy that were unlikely to be exacerbated by treatment with study drug. – Ongoing hormone treatment for previously treated breast cancer was permitted, – Refer also to inclusion criteria for guidelines pertaining to prior maintenance therapy. • Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first dose of study drug or had ongoing requirement for these medications. • Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to first dose of study drug; in all cases, the patient must have been sufficiently recovered and stable before treatment administration. Presence of any other condition that may have increased the risk associated with study participation, or may have interfered with the interpretation of study results and, in the opinion of the investigator, would make the patient inappropriate for entry into the study.
Settings and locations where the data were collected	• Clinical laboratory analyses (haematology and serum chemistry) were performed by a Q^2 Solutions' central laboratory (exact location depending on region of the investigational site). • Analysis of PK samples from all sites was performed at Q^2 Solutions (formerly Quintiles BioScience Inc [Ithaca, New York, USA]) for analysis. • Analysis of CA-125 and AAG analysis from all sites was performed at Q^2 Solutions (formerly Quest Diagnostics Nichols Institute of Valencia, Inc; Valencia, California, USA). • Mutation analysis of BRCA1/2 and other genes involved in homologous recombination, as well as genomic LOH analysis from DNA extracted from tumour tissue was performed by FMI; Cambridge, Massachusetts, USA. The gene mutation analysis was performed prior to randomisation and used for stratification.

	• Computed tomography scans and other imaging were submitted to AG Mednet (Boston, Massachusetts USA) and then read by Bioclinica (Princeton, New Jersey, USA) for BICR. • An IDMC was established to monitor data on an ongoing basis to ensure the continuing safety of patients.
Trial drugs	• **Rucaparib:** 600mg of oral rucaparib twice daily in continuous 28-day cycles (n=375). • **Placebo:** matched oral placebo twice daily in continuous 28-day cycles (n=189). Treatment with rucaparib was held if any of the following was observed and a dose reduction was considered or implemented: • Grade 3 or 4 haematological toxicity • Grade 3 or 4 non-haematological toxicity (except for alopecia, nausea, vomiting, or diarrhoea adequately controlled with systemic antiemetic/antidiarrheal medication, administered in standard doses according to the study centre routines) • In addition, and at the discretion of the investigator, the dose of study drug may have been held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care • Grade 4 ALT/AST elevations – the study drug was held until values had returned to Grade 2 or better, then resumed with a dose reduction. Liver function tests were monitored weekly for 3 weeks after the study drug had been restarted • Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, were managed as follows: – Liver function tests were monitored weekly until resolution to ≤ Grade 2 – Continuation of the study drug with elevation of ALT/AST up to Grade 3 was permitted, provided bilirubin was < ULN and alkaline phosphatase (ALP) was < 3 x ULN – If a patient had Grade 3 ALT/AST and continued on the study drug, and levels did not decline within 2 weeks or they continued to rise, treatment interruption and resolution to ≤ Grade 2 was required before study drug could be resumed, either at the same dose or at a reduced dose. Treatment with the study drug was held until the toxicity resolved to ≤ CTCAE Grade 2. Twice daily dosing could then be resumed at either the same dose or a lower dose, as per investigator discretion. If treatment was resumed at the same dose, and the patient experienced the same toxicity, the dose was reduced following resolution of the event to ≤ CTCAE Grade 2. If the patient continued to experience toxicity, additional dose reduction steps were permitted; however, the investigator consulted with the sponsor's medical monitor before reducing to 240mg BID. If a patient continued to experience toxicity despite two dose reduction steps (that is to a dose of 360mg BID rucaparib or placebo), or if dosing with the study drug was interrupted for >14 consecutive

	days due to toxicity, treatment was discontinued unless otherwise agreed between the investigator and the sponsor. Dose re-escalation upon resolution of toxicity to ≤ CTCAE Grade 1 was permitted at the discretion of the investigator. The starting dose of rucaparib was 600mg BID, dose reduction steps included: • Dose level -1 = 480mg BID • Dose level -2 = 360mg BID • Dose level -3 = 240mg BID (a medical monitor was consulted before reducing to this dose)
Permitted and disallowed concomitant medication	• During the study, supportive care (for example, antiemetics; analgesics for pain control) was used at the investigator's discretion and in accordance with institutional procedures. • No anti-cancer therapy was permitted to have been administered as maintenance treatment in the interval period between completion of the most recent platinum-based chemotherapy and initiation of maintenance treatment in this study. • No other anti-cancer therapies (including chemotherapy, radiation, hormonal treatment, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind were permitted while the patient was participating in the study, with the exception of ongoing hormone treatment for previously treated breast cancer. • Erythropoietin, darbepoetin alfa, and/or haematopoietic colony stimulating factors for treatment of cytopenias were administered, according to institutional guidelines. Transfusion thresholds for blood product support were in accordance with institutional guidelines. • Based on *in vitro* CYP interaction studies, caution was used for concomitant medications with narrow therapeutic windows that are substrates of CYP2C19, CYP2C9, and/or CYP3A. The selection of an alternative concomitant medication was recommended. • Bisphosphonates were permitted. • Caution was exercised in patients who received the study drug and concomitant warfarin (Coumadin®) as rucaparib showed a mixed inhibition of CYP2C9 *in vitro*. If appropriate, low molecular weight heparin was considered as an alternative treatment. Patients who took warfarin had their INR monitored regularly as per standard clinical practice. • Therapies considered necessary for the patient's wellbeing were given at the discretion of the investigator and documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life threatening medical problems, were avoided.

	Herbal and complementary therapies were not encouraged because of unknown side effects and potential drug interactions, but any taken by the patient were documented appropriately on the eCRF. • Because rucaparib is a moderate inhibitor of P-gp *in vitro*, caution was exercised for patients who received the study drug and required concomitant medication with digoxin. Patients who took digoxin had their digoxin levels monitored after starting the study drug and then regularly as per standard clinical practice. Caution was exercised for concomitant use of certain statin drugs (for example, rosuvastatin and fluvastatin) due to a potential increase in exposure from inhibition of BCRP and CYP2C9.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint comparing the rucaparib group to the placebo group was: • PFS as assessed by the investigator, defined as time (from randomisation) to disease progression by RECIST v1.1 or death from any cause, in molecularly-defined HRD subgroups. Patients were assessed for disease status as per RECIST v1.1 every 12 weeks, until disease progression or death.
Other outcomes used in the economic model/specified in the scope	Key secondary endpoints comparing the rucaparib group to the placebo group included: • PFS as assessed by BICR, defined as time (from randomisation) to disease progression by RECIST v1.1, or death from any cause, in molecularly-defined HRD subgroups. • PRO as assessed by time (from randomisation) to worsening in the DRS-P Subscale of FOSI-18 (defined as ≥4 point decrease) • PRO as assessed by time (from randomisation) to worsening of total score of FOSI-18 (defined as ≥8 point decrease) • Overall survival, defined as time (from randomisation) to death from any cause • Safety • Population PK of rucaparib. Patients were asked to complete PRO questionnaires at screening, on Day 1 of each treatment cycle, at treatment discontinuation, and at the 28-day post-treatment discontinuation follow-up. Patients were continuously monitored for safety up to 28 days after the last dose of study drug. Patients were followed for survival, subsequent treatment and monitoring for secondary malignancy every 12 weeks until death, loss to follow-up, withdrawal of consent, or study closure. Exploratory objectives included: • Association between the change from baseline in CA-125 measurements and investigator-assessed PFS • PFS2 as assessed by the investigator, defined as time (from initial disease progression) to the next event of disease progression or death from any cause

	• ORR as per RECIST v1.1, as assessed by both the investigator and BICR, in patients who have measurable disease at study entry • DoR as per RECIST v1.1, as assessed by both the investigator and BICR • PRO as measured by the total score on the EQ-5D.
Pre-planned subgroups	Subgroup analyses were performed based on randomisation stratification subgroups, HRD and gene mutation information, and baseline demographic characteristics, as follows: • Age (<65, 65–74, ≥75 years) • Race (White, non-white, unknown) • BRCA mutant (BRCA1, BRCA2, germline, somatic) • BRCA wild-type (LOH high, LOH low, LOH indeterminate) • Measurable disease at baseline (yes, no) • Bulky disease at baseline (yes, no) • Number of previous chemotherapy regimens (2, ≥3) • Previous bevacizumab use (yes, no) • Number of previous platinum regimens (2, ≥3) • Time to progression with penultimate platinum (6 to ≤12 months, ≥12 months) • Response to last platinum therapy (CR, PR). Subgroup analyses were planned when the number of patients in the subgroups permitted.
Key: AAG, alpha-1 acid glycoprotein; AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BCRP, breast cancer resistance protein; BICR, blinded independent central radiology review; BRCA1, breast cancer 1 gene; BRCA2, breast cancer 2 gene; CA-125, cancer antigen 125; CNS, central nervous system; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CYP, cytochrome P450; DNA, deoxyribonucleic acid; DoR, duration of response; DRS-P, disease-related symptoms–physical; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EQ-5D, Euro-Quality of Life 5D; FFPE, formalin-fixed paraffin-embedded; FMI, Foundation Medicine, Incorporated; FOSI-18, Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18; GCIG, Gynaecologic Cancer Inter Group; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; HRD, homologous recombination deficiency; ICF, informed consent form; IDMC, Independent Data Monitoring Committee; IEC, Independent Ethics Committee; INR, international normalised ratio; IRB, Institutional Review Board; LOH, loss of heterozygosity; NCI, National Cancer Institute; ORR, overall response rate; PARP, poly(ADP-ribose) polymerase; PARPi, PARP inhibitor; P-gp, P-glycoprotein; PFS, progression-free survival; PFS2, progression-free survival on a subsequent line of treatment; PK, pharmacokinetic; PR, partial response; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal. **Source**: Coleman *et al*. 2017;[37] ARIEL3 CSR.[38]	

Genomic testing

As described above, the population enrolled to the ARIEL3 study was unselected with regard to the molecular characteristics of the tumour, but patients were stratified at the time of randomisation into BRCA mutant and BRCA wild-type patients (non-BRCA HRD and biomarker negative) through identification of mutations in 30 HRD genes (tumour-based CTA testing). Further testing was conducted in order to group patients into pre-specified efficacy analysis cohorts and patient subgroups.

Patients identified through tumour-based CTA testing as having mutations in the BRCA1 or BRCA2 gene were further grouped by mutation type (germline versus somatic versus unknown [not tested]) through blood-based germline mutation testing (Myriad Genetics, Salt Lake City, UT).

Patients identified through tumour-based CTA testing as BRCA wild-type were further grouped by the extent of loss of heterozygosity (LOH) (low [<16%] versus high [≥16%] versus indeterminate [not evaluable]) through tumour-based T-5 next-generation sequencing, developed by FMI. LOH is a proposed marker of HRD and thus PARPi activity. LOH thresholds were informed by data from Part 1 of the ARIEL2 trial – an ongoing Phase II study evaluating the efficacy and safety of oral rucaparib as treatment in patients with pre-treated, high-grade serous or endometroid epithelial ovarian, fallopian tube, or primary peritoneal cancer.[39]

The results of the CTA, germline mutation, and LOH testing in the intention-to treat (ITT) population, were used to categorise patients into predefined subgroups and pre-specified efficacy analysis cohorts, detailed in Section B.2.4. Throughout this submission, data for all pre-specified efficacy analysis cohorts will be presented alongside one another.

Endpoints

The primary efficacy endpoint in the ARIEL3 study is investigator-assessed progression-free survival (PFS). Investigator assessment allows real-time evaluation and determination of disease progression and allows investigators to make timely decisions regarding the optimal clinical management for their patients. PFS as

assessed by blinded independent central radiology review (BICR) was also evaluated as a secondary efficacy endpoint.

Overall survival (OS) is a further secondary efficacy endpoint in the ARIEL3 trial but at the time of the primary analysis presented in this submission, only an interim OS analysis is available and OS data are immature and heavily censored (see Section B.2.4).

Patient reported outcome (PRO) measures were assessed using both the disease specific Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18 (FOSI-18) and the EQ-5D instruments. Data were collected at screening, on Day 1 of every treatment cycle, at treatment discontinuation, and at the 28-day follow-up visit.

The FOSI-18 instrument is a comprehensive 18-item form, made up of four subscales, that assess emotional and functional wellbeing, as well as disease symptoms and treatment-related side effects. It is a shorter, more focused subset FACT-ovarian (FACT-O) instrument, which is a reliable and validated quality of life assessment for people with OC.[40] FOSI-18 is a composite endpoint, as the total score combines subscales that assess emotional and function/wellbeing, as well as disease symptoms and treatment-related side effects. The disease-related symptoms-physical (DRS-P) subscale of the FOSI-18, and total score, were predefined as secondary endpoints in the ARIEL3 study. The EQ-5D instrument was used as a generic quality of life instrument as the preferred instrument for health technology assessment agencies (and a named exploratory endpoint).

Trial endpoints and their relevance are discussed further in Section B.2.13.

Baseline demographics

Baseline characteristics for patients in the ITT population of the ARIEL3 study are presented in Table 6; they were generally well balanced between the treatment arms. All patients were female, with an overall median age of 61.0 years and, in accordance with the study inclusion criteria (see Table 4), all had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at baseline.

The majority of patients had high-grade EOC and serous histology. Overall, less than 10% of patients had either FTC or PPC. At initial diagnosis, the majority of patients were diagnosed with extensive disease, represented by FIGO Stage IIIC and FIGO Stage IV disease. Approximately two-thirds of patients had a BRCA mutation and of those patients, most had a germline BRCA mutation. Of the patients in the BRCA wild-type group, 42.9% were determined to be BRCA wild-type LOH high (Table 6).

Patients were eligible for ARIEL3 enrolment regardless of residual tumour burden. A similar percentage of patients in the rucaparib arm (37.6%) and the placebo arm (34.9%) had residual measurable disease and residual bulky disease (lesion >20mm) (18.9% rucaparib versus 15.3% placebo) at baseline.

Table 6: Baseline characteristics of the intention-to-treat population in ARIEL3

	Rucaparib (n=375)	**Placebo (n=189)**	**Total (n=564)**
Age, median (range) [years]	61·0 (53·0–67·0)	62·0 (53·0–68·0)	61.0 (36.0-85.0)
Age group, n (%)			
<65 years	[redacted]	[redacted]	[redacted]
65–74 years	[redacted]	[redacted]	[redacted]
75–85 years	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	302 (80.5)	149 (78.8)	451 (80.0)
Non-white	26 (7.0)	13 (6.9)	39 (6.9)
Unknown	47 (12.5)	27 (14.3)	74 (13.1)
ECOG performance status, n (%)			
0	280 (74.7)	136 (72.0)	416 (73.8)
1	95 (25.3)	53 (28.0)	148 (26.2)
Type of ovarian cancer, n (%)			
Epithelial ovarian cancer	312 (83.2)	159 (84.1)	471 (83.5)
Fallopian tube cancer	32 (8.5)	10 (5.3)	42 (7.4)
Primary peritoneal cancer	31 (8.3)	19 (10.1)	50 (8.9)
High-grade serous adenocarcinoma*	0	1 (0.5)	1 (0.2)
Histology, n (%)			
Serous	357 (95.2)	179 (94.7)	536 (95.0)
Endometrioid	16 (4.3)	7 (3.7)	23 (4.1)
Mixed	1 (0.3)	3 (1.6)	4 (0.7)
Transitional	1 (0.3)	0	1 (0.2)

	Rucaparib (n=375)	Placebo (n=189)	Total (n=564)
FIGO Stage at diagnosis, n (%)			
Stage IA	0	2 (1.1)	2 (0.4)
Stage IB	1 (0.3)	1 (0.5)	2 (0.4)
Stage IC	11 (2.9)	4 (2.1)	15 (2.7)
Stage IIA	5 (1.3)	2 (1.1)	7 (1.2)
Stage IIB	7 (1.9)	1 (0.5)	8 (1.4)
Stage IIC	14 (3.7)	10 (5.3)	24 (4.3)
Stage IIIA	14 (3.7)	2 (1.1)	16 (2.8)
Stage IIIB	24 (6.4)	12 (6.3)	36 (6.4)
Stage IIIC	238 (63.5)	120 (63.5)	358 (63.5)
Stage IV	54 (14.4)	30 (15.9)	84 (14.9)
Other	4 (1.1)	2 (1.1)	6 (1.1)
Missing	3 (0.8)	3 (1.6)	6 (1.1)
Randomisation stratification groups by CTA, n (%)			
BRCA mutant	130 (34.7)	66 (34.9)	196 (34.8)
Non-BRCA HRD	28 (7.5)	15 (7.9)	43 (7.6)
Biomarker negative	217 (57.9)	108 (57.1)	325 (57.6)
BRCA mutant subgroups, n (%)	130 (34.7)	66 (34.9)	196 (34.8)
BRCA1	80 (21.3)	37 (19.6)	117 (20.7)
BRCA2	50 (13.3)	29 (15.3)	79 (14.0)
Germline[a]	82 (21.9)	48 (25.4)	130 (23.0)
Somatic[a]	40 (10.7)	16 (8.5)	56 (9.9)
Unknown[a]	8 (2.1)	2 (1.1)	10 (1.8)
BRCA wild-type subgroups[b], n (%)	245 (65.3)	123 (65.1)	368 (65.2)
LOH high[c]	106 (28.3)	52 (27.5)	158 (28.0)
LOH low[d]	107 (28.5)	54 (28.6)	161 (28.5)
LOH indeterminate[e]	32 (8.5)	17 (9.0)	49 (8.7)
Time since cancer diagnosis, median (range) [months]	37.3 (15.4- 265.2)	38.4 (15.0- 249.9)	37.5 (15.0- 265.2)
Time since cancer diagnosis group, n (%)			
>12-24 months	52 (13.9)	25 (13.2)	77 (13.7)
>24 months	323 (86.1)	164 (86.8)	487 (86.3)
Measurable disease at baseline (as per investigator), n (%)			
Yes	141 (37.6)	66 (34.9)	207 (36.7)
No	234 (62.4)	123 (65.1)	357 (63.3)
Bulky disease (any lesion >2cm) at baseline (as per BICR), n (%)			
Yes	71 (18.9%)	29 (15.3%)	100 (17.7)
No	304 (81.1)	160 (84.7)	464 (82.3)

	Rucaparib (n=375)	Placebo (n=189)	Total (n=564)
Number of prior previous chemotherapy regimens			
Median (range)	2 (2-6)	2 (2-6)	2 (2-6)
2, n (%)	231 (61.6%)	124 (65.6%)	355 (62.9)
≥3, n (%)	144 (38.4%)	65 (34.4%)	209 (37.1)
Previous bevacizumab use, n (%)§	83 (22.1%)	43 (22.8%)	126 (22.3)
Number of platinum-based regimens			
Median (range)	2 (2-6)	2 (2-5)	2 (2-6)
2, n (%)	236 (62.9)	126 (66.7)	362 (64.2)
≥3, n (%)	139 (37.1)	63 (33.3)	202 (35.8)
Penultimate progression-free interval after last dose of platinum, median (range) [months]	13.8 (5.8-120.0)	14.6 (6.0-238.5)	14.1 (5.8-238.5)
Randomisation stratification: penultimate progression-free interval, n (%)			
6–12 months, n (%)	151 (40.3)	76 (40.2)	227 (40.2)
>12 months, n (%)	224 (59.7)	113 (59.8)	337 (59.8)
Randomisation stratification: best response from previous platinum therapy, n (%)			
RECIST CR	126 (33.6)	64 (33.9)	190 (33.7)
RECIST / CA-125 PR	249 (66.4)	125 (66.1)	374 (66.3)

Key: BICR, blinded independent central radiology review; BRCA, breast cancer gene; CA-125, cancer antigen 125; CR, complete response; CSR, clinical study report; 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; *, according to patient records, the origin was fallopian tube or ovary; †, the tumour sample was BRCA mutant according to Foundation Medicine's T5 next generation sequencing assay, but a blood sample was not available for central germline testing; ‡, a tumour sample was not evaluable for percentage of genomic LOH because of low tumour content or aneuploidy; §, previous treatment with bevacizumab was permitted as part of penultimate or earlier treatment.
Source: Coleman *et al*. 2017;[37] ARIEL3 CSR.[38]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The hypothesis and associated statistical analysis methods adopted for primary endpoint analyses in the ARIEL3 trial are tabulated in Table 7.

Analysis populations

The following predefined analysis populations were used to analyse the ARIEL3 trial data:

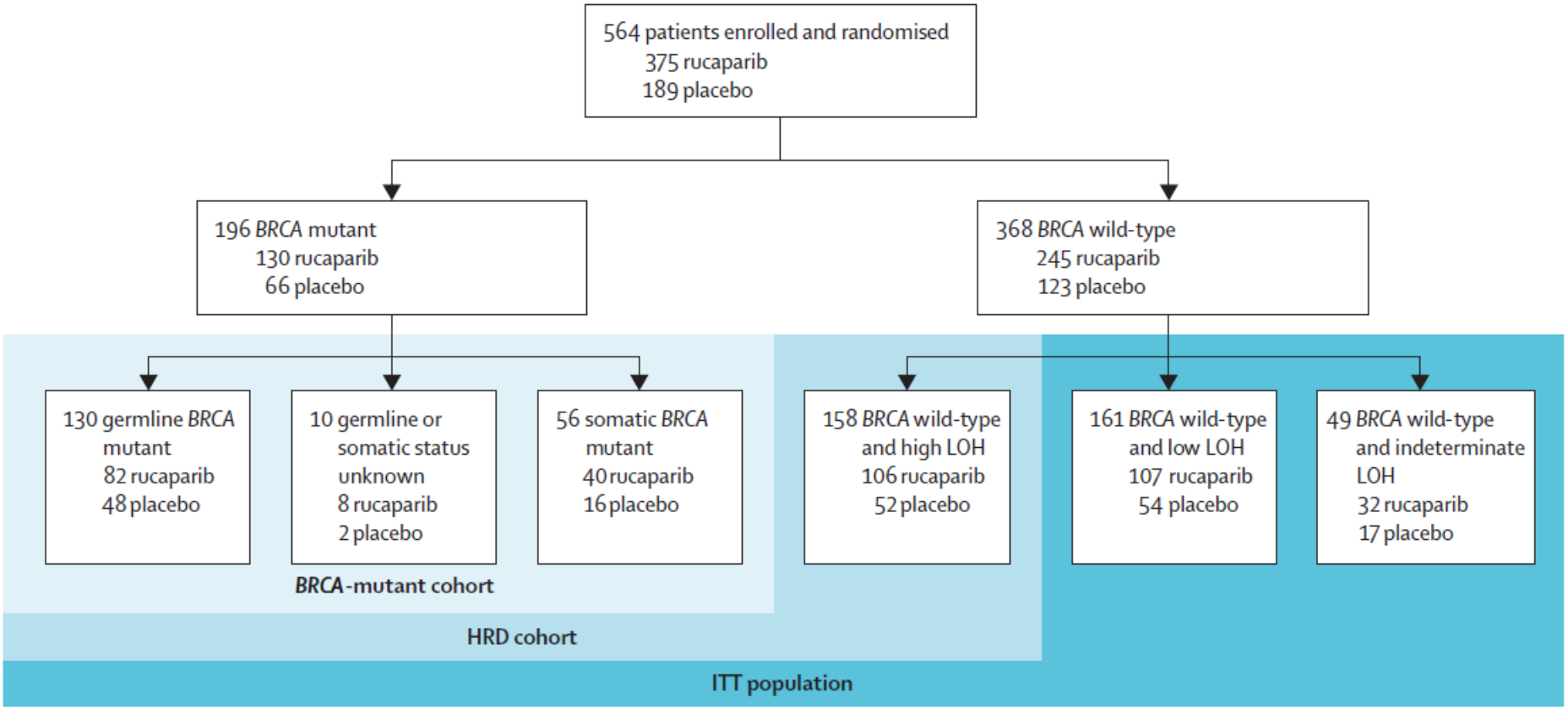
- **ITT population:** The ITT population consisted of all randomised patients, which included patients who were classed as BRCA mutant (germline, somatic, germline/somatic status unknown) and BRCA wild-type (LOH high, LOH low, and LOH indeterminate; see Figure 2)
- **Safety population:** The safety population consisted of all patients who received at least one dose of protocol-specified treatment.

As described in Section B.2.3, the results of the CTA, germline mutation and LOH testing in the ITT population (Table 5) were used to categorise patients into two further pre-specified efficacy analysis cohorts (nested cohorts):

- **BRCA mutant cohort:** The BRCA mutant cohort consisted of all BRCA mutant patients irrespective of germline mutation status (germline, somatic, germline/somatic status unknown; see Figure 2).
- **HRD cohort:** The HRD cohort consisted of all BRCA mutant patients (germline, somatic, germline/somatic status unknown) and BRCA wild-type LOH high patients (see Figure 2).

Figure 2 presents the number of patients in each pre-defined subgroup and pre-specified efficacy analysis cohorts.

Figure 2: Efficacy analysis cohorts



Key: BRCA, breast cancer gene; HRD, homologous recombination deficiency; ITT, intention-to treat; LOH, loss of heterozygosity.
Source: Coleman *et al*. 2017.[37]

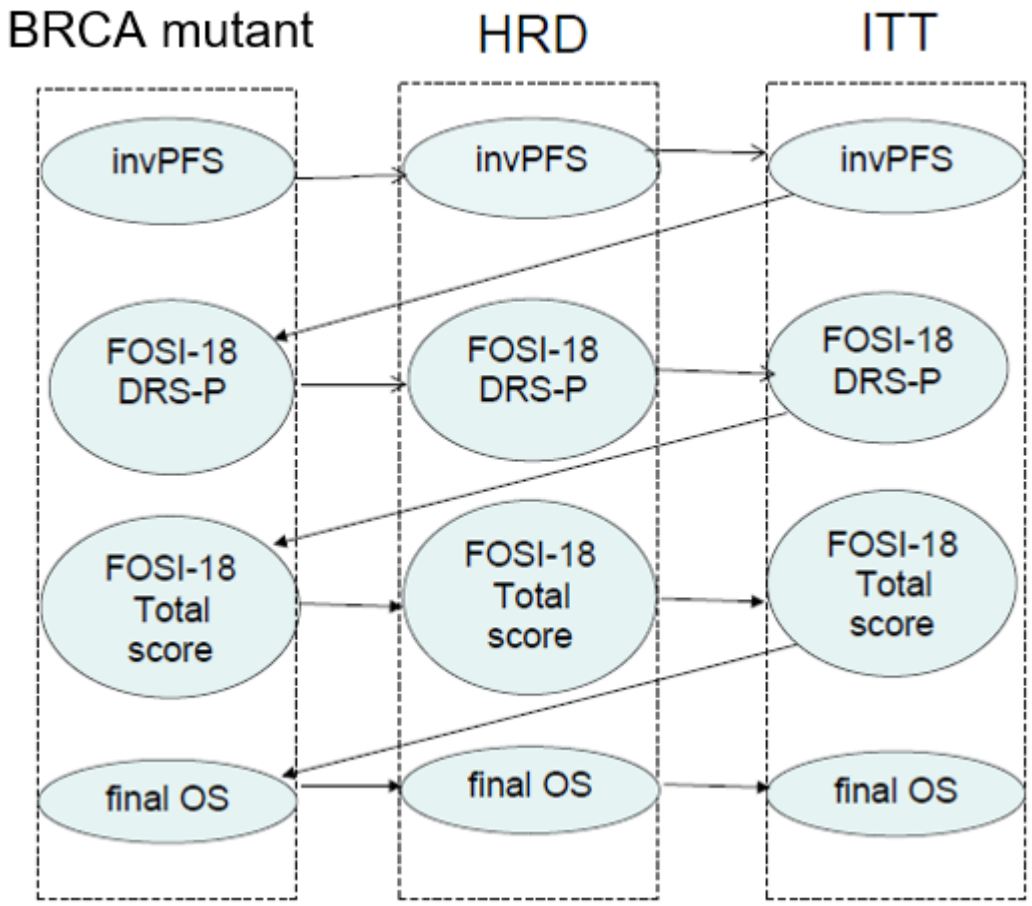
Multiple comparison step-down procedure

The primary and key secondary endpoints were tested among the BRCA mutant cohort, HRD cohort, and ITT population, using an ordered step-down multiple comparisons procedure, illustrated in Figure 3.

Investigator-assessed PFS in the BRCA mutant cohort was tested first at a one-sided 0.025 significance level. If the investigator-assessed PFS in the BRCA mutant cohort was statistically significant, then the investigator-assessed PFS was tested in the HRD cohort, followed by the ITT population. Continuing in an ordered step-down manner, the remaining secondary endpoints were tested at the one-sided 0.025 significance level in the BRCA mutant cohort, HRD cohort, and ITT population. Once statistical significance was not achieved for one test, statistical significance was not declared for all subsequent analyses in the ordered step-down procedure.

To ensure the results in the HRD cohort and ITT population were not solely driven by the results in the BRCA mutant cohort, the primary and secondary efficacy endpoints were also evaluated in the three predefined BRCA wild-type subgroups: LOH high, LOH low, and LOH indeterminate. In order to claim a significant result in the HRD cohort, the size of the estimated effect in the BRCA wild-type LOH high subgroup should have been clinically relevant and at least as large as what would have been needed to achieve ’statistical significance’ in an analysis conducted in the entire HRD cohort. Similarly, for the ITT population results to be considered significant and not solely driven by the results of the BRCA mutant or HRD cohorts, the size of the estimated effect in the BRCA wild-type LOH low and indeterminate subgroups should have been clinically relevant, and at least as large as what would have been needed to achieve ‘statistical significance’ in an analysis conducted in the entire ITT population.

Figure 3: Ordered step-down procedure



Key: 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.[38]

Analysis of the primary endpoint

Data analysis for the primary endpoint in the ARIEL3 study was to be conducted after 70% of patients in the BRCA mutant cohort had an observed event of investigator-assessed disease progression or death. The target number of progression events in the BRCA mutant cohort (deleterious mutation in BRCA1 or BRCA2 detected in tumour tissue, including germline and somatic) was achieved as of the 15 April 2017, at which point the database lock was triggered for the primary endpoint analysis. Data presented for the primary endpoint analysis are from this database lock, and include all data up to and including this date in the study

analyses. The population analysed for efficacy comprised all 564 patients randomised (i.e. ITT population) to either rucaparib (n=375) or placebo (n=189).

Analyses of secondary and exploratory endpoints occurred alongside the primary endpoint analysis. However, at the time of the database lock for the primary endpoint analysis (15 April 2017), data for a number of endpoints were immature (the minimum follow-up duration at this database lock was approximately 9 months).

In accordance with the statistical analysis plan for ARIEL 3, the final analysis of OS will occur when 70% of patients have died. At the 15 April 2017 visit cut-off for the primary endpoint analysis, the OS data were heavily censored (>80% of patients). Although an interim OS analysis was performed (using the same statistical test used for the primary endpoint), results should be interpreted with caution. Data for progression-free survival on the next line of therapy (PFS2) and time to second subsequent anti-cancer treatment (TSST) were similarly immature at the time of the primary endpoint analysis database lock.

An additional database lock for updated safety data occurred on 31 December 2017. At the 31 December 2017 visit cut-off for the updated safety data, OS data were still heavily censored (>70% of patients) and no updated analyses were performed, as the OS data were still immature. An updated analysis of PFS2 is however provided with a 31 December 2017 data cut-off date.

See Appendix D for the number of participants eligible to enter the ARIEL3 trial and the CONSORT flow chart for patient disposition.

Table 7: Summary of statistical analyses of ARIEL3

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT01968213 (ARIEL3)	The primary hypothesis objective was that rucaparib treatment will prolong investigator-assessed PFS within each of the efficacy analysis cohorts (BRCA mutant, HRD and ITT population).	The time to investigator-assessed PFS was calculated in months as the time from randomisation to disease progression +1 day, as determined by RECIST v1.1 criteria, or death due to any cause, whichever occurred first. The stratified log-rank test was considered the primary analysis for investigator-assessed PFS comparing rucaparib to placebo. In addition, a stratified Cox proportional hazard model was used to calculate the HR between the treatment arms. Months were calculated as number of days divided by 30.4375. The primary endpoint was tested among the BRCA mutant cohort, HRD cohort, and ITT population using an ordered step-down multiple comparison procedure, illustrated in Figure 3. Investigator-assessed PFS in the BRCA mutant cohort was tested first at a one-sided 0.025 significance level. If investigator assessed PFS in the BRCA mutant cohort was statistically significant, then	Approximately 540 patients were randomised (2:1) to receive either rucaparib or placebo. A minimum of 180 and a maximum of 200 BRCA mutant patients were to be enrolled, which included no more than 150 germline BRCA mutant patients. No more than 360 BRCA wild-type patients were to be enrolled. These group sizes were calculated to result in a 90% power to establish a significant difference between rucaparib and placebo at a one-sided α level of 0.025 given the following assumptions for investigator-assessed median PFS for each efficacy analysis cohort: • BRCA mutant cohort: 12.0 months in the rucaparib arm versus 6.0 months in the placebo arm; HR 0.5 • HRD cohort: 10.0 months vs 6.0 months; HR 0.6	All data were used to their maximum possible extent without any imputations for missing data. Only scans and deaths prior to the start of any subsequent anti-cancer treatment, or within 90 days of treatment end date, were included in the analysis. Patients without a documented event of progression were censored on the date of their last tumour assessment (that is, radiological assessment) prior to the start of any subsequent anti-cancer treatment or within 90 days of the treatment end date. Patients who withdrew without a disease progression event and did not have any post-baseline tumour assessment were censored at the date of randomisation.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		investigator assessed PFS was tested in the all HRD cohort, followed by the ITT population.	• ITT population: 8.5 months vs 6.0 months; HR 0.7. Tumour HRD status by the CTA was determined after randomisation, but before the final efficacy analysis, so that the primary endpoint (PFS in molecularly defined HRD subgroups) could be assessed prospectively.	

Key: BRCA, breast cancer gene; CTA, clinical trial assay; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
Source: Coleman *et al.* 2017;[37] ARIEL3 CSR.[38]; ARIEL3 statistical analysis plan[41]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

ARIEL3 is considered to be a good quality study, being conducted in accordance with Good Clinical Practice guidelines, with a single protocol to promote consistency across sites, and measures taken to minimise bias.

The accuracy and reliability of the ARIEL3 study data provided in this submission were assured by the selection of qualified investigators and an appropriate study centre, review of protocol procedures with the investigator and associated personnel before the study, and by periodic monitoring visits by the sponsor. In addition, an independent data monitoring committee was established to review safety and efficacy data in compliance with a prospective charter.

Randomisation and allocation concealment methods in the ARIEL3 study were appropriate and successful, such that baseline characteristics of patients were well balanced across treatment arms, and patients, investigators and clinical site staff remained blinded throughout the study to avoid bias in the interpretation of efficacy and safety results. To ensure that ITT comparisons were not driven by patients expected to have the largest treatment effect size (patients with BRCA mutations), enrolment of these patients was limited, and primary and secondary outcome assessments were conducted in an ordered, step-down, multiple comparison procedure. One potential source of bias against rucaparib is the possible use of subsequent PARPi treatment in placebo-treated patients post-progression. This may have an impact on the final OS results, as the use of post-progression PARPi treatment may mask the true treatment effect of rucaparib versus placebo.

A complete quality assessment in accordance with the NICE recommended checklist for randomised clinical trial (RCT) assessment of bias is presented in Appendix D. The overall risk of bias in ARIEL3 is considered to be low.

B.2.6. Clinical effectiveness results of the relevant trials

Primary endpoint: PFS as assessed by the investigator

Across all primary efficacy analysis cohorts (and thus irrespective of BRCA status), rucaparib significantly reduced the risk of disease progression or death compared with placebo in patients with platinum-sensitive OC who had responded to platinum-based chemotherapy, as summarised in Table 8.

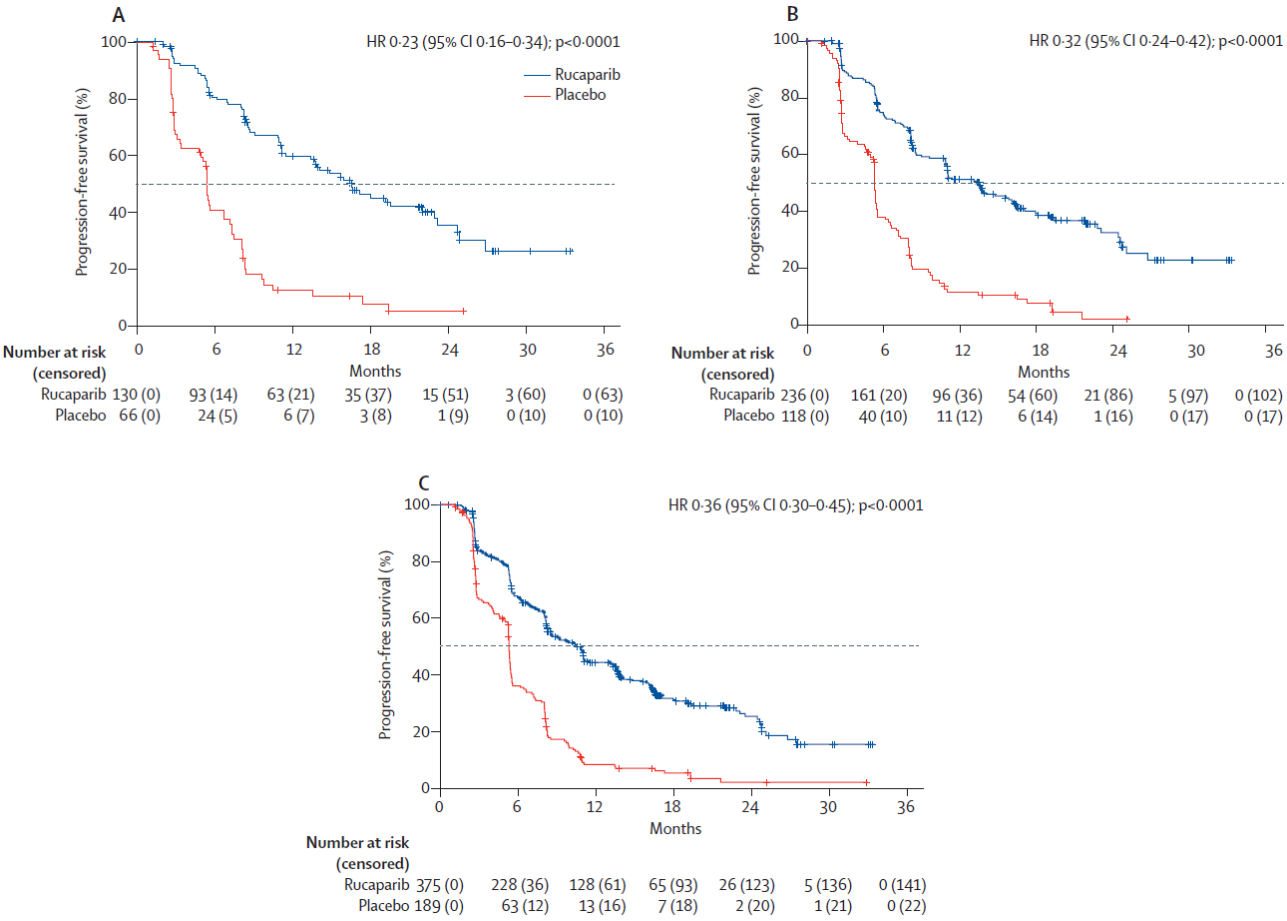
Table 8: Summary of progression-free survival as assessed by the investigator

	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)**
Median PFS, months (95% CI)	10.8 (8.3,11.4)	5.4 (5.3,5.5)	13.6 (10.9,16.2)	5.4 (5.1,5.6)	16.6 (13.4,22.9)	5.4 (3.4,6.7)
HR (95% CI) p-value	0.36 (0.30,0.45) <0.0001		0.32 (0.24,0.42) <0.0001		0.23 (0.16,0.34) <0.0001	
Progression-free at 6 months, %	67.9	36.4	74.9	38.2	80.5	41.0
Progression-free at 12 months, %	44.6	8.8	51.4	11.8	59.9	12.9
Progression-free at 18 months, %	32.0	5.8	40.3	8.0	46.5	8.1
Progression-free at 24 months, %	26.0	2.6	32.6	2.4	35.7	5.4

Key: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; 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;[37] ARIEL3 CSR.[38]

As can be observed in the Kaplan–Meier (KM) curves presented in Figure 4, there was evidence of benefit with rucaparib treatment by the time of the first tumour scan (at approximately 3 months), which was maintained throughout follow-up.

Figure 4: Kaplan–Meier estimates of progression-free survival as assessed by the investigator



Key: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention to treat.
Notes: A, BRCA mutant cohort; B, HRD cohort; C, ITT population.
Source: Coleman *et al*. 2017.[37]

As described in Section B.2.4, to ensure the results in the HRD cohort and ITT population were not solely driven by the results in the BRCA mutant cohort, the primary efficacy endpoint was also evaluated in the three pre-specified BRCA wild-type subgroups (LOH high, LOH low, and LOH indeterminate).

The stratified log-rank analysis of the BRCA wild-type LOH high subgroup demonstrated a substantial improvement in investigator-assessed PFS with rucaparib treatment compared to placebo (stratified log-rank, p<0.0001). This demonstrates that the results observed for the HRD cohort were not solely driven by the BRCA mutant cohort, as benefit was observed in both the BRCA mutant cohort

and the wild-type LOH high subgroup. Similarly, an improvement of investigator-assessed PFS with rucaparib treatment compared with placebo was observed for both the BRCA wild-type LOH low (stratified log-rank, p=0.004) and BRCA wild-type LOH indeterminate subgroups (stratified log-rank, p=0.0003). These results demonstrate the results observed for the ITT population were not solely driven by the HRD cohort, as benefit was observed in both the BRCA wild-type LOH low and BRCA wild-type LOH indeterminate subgroups. The results of these analyses are presented in Appendix L.

Sensitivity analyses were also performed for the primary efficacy endpoint to evaluate the impact of censored patients on results (using all tumour scans and clinical progression included as an event), the interaction between treatment and HRD status, and using actual strata allocation if patients were allocated incorrectly. The results of the sensitivity analyses were similar to and support the results of the primary efficacy analysis presented above. Further details of these sensitivity analyses, including results, are presented in Appendix L.

Secondary endpoints

Progression-free survival as assessed by blinded independent central review

PFS as assessed by BICR using RECIST v1.1, estimated by the KM method, was used as a key standalone, secondary endpoint in support of the primary endpoint of investigator-assessed PFS.

Across all efficacy analysis cohorts (and thus irrespective of BRCA status), rucaparib significantly reduced the risk of disease progression or death as assessed by BICR, compared with placebo, in patients with platinum-sensitive OC who had responded to platinum-based chemotherapy, as summarised in Table 8.

Table 9: Summary of progression-free survival as assessed by blinded independent central review

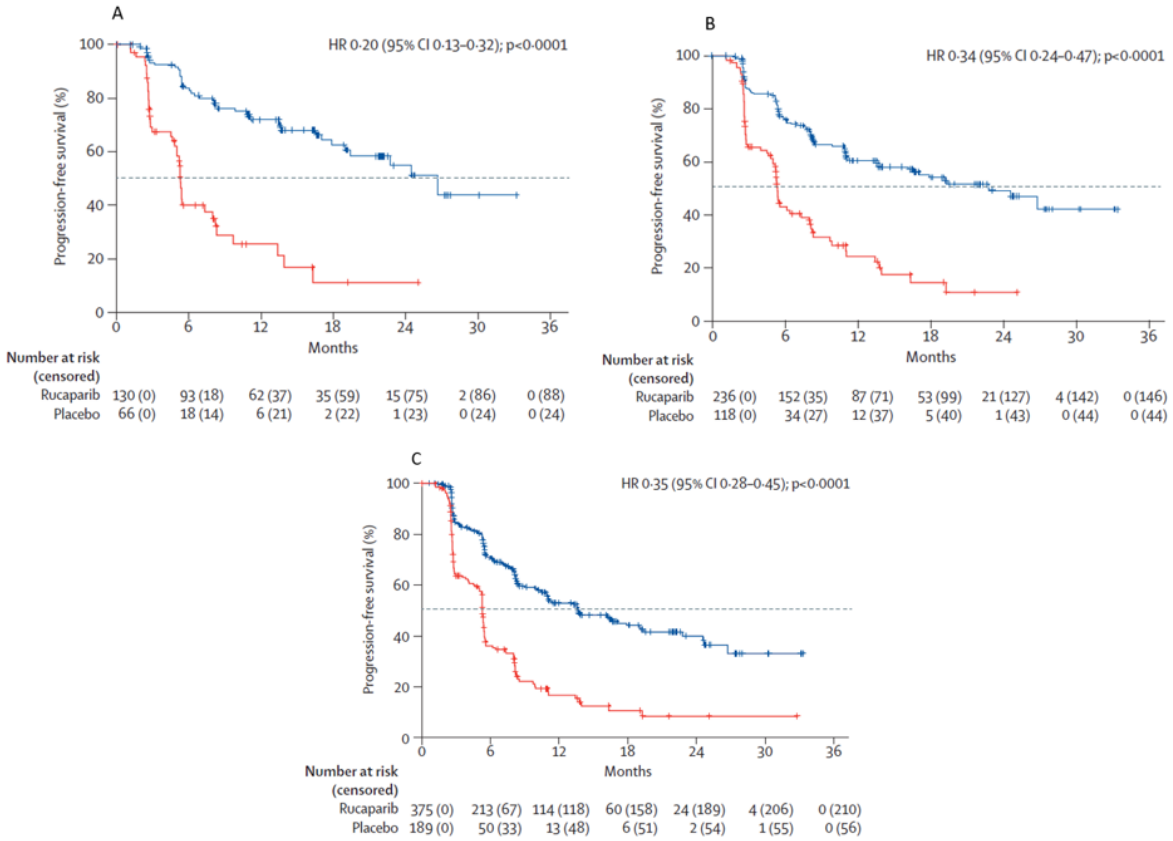
	ITT population		HRD cohort		BRCA mutant cohort	
	Rucaparib (n=375)	**PBO (n=189)**	**Rucaparib (n=236)**	**PBO (n=118)**	**Rucaparib (n=130)**	**PBO (n=66)**
Median PFS, months (95% CI)	13.7 (11.0, 19.1)	5.4 (5.1, 5.5)	22.9 (16.2, NR)	5.5 (5.1, 7.4)	26.8 (19.2, NR)	5.4 (4.9, 8.1)
HR (95% CI) p-value	0.35 (0.28, 0.45) p<0·0001		0.34 (0.24, 0.47) p<0·0001		0.20 (0.13, 0.32) p<0·0001	
Progression-free at 6 months, %	71.0	36.3	76.8	43.2	83.5	36.3
Progression-free at 12 months, %	53.0	16.9	60.5	24.6	71.9	25.8
Progression-free at 18 months, %	45.1	10.8	55.3	14.8	64.5	11.5
Progression-free at 24 months, %	40.1	8.7	49.4	11.1	55.0	11.5

Key: BICR, blinded independent central radiology review; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; NR, not reached; PBO, placebo.
Notes: Data are presented from the primary endpoint analysis database lock of 15 April 2017.
Source: Coleman *et al*. 2017.[37]; ARIEL3 CSR[38]

As can be observed in the KM curves presented in Figure 5, there was evidence of benefit with rucaparib treatment by the time of the first tumour scan (at approximately 3 months), which was maintained throughout follow-up.

As observed for the primary endpoint, BRCA wild-type subgroup analyses demonstrated that the results observed for PFS assessed by BICR in the HRD cohort and ITT population were not solely driven by the BRCA mutant cohort and HRD cohort, respectively. These analyses are presented in Appendix L.

Figure 5: Kaplan–Meier estimates of progression-free survival as assessed by blinded independent central review



Key: BICR, blinded independent central radiology review; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention to treat; PFS, progression-free survival.
Notes: A, BRCA mutant cohort; B, HRD cohort; C, ITT population.
Source: Coleman *et al*. 2017.[37]

Overall, results for PFS as assessed by BICR were consistent with, and supportive of, the investigator-assessed PFS result. While the HRs were consistent between investigator- and BICR-assessed PFS, the median point estimates with 95% confidence intervals of PFS as assessed by BICR were longer than those of the investigator-assessed PFS in the rucaparib arm for the primary analysis cohorts (BRCA mutant, HRD, and ITT; Table 8 and Table 9), as well as the exploratory analysis in the three pre-specified BRCA wild-type subgroups (LOH high, LOH low, and LOH indeterminate; Appendix L). This phenomenon has been observed in all three of the pivotal clinical studies of PARP inhibitors within the OC maintenance setting.[42-44]

FOSI-18

As summarised in Table 10, while there was a shortening of time to worsening in the FOSI-18 DRS-P subscale (defined as ≥4 point decrease) and total score (defined as ≥8 point decrease) in patients treated with rucaparib, no significant differences in self-reported quality of life between treatment groups were observed in ARIEL3. Definitions of worsening were based on an approximate 10% decrease in the maximum possible total score without additional clinical validation. A summary of the completion rate of the FOSI-18 is presented in Appendix L.

These data may reflect the short-term impact of treatment side effects on patients as several questions in the DRS-P subscale ask about symptoms that are also common adverse effects of rucaparib treatment, for example, fatigue and gastrointestinal events (see Section B.2.10).

Table 10: Summary of FOSI-18 outcomes

	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)**
Median TTW in DRS-P subscale* months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]		[redacted]		[redacted]	
Median TTW in total score ‡ months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]		[redacted]		[redacted]	

Key: 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; HRD, homologous recombination deficiency; ITT, intention-to-treat; NE, not estimable; 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: ARIEL3 CSR.[38]

In accordance with the pre-specified hierarchical step-down procedure used for adjusting for multiplicity testing in ARIEL3 (see Section B.2.4), the lack of statistical significance observed in the time to worsening in the FOSI-18 DRS-P subscale for

the BRCA mutation cohort means significance could not be established for the remaining secondary analyses (although p-values are presented descriptively).

Interim OS

As anticipated, at the data cut-off for the primary endpoint analysis (15 April 2017), the number of deaths in all primary efficacy analysis cohorts were small and, due to the immaturity of interim OS data, the median survival could not be determined and no differences in survival were observed in the KM estimates (see Table 11). The KM curves for interim OS are presented in Appendix L.

Table 11: Summary of interim overall survival

	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)**
Events (deaths), n (%)	81 (21.6)	42 (22.2)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	

Key: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PBO, placebo.
Notes: Data are presented from the primary endpoint analysis database lock of 15 April 2017.
*, p values are presented descriptively but are not representative of significance.
Source: Coleman *et al*. 2017;[37] ARIEL3 CSR.[38]

No updated analyses of OS were performed at the updated safety data cut-off date (31 December 2017), as the OS data were still immature. As of the updated safety data cut-off, a death event had been reported in only 30% of patients.[45] Thus, OS results are not likely to be different from those presented in Table 11, when death events were reported in approximately 22% of patients in the ITT population.

Exploratory endpoints

Cancer antigen 125

Across all efficacy analysis cohorts, rucaparib substantially suppressed the change from baseline in CA-125 compared with placebo, and an association between improved PFS and minimum changes in CA-125 was observed, further supporting

improved disease control with rucaparib versus placebo. Appendix L presents results for changes from baseline in CA-125 by visit for the efficacy analysis cohorts, and the association between improved PFS and minimum changes in CA-125.

Although mean percentage increases were observed for both treatment groups at each assessment, the percentage changes observed for the rucaparib group were substantially suppressed compared with the placebo group. Using an analysis of convenience (analysis of covariance [ANCOVA]) model, a substantial difference was observed in favour of rucaparib for the BRCA mutant cohort ( ) and HRD cohort ( ) at Cycle 4, which was sustained through Cycle 10. No difference between treatments was observed in the ITT population at Cycle 4 ( ), but of the patients assessed at Cycles 7 and 10, the difference in least square mean showed a benefit in favour of rucaparib compared with placebo ( ).

Chemotherapy free-interval and time to start of first subsequent anti-cancer treatment

Across all efficacy analysis cohorts, rucaparib significantly prolonged the chemotherapy-free interval time and time to first subsequent anti-cancer treatment (TFST), delaying the potentially deleterious effects of further chemotherapy treatment, as summarised in Table 12. Further details and the KM curves for chemotherapy-free interval time and TFST are presented in Appendix L.

Table 12: Summary of chemotherapy-free interval and time to first subsequent anti-cancer treatment

	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)
Chemotherapy-free interval, median (95% CI) [months]						
HR (95% CI) p-value						
TFST, median (95% CI) [months]						

HR (95% CI) p-value	[redacted]	[redacted]	[redacted]

Key: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; NR, not reached; OS, overall survival; PBO, placebo; 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.[38]

Progression-free survival 2 and time to start of second subsequent anti-cancer treatment

Across all efficacy analysis cohorts, fewer patients treated with rucaparib had a second event of disease progression/death and TSST was significantly prolonged compared with placebo, highlighting that the positive effects of rucaparib maintenance treatment extend to subsequent lines of therapy. Results are summarised in Table 13 and further details, including the KM curves for PFS-2 (that is, progression-free survival on next line of therapy) and TSST, are presented in Appendix L.

At the 31 December 2017 visit cut-off for the updated safety data, prolonged median time to PFS2 was observed with rucaparib treatment compared to placebo in all efficacy analysis cohorts (Table 13). Although this is a slightly more mature dataset than the 15 April 2017 data cut-off used for the original analysis (for which there was 54.9% censoring for the rucaparib group in the ITT population), there was still a high rate of censoring in the rucaparib group (40.5% in the ITT population).

Table 13: Summary of progression-free survival 2 and time to start of second subsequent anti-cancer treatment

	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						
Median PFS-2, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	

TSST, median (95% CI) [months]						
HR (95% CI) p-value						
Visit cut-off date: 31 December 2017						
Median PFS-2, months (95% CI)						
HR p-value						

Key: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; PBO, placebo; TSST, time to second subsequent anti-cancer treatment.
Notes: *, median time to the start of the second subsequent anti-cancer treatment for the BRCA mutant could not be determined for patients who received rucaparib in this study, as only 42 of 130 patients had initiated a second subsequent anti-cancer treatment. Therefore, the degree of censoring was high.
Source: ARIEL3 CSR;[38] Summary of clinical efficacy[45]

Response in patients with measurable disease at baseline

Most patients (66.3%) in the ARIEL3 study achieved a PR to their previous platinum-based therapy (Table 6). A pre-specified exploratory analysis of confirmed overall response rate was conducted in this subgroup of patients who had measurable disease (i.e. measurable target lesions) at baseline.

The best overall response, duration of response and change from baseline in the sum of the diameters of target lesions, as assessed by the investigator, were also analysed in these patients. Across all efficacy analysis cohorts, rucaparib further reduced carcinoma burden in a proportion of patients with measurable residual disease at baseline, as summarised in Table 14. Results for change from baseline in the sum of the diameters of target lesions and the dose–response curves for duration of response KM curves are presented in Appendix L.

Table 14: Confirmed response rate by investigator – patients with measurable disease at baseline

	ITT population		HRD cohort		BRCA mutant cohort	
	Rucaparib (n=141)	**PBO (n=66)**	**Rucaparib (n=85)**	**PBO (n=41)**	**Rucaparib (n=40)**	**PBO (n=23)**
Confirmed ORR, n (%)	26 (18.4)	5 (7.6)	23 (27.1)	3 (7.3)	15 (37.5)	2 (8.7)
95% CI	12.4, 25.8	2.5,16.8	18.0, 37.8	1.5, 19.9	22.7, 54.2	1.1, 28.0
p-value*	0.0069		0.0031		0.0055	
BOR as per RECIST v1.1, n (%)						
CR	10 (7.1)	1 (1.5)	10 (11.8)	0	7 (17.5)	0
PR	16 (11.3)	4 (6.1)	13 (15.3)	3 (7.3)	8 (20.0)	2 (8.7)
SD	71 (50.4)	29 (43.9)	43 (50.6)	17 (41.5)	19 (47.5)	8 (34.8)
PD	38 (27.0)	32 (48.5)	18 (21.2)	21 (51.2)	5 (12.5)	13 (56.5)
NE	6 (4.3)	0	1 (1.2)	0	1 (2.5)	0
Duration of response, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	

Key: BOR, best overall response; BRCA, breast cancer gene; CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CR, complete response; CTA, clinical trial assay; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; NE, not evaluable; ORR, overall response rate; PBO, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
Notes: Data are presented from the primary endpoint analysis database lock of 15 April 2017.
*, calculated using a stratified CMH test comparing the confirmed response rate between treatments with adjustment for the randomisation strata of HRD classification by CTA (for HRD and ITT), best response, and penultimate platinum progression-free interval and treatment as fixed effects.
Source: Coleman *et al*. 2017;[37] ARIEL3 CSR.[38]

EQ-5D visual analogue scale

HRQL was not detrimentally impacted with rucaparib treatment, with no difference in patients' self-rated health observed across treatment groups from baseline to end of treatment, as summarised in Table 15.

Table 15: Percentage change in EQ-5D visual analogue scale from baseline to end of treatment

	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)
Baseline mean, (SD)	[redacted]					
End of treatment mean (SD)	[redacted]					
Percentage change from baseline, mean (SD)	[redacted]					
LS mean difference versus placebo (95% CI) p-value	[redacted]					

Key: BRCA, breast cancer gene; CI, confidence interval; HRD, homologous recombination deficiency; ITT, intention-to-treat; LS, least squares; PBO, placebo; SD, standard deviation.
Notes: Data presented from the primary endpoint analysis database lock of 15 April 2017.
Source: ARIEL3 CSR.[38]

To further explore the potential HRQL benefit of rucaparib maintenance treatment, post-hoc analysis of ARIEL3 data were conducted that incorporated both quality and quantity of life, combining PFS estimates with patient-centered outcomes, including the main AEs experienced by patients. Two different methods were adopted: quality-adjusted progression-free survival (QA-PFS) and quality-adjusted time without symptoms or toxicity (Q-TWiST), both of which used utility values derived from the EQ-5D. These methods are fully described in the post-hoc analysis reported provided in the reference pack.[46]

A significantly longer mean quality-adjusted survival time was observed for rucaparib patients compared to placebo patients across ITT and BRCA mutant cohorts in both analyses, as summarised in Table 16. Differences in mean quality-adjusted survival time ranged from [redacted] (QA-PFS) to [redacted] (TOX 1 weighted Q-TWiST) months in the ITT population and [redacted] (TOX 0 weighted Q-TWiST) to [redacted] (TOX 1 weighted Q-TWiST) months in the BRCA mutant cohort. When using a utility weight of [redacted] and

[redacted] in Q-TWiST analysis for the ITT population and BRCA mutant cohort, respectively, which were derived from the EQ-5D estimates observed in ARIEL3 for the TOX state, the difference in mean quality-adjusted survival time was [redacted] months in the ITT population and [redacted] months in the BRCA mutant cohort; these differences were statistically significant and in favour of rucaparib.

Table 16: Quality-adjusted progression-free survival and quality-adjusted time without symptoms or toxicity (all Grade ≥3 TEAEs)

	ITT population			BRCA mutant cohort		
	Rucaparib (n=375)	**PBO (n=189)**	**Difference**	**Rucaparib (n=130)**	**PBO (n=66)**	**Difference**
Mean QA-PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q-TWiST health states						
Mean PFS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean TOX, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean TWiST, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quality-adjusted survival time for different utility values during the TOX health state, mean months (95% CI)						
TOX 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOX 0.25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOX 0.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOX 0.75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOX 0.89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOX 0.90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TOX 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BRCA, breast cancer gene; CI, confidence interval; ITT, intention-to-treat; PBO, placebo; PFS, progression-free survival; TOX, toxicity; TWiST, time without symptoms or toxicity; QA-PFS, quality-adjusted progression-free survival; Q-TWiST, quality-adjusted time without symptoms or toxicity.
Source: ARIEL3 post-hoc analysis.[46]

B.2.7. Subgroup analysis

In the pre-specified subgroup analyses of the ARIEL3 study, a consistent benefit in favour of rucaparib for reducing the risk of disease progression or death was observed in subgroups with adequate numbers of patients, as summarised in Appendix E.

Of particular interest, rucaparib treatment improved both PFS as assessed by the investigator, and PFS as assessed by BICR, versus placebo in all three predefined efficacy analysis cohorts for groups of patients with and without bulky residual disease (residual tumour burden >2cm; Table 17). Rucaparib is the only PARPi maintenance treatment to date, reported to reduce tumour burden further in patients with bulky disease, emphasising its efficacy.

Table 17: Investigator-assessed progression-free survival in patients with or without residual bulky disease at baseline

Cohort	Rucaparib, n	Placebo, n	PFS (investigator review)		PFS (BICR)	
			HR (95% CI)	Median PFS, months; p value*	HR (95% CI)	Median PFS, months; p value*
			Rucaparib vs placebo		Rucaparib vs placebo	
Bulky disease at baseline (as per BICR)						
Yes						
ITT population	71	29	0.40 (0.24–0.69)	8.2 versus 2.9; p=0.0007	0.46 (0.26–0.81)	8.3 versus 3.0; p=0.0057
HRD cohort	39	18	0.30 (0.13–0.69)	8.3 versus 2.8; p=0.0030	0.58 (0.25–1.34)	8.3 versus 2.9; p=0.1994

BRCA mutant cohort	21	10	0.09 (0.02–0.37)	11.1 versus 2.8; p=0.0002	0.13 (0.03–0.55)	17.1 versus 2.9; p=0.0028
No						
ITT population	304	160	0.36 (0.29–0.46)	11.0 versus 5.4; p<0.0001	0.34 (0.26–0.45)	16.2 versus 5.4; p<0.0001
HRD cohort	197	100	0.31 (0.23–0.43)	13.8 versus 5.5; p<0.0001	0.32 (0.22–0.47)	24.7 versus 5.6; p<0.0001
BRCA mutant cohort	109	56	0.26 (0.17–0.40)	16.6 vs 5.6; p<0.0001	0.22 (0.13–0.37)	26.8 versus 5.5; p<0.0001
Key: BICR, blinded independent central radiology review; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; PFS, progression-free survival. **Notes**: *, stratified log-rank p value. **Source:** Aghajanian *et al*. 2018.[47]						

B.2.8. Meta-analysis

Meta-analysis is not applicable as a single RCT provided data for rucaparib.

B.2.9. Indirect and mixed treatment comparisons

As detailed in Appendix D, four trials (reported across 19 citations) were identified through a systemic literature review that could be considered for inclusion in an ITC of interest to this appraisal; these trials investigated rucaparib, olaparib, and/or routine surveillance. One trial was excluded during feasibility assessment (see Appendix D), meaning three trials provided the evidence base utilised for the ITC.

Alongside the ARIEL3 trial, this evidence base included two trials comparing olaparib to placebo for the maintenance treatment of ovarian, primary peritoneal, or fallopian tube carcinoma: SOLO2 and Study 19. Details of these studies are provided in Appendix D. A comparative summary of methods is summarised in Table 18 and key patient characteristics in Table 19.

As can be seen from these data, there is observed heterogeneity across studies with regard to trial design and patient population. Key differences include:

- ARIEL3 and SOLO2 are Phase III studies whereas Study 19 is Phase II
- ARIEL3 enrolled patients with high-grade serous or endometrioid OC whereas SOLO2 and Study 19 only enrolled patients with high-grade serous OC
- SOLO2 only enrolled patients with germline BRCA mutant OC whereas ARIEL3 and Study 19 enrolled patients with BRCA mutant and non-BRCA mutant OC
  - ARIEL3 used BRCA status as one stratification factor in the randomisation process; Study 19 used ancestry (Jewish vs. non-Jewish) as a proxy of BRCA status in the stratified randomisation
- Olaparib in tablet formulation was dosed at 600mg/day in SOLO2; ; olaparib in capsule formulation was dosed at 800mg/day in Study 19
- 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
- The proportion of patients with a complete response to last line of platinum chemotherapy was higher in SOLO2 (47%) and Study 19 (46%) compared to ARIEL3 (34%)

Table 18: Comparative summary of studies considered for indirect treatment comparison

	ARIEL3	**SOLO2**	**Study 19**
Study design	Randomised, double-blind, placebo-controlled, multicentre, Phase III.	Randomised, double-blind, placebo-controlled, multicentre, Phase III.	Randomised, double-blind, placebo-controlled, multicentre, Phase II.
Population	Adult patients with platinum-sensitive, relapsed, high-grade serous or endometrioid OC who have received ≥2 platinum-based chemotherapies and had a PR or CR to their most recent platinum-based regimen.	Adult patients with platinum-sensitive, relapsed, germline BRCA mutant, high-grade serous OC who have received ≥2 platinum-based chemotherapies and had a PR or CR to their most recent platinum-based regimen.	Adult patients with platinum-sensitive, relapsed, high-grade serous OC who have received ≥2 platinum-based chemotherapies and had a PR or CR to their most recent platinum-based regimen.
Intervention	Rucaparib 1,200mg/day (n=375)	Olaparib 600mg/day (n=196)	Olaparib 800mg/day (n=136)

	ARIEL3	SOLO2	Study 19
Comparator	Placebo (n=189)	Placebo (n=99)	Placebo (n=129)
Primary endpoint	invPFS	invPFS	invPFS
Median follow-up duration	Minimum follow-up duration ~9 months	Olaparib arm – 22.1 months Placebo arm – 22.2 months	78 months

Key: BRCA, breast cancer gene; CR, complete response; inv, investigator; invPFS, investigator-assessed progression-free survival; OC, ovarian cancer; PFS, progression-free survival; PR partial response.
Source: Coleman *et al*. 2017[37]; Ledermann *et al*. 2012[48]; Pujade-Lauraine *et al*. 2017.[43]

Table 19: Patient characteristics at baseline for studies considered for indirect treatment comparison (total trial population data)

	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 (53–67)	62 (53–68)	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, %: 2: 56.1 3: 30.6 4: 9.2 ≥5: 3.6	Number, %: 2: 62.6 3: 20.2 4: 12.1 ≥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

	ARIEL3		SOLO2		Study 19	
	Rucaparib (n=375)	**PBO (n=189)**	**Olaparib (n=196)**	**PBO (n=99)**	**Olaparib (n=136)**	**PBO (n=129)**
Response to most recent platinum chemotherapy, %	CR: 34 PR: 66	CR: 34 PR: 66	CR: 46 PR: 54	CR: 47 PR: 53	CR: 42 PR: 58	CR: 49 PR: 51

Key: BRCA, breast cancer gene; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; NR, not reported; PBO, placebo; PR, partial response.
Source: Coleman *et al*. 2017[37]; Ledermann *et al*. 2016[49]; Pujade-Lauraine *et al*. 2017.[43]

In order to provide a comparison of relevance to this appraisal, data for people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy (herein referred to as the BRCA 3L+ group) were sought. Data availability for this group varied across studies, as shown in Table 20, and analyses in the BRCA 3L+ group were not pre-planned.

Table 20: Data availability for BRCA 3L+ group

	ARIEL3	SOLO2	Study 19
PFS – INV	Yes	Yes*	Yes
PFS – BICR	Yes	No	No
OS	Yes	No	Yes
TFST	Yes	No	Yes
TSST	Yes	No	Yes

Key: BICR, blinded independent central radiology review; INV, investigator assessed; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; TFST, time to first subsequent anti-cancer treatment; TSST, time to second subsequent anti-cancer treatment.
Note: *, data available for 3L or 4L+. In the NMA, data for 3L were used as a proxy for 3L+; similarity in outcomes across these groups supported this approach. In the MAIC, data for 3L and 4L+ were pooled.

The raw data used to populate the ITC for this group are provided in Table 21. Patient characteristics for this group are provided in Appendix D. Of note, data for the BRCA 3L+ group in SOLO2 were taken from a poster presented at the European Society for Medical Oncology (ESMO) 2017 conference that provided PFS data based on treatment history.[50] Data were not presented for this group *per se* but were provided for people who were in response to third-line platinum chemotherapy

(BRCA 3L) and for people who were in response to fourth- or later-line platinum chemotherapy (BRCA 4L+). Results across the BRCA 3L and BRCA 4L+ groups were very similar (Table 21).

Table 21: Summary of outcomes for the BRCA 3L+ group

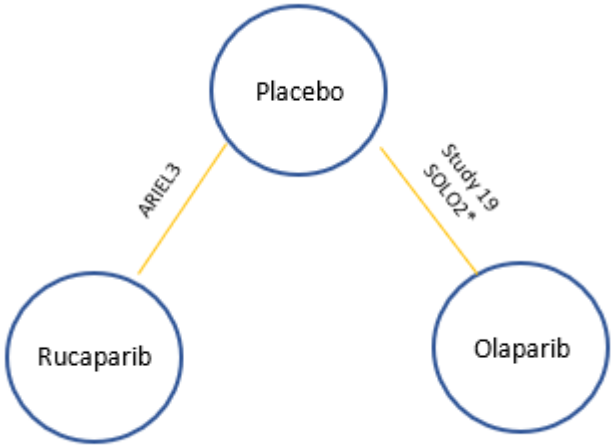
HR (95% CI)	Rucaparib versus placebo	Olaparib versus placebo		
	ARIEL3	SOLO2 BRCA 3L	SOLO2 BRCA 4L+	Study 19
PFS-INV	[redacted]	0.24 (0.13, 0.42)	0.26 (0.13, 0.51)	0.11 (0.05, 0.23)
OS – unadjusted	[redacted]	-	-	0.69 (0.38, 1.27)
OS – adjusted[a]	[redacted]	-	-	0.56 (0.26, 1.20)
TFST	[redacted]	-	-	0.28 (0.16, 0.49)
TSST	[redacted]	-	-	0.41 (0.24, 0.70)

Key: 3L+, third and later line; 4L+, fourth and later line; CI, confidence interval; HR, hazard ratio; INV, investigator assessed; OS, overall survival; PFS, progression-free survival; TFST, time to first subsequent anti-cancer treatment; TSST, time to second subsequent anti-cancer treatment.
Notes: Shaded cells represent statistical advantage observed; [a], for OS - adjusted data, sites where 'switching' took place were removed from the dataset - a small resulting sample size in ARIEL3 (n=29) means data should be interpreted with caution.
Source: ARIEL3 data on file; NICE Committee Papers - ID735[51]; Penson et al. 2017.[50]

Network meta-analysis – methods

ARIEL3, SOLO2, and Study 19 share a common comparator in placebo and, therefore, could be linked in a network of evidence, as shown in Figure 6.

Figure 6: Network diagram



Key: 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.

Full details of the methods adopted for network meta-analysis (NMA) are provided in Appendix D and followed those recommended by NICE.[52, 53] Bayesian fixed effects NMAs were preferred for all outcomes given the limited evidence base, and a proportional hazards assumption test supported the use of HRs as a summary measure for outcomes of interest.

When considering OS data, an additional complication of accounting for patients who 'switched' to PARPi treatment after progression on placebo was faced. Marked differences were observed in the placebo to PARPi treatment rates across ARIEL3 and Study 19, with almost [redacted] as many patients in the placebo arm of ARIEL3 going onto receive subsequent PARPi treatment, as summarised in Table 22.

Table 22: Patients receiving subsequent PARPi treatment across studies, BRCA mutant cohort

	ARIEL3		Study 19	
	Rucaparib (n=130)	Placebo (n=66)	Olaparib (n=74)	Placebo (n=62)
Olaparib, %	[redacted]	[redacted]	0	22.6
Niraparib, %	[redacted]	[redacted]	0	0
Rucaparib, %	[redacted]	[redacted]	0	0
Any PARPi, %	[redacted]	[redacted]	0	22.6

Key: PARPi, poly ADP ribose polymerase inhibitor.
Source: ARIEL3 data on file; Matulonis *et al*. 2016.[54]

OS analyses were therefore conducted on the unadjusted data and adjusted data accounting for post-progression PARPi treatment by excluding sites where 'switching' took place were removed from the dataset. Of note, the remaining sample size for ARIEL3 was small ([redacted]) so these data should be interpreted with caution.

Network meta-analysis – results

Results of efficacy NMAs, conducted on the population of interest in this appraisal for comparison to olaparib, are summarised in Table 23.

No statistical advantage (defined as HRs less than 0.80 or greater than 1.25 with credible intervals [CrIs] not crossing one) was observed between PARPi treatments for any outcome; trends and probability of best analyses favoured rucaparib for some outcomes (OS, TFST) but not others (PFS, TSST).

Table 23: NMA outcomes, BRCA 3L+ group

	Rucaparib versus placebo	Olaparib versus placebo	Rucaparib versus olaparib
PFS-INV HR (95% CrI) Probability of best	[redacted]	[redacted]	[redacted]
OS – unadjusted HR (95% CrI) Probability of best	[redacted]	[redacted]	[redacted]

	Rucaparib versus placebo	Olaparib versus placebo	Rucaparib versus olaparib
OS – adjusted HR (95% CrI) Probability of best	[redacted]	[redacted]	[redacted]
TFST HR (95% CrI) Probability of best	[redacted]	[redacted]	[redacted]
TSST HR (95% CrI) Probability of best	[redacted]	[redacted]	[redacted]

Key: CrI, credible intervals; HR, hazard ratio; INV, investigator assessed; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; TFST, time to first subsequent anti-cancer treatment; TSST, time to second subsequent anti-cancer treatment.
Notes: Shaded cells represent statistical advantage observed.

Results of safety NMAs, 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), are summarised in Table 24.

Unsurprisingly, placebo demonstrated the [redacted] probability of being the best treatment across all safety outcomes. A statistical advantage (defined as above) in favour of olaparib was observed in any Grade ≥3 treatment emergent adverse event (TEAE) analyses but this did not follow through to a statistical advantage in discontinuations due to adverse event. Differences in safety profiles were observed: rucaparib had a lower risk of Grade ≥3 fatigue whereas olaparib had a lower risk of Grade ≥3 anaemia, neutropenia and thrombocytopenia according to NMA but event rates were low across rucaparib and olaparib trials (see Appendix D).

the proportion of patients experiencing a Grade 3/4 TEAE with rucaparib treatment in ARIEL3 (54%[37]) was similar to the proportion of patients experiencing a Grade ≥3 TEAE with olaparib treatment in SOLO2 (36%[43]) and Study 19 (35%[48]). Differences in safety profiles were observed: rucaparib had a lower risk of Grade ≥3 fatigue whereas olaparib had a lower risk of Grade ≥3 anaemia, neutropenia and thrombocytopenia according to NMA.

Table 24: Safety NMA outcomes, ITT population – relapsed setting

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

Key: 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.
Notes: Shaded cells represent statistical advantage observed.

Matching-adjusted indirect comparison – methods

The key assumption of NMA is that any effect modifiers are balanced across trials. While there were broad similarities across the patients enrolled in the studies considered for ITC, there were important differences that question the validity of NMA.

The impact of some of these (that is, differences in the proportion of patients with BRCA mutation and differences in treatment history) were minimised by conducting the NMA in a focused cohort of patients, but this does have its own limitations (see the uncertainties discussion). The impact of others (for example, differences in response to latest platinum-based chemotherapy) could not be addressed through NMA.

Therefore, in addition to the NMA, the following matching-adjusted indirect comparison (MAIC) models were analysed:

- Anchored MAIC adjusting for clinically validated effect modifiers (EMs)
- Anchored MAIC adjusting for all available matching factors (sensitivity analyses)
- Unanchored MAIC adjusting for clinically validated EMs and prognostic factors for OS given the differences in 'switching' to PARPi treatment in placebo arms of PARPi maintenance trials (Table 22)

Full details of the methods adopted for MAIC are provided in Appendix D and followed NICE technical guidance.[55] In summary, patient-level data from ARIEL3 were matched to aggregate data from SOLO2 and Study 19, and comparisons were carried out on the linear predictor scale.

Exploration into prognostic factors and treatment EMs is detailed in Appendix D. EMs adjusted for in the anchored MAIC were:

- BRCA mutation status
- Prior lines of platinum therapy
- Platinum-free interval
- Response to platinum therapy

Of note, body–mass index (BMI) was also an identified EM but could not be adjusted for as data were not reported for this characteristic in Study 19 or SOLO2.

Characteristics adjusted for in the anchored MAIC sensitivity analyses and the unanchored MAIC also included:

- ECOG status
- Prior lines of chemotherapy
- Location of primary tumour
- Histological class
- FIGO classification
- Prior use of bevacizumab
- Age
- Race
- Jewish ancestry

Baseline characteristics of the rucaparib and placebo populations of the ARIEL3 trial before and after matching are provided in Appendix D.

Matching-adjusted indirect comparison – results

Results of the anchored MAIC adjusting for EM and the unanchored MAIC conducted on the ITT population, the BRCA mutated cohort and the BRCA 3L+ group are summarised in Table 25. Results of the anchored MAIC adjusting for all available matching factors are provided in Appendix D.

Results did differ across adjusted analyses, suggesting that adjustment for imbalances on treatment EMs between trials is appropriate. However, no consistent trends in favour of one treatment or another were observed when comparing across the PARPi maintenance treatments.

There were clear differences in outcomes depending on the source of olaparib data. Comparative PFS estimates for the BRCA 3L+ group favoured rucaparib when using SOLO-2 data for olaparib ([redacted]), but olaparib was favoured when using Study 19 data ([redacted]). Pooling these results gives a HR of [redacted] (95% CI: [redacted]).

While Study 19 provides a more mature dataset than SOLO2 (and any other PARPi maintenance treatment trial), survival rates are high and have not been replicated in more recent trials. SOLO2 is thought to provide an overall more robust dataset and more comparable dataset for the BRCA 3L+ group of interest to this appraisal (as represented by the larger effective sample size in MAIC synthesis using ARIEL3 and SOLO2 compared to MAIC synthesis using ARIEL3 and Study 19 - see Appendix D).[56] Importantly, SOLO2 also provides data relating to the licensed dose of olaparib.

Table 25: Anchored base case and unanchored MAIC outcomes

	ITT population - relapsed setting	BRCA mutated cohort - relapsed setting		BRCA 3L+ group	
	Rucaparib versus olaparib (Study 19)	Rucaparib versus olaparib (SOLO-2)	Rucaparib versus olaparib (Study 19)	Rucaparib versus olaparib (SOLO-2)	Rucaparib versus olaparib (Study 19)
ESS – anchored BC Rucaparib Placebo **ESS – unanchored** Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS-INV HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS – anchored HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS – unanchored HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TFST HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TSST HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS2 HR (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	ITT population - relapsed setting	BRCA mutated cohort - relapsed setting		BRCA 3L+ group	
	Rucaparib versus olaparib (Study 19)	**Rucaparib versus olaparib (SOLO-2)**	**Rucaparib versus olaparib (Study 19)**	**Rucaparib versus olaparib (SOLO-2)**	**Rucaparib versus olaparib (Study 19)**
Key: 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; OS, overall survival; TFST, time to first subsequent anti-cancer treatment; TSST, time to second subsequent anti-cancer treatment.					

Uncertainties in the indirect and mixed treatment comparisons

There was marked heterogeneity across studies investigating rucaparib and those investigating olaparib with regard to trial design, patient population and subsequent PARPi treatment use in particular. Differences were most likely to bias against rucaparib, for example:

- The higher proportion of patients with residual disease at baseline (represented by the lower proportion of patients with a complete response to the last line of platinum-based chemotherapy) in the ARIEL3 trial denotes this trial population to have a poorer prognosis than the populations of SOLO2 and Study 19
- The higher proportion of patients with post-progression PARPi treatment in the placebo arm of the ARIEL3 trial denotes the relative efficacy estimates from this trial to be smaller in magnitude than might be observed in the other trials.

Additional complexity is introduced when considering the population of relevance to this appraisal which for this comparison (rucaparib vs olaparib) is people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy. Data for this group are limited, both in terms of availability and in terms of patient numbers where available, which restricts the interpretation of results.

There was high uncertainty in the ITC results as demonstrated by the width of the 95% CrIs. This is driven not only by low patient numbers as noted above, but also by the low number of events in some outcomes (including OS and TTST, which was immature in ARIEL3 and SOLO2), which further restricts the interpretation of results. The NMA modelling attempted to adjust for the low event rate by using a continuity correction, but the precision of the estimates remained very low. As data mature, a more meaningful analysis of longer-term benefit across treatments may be possible. The uncertainty is further demonstrated in the lack of clear trends observed across methods of ITC and data sources.

Marked differences were observed in results between the unadjusted and adjusted NMA analyses, and anchored and unanchored MAIC analyses for OS, which may be explained by the higher proportion of placebo patients in ARIEL3 who switched to a

PARPi upon progression, compared to Study 19 (Table 22). Unadjusted NMA and anchored MAIC analyses are affected by treatment switching because the relative efficacy of rucaparib versus comparators is estimated via the estimated relative efficacy of rucaparib versus placebo. In contrast, adjusted NMA analyses attempt to account for these differences, and unanchored MAIC analyses compare active treatments directly, thus reducing the impact of treatment 'switching' on the estimation of the HR comparing rucaparib vs olaparib. Despite this advantage of adjusted NMA and unanchored MAIC, both should be treated with caution as they are subject to important limitations including the breaking of randomisation and the risk of bias due to unobserved confounding factors.

In summary, while every attempt has been made to provide a robust ITC for the comparison of rucaparib to olaparib of relevance to this appraisal, that is, in patients with BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy (the BRCA 3L+ group), limitations in data availability, maturity, and heterogeneity prohibit such robustness. All things considered, the ITC analyses suggest that rucaparib provides a comparable if not better long-term efficacy profile to olaparib, but no stronger conclusions can be drawn.

B.2.10. Adverse reactions

The target number of progression events in the BRCA mutant cohort was achieved as of 15 April 2017, at which point the database lock was triggered for primary endpoint analysis and safety data were collected. An additional data base lock for an updated safety data analysis occurred on 31 December 2017. Both sets of safety data are presented in the submission. The safety population comprised 561 patients who initiated treatment with 600mg twice daily rucaparib or placebo (372 patients in the rucaparib group and 189 patients in the placebo group).

Treatment exposure and subsequent treatment

Treatment exposure and subsequent data are provided in Appendix L.

As of 31 December 2017, the median number of treatment cycles initiated was [redacted] in the rucaparib group and [redacted] in the placebo group.

The median duration of treatment was [redacted] for the rucaparib group and [redacted] for the placebo group. More patients were exposed to rucaparib for over 1 year ([redacted]) compared to placebo ([redacted]), and the majority of patients who received rucaparib were exposed for at least 6 months ([redacted]), compared to [redacted] of placebo patients. A total of [redacted] patients in the rucaparib group had dose reduction compared with [redacted] in the placebo group. Of those patients with a dose reduction in the rucaparib group, [redacted] required only one dose reduction. Of the dose reductions, the majority were reduced to 480mg twice daily, which was the next dose level permitted.

As of 15 April 2017, [redacted] of patients in the rucaparib group and [redacted] of the placebo group had received a subsequent treatment. The most common subsequent treatments were carboplatin (received by [redacted] of the rucaparib group and [redacted] of the placebo group), PLD (received by [redacted] of the rucaparib group and [redacted] of the placebo group), paclitaxel (received by [redacted] of the rucaparib group and [redacted] of the placebo group), gemcitabine (received by [redacted] of the rucaparib group and [redacted] of the placebo group) and bevacizumab (received by [redacted] of the rucaparib group and [redacted] of the placebo group). With the exception of bevacizumab (that is not recommended within its marketing authorisation for OC indications by NICE), these treatments are available in NHS England. This is discussed further in Section B.3.5.

Adverse events

At both the primary analysis database lock (15 April 2017) and the additional database lock for the updated safety data (31 December 2017), the safety profile of rucaparib was consistent across all patient efficacy cohorts; therefore, data are provided for the largest group of the total safety population. An overview of the treatment emergent adverse events (TEAEs) for the safety population at both data cut-off dates are summarised in Table 26.

As of the 15 April 2017, the majority of patients in the safety population experienced at least one TEAE (100% rucaparib; 96.3% placebo), with treatment-related TEAEs reported for [redacted] and [redacted] of rucaparib and placebo patients, respectively. A greater percentage of patients in the rucaparib group had at least one serious TEAE

(21.0% rucaparib; 10.6% placebo), but less than [redacted] of patients in either treatment group had a treatment-related serious TEAE. A total of six patients (1.6%) who received rucaparib, and two patients (1.1%) who received placebo, had a fatal TEAE; of those, two patients (0.5%) in the rucaparib group had the fatal event assessed by the investigator as related to study treatment. The majority of patients in the rucaparib group (70.7%) had at least one TEAE that led to study drug interruption or dose reduction compared with 10.6% of placebo patients. These events are described in the following sections. Compared with placebo, rucaparib treatment resulted in a greater incidence of Grade 3 or higher (≥3) TEAEs (56.2% rucaparib; 14.8% placebo) and TEAEs that led to study drug discontinuation [redacted]. These events are described in the following sections.

The results observed in the updated safety data analysis, with a 31 December 2017 visit cut-off date, are comparable to the results observed at the primary analysis database lock (15 April 2017; Table 26). Any slight increases in incidences of TEAEs observed in the updated safety data are not unexpected considering the increased duration of treatment after the primary analysis visit cut-off date.

Table 26: Overall summary of treatment-emergent adverse events (safety population)

TEAE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)	
	Rucaparib (n=372)	Placebo (n=189)	Rucaparib (n=372)	Placebo (n=189)
One or more TEAEs	372 (100.0)	182 (96.3)	[redacted]	[redacted]
One or more treatment-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
One or more serious TEAEs	78 (21.0)	20 (10.6)	[redacted]	[redacted]
One or more serious treatment-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs of Grade 3 or higher	209 (56.2)	28 (14.8)	[redacted]	[redacted]
One or more treatment-related TEAEs of Grade 3 or higher	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs leading to death	6 (1.6)	2 (1.1)	[redacted]	[redacted]
One or more treatment-related TEAEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs leading to study drug discontinuation	50 (13.4)	3 (1.6)	[redacted]	[redacted]
One or more treatment-related TEAEs leading to study drug discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs leading to study drug interruption	237 (63.7)	19 (10.1)	[redacted]	[redacted]
One or more treatment-related TEAEs leading to study drug interruption	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs leading to study drug dose reduction	203 (54.6)	8 (4.2)	[redacted]	[redacted]
One or more treatment-related TEAEs leading to study drug dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs leading to dose reduction or interruption	263 (70.7)	20 (10.6)	[redacted]	[redacted]
One or more treatment-related TEAEs leading to dose reduction or interruption	[redacted]	[redacted]	[redacted]	[redacted]

Key: TEAE, treatment emergent adverse event.
Source: Coleman *et al*. 2017;[37] ARIEL3 CSR;[38] Summary of clinical safety - May 2018.[57]

Common TEAEs

At both the primary analysis database lock (15 April 2017) and the additional database lock for the updated safety data (31 December 2017), all patients (100%) in the rucaparib group and 96.3% of patients in the placebo group experienced at least one TEAE. The TEAEs that occurred in ≥20% of patients in either treatment arm at both data cut off dates are summarised in Table 27.

As of the 15 April 2017, the most common TEAEs that occurred in the rucaparib group were nausea (75.3%), combined asthenia/fatigue (69.4%), dysgeusia (39.2%), and combined anaemia/low or decreased haemoglobin (37.4%). Although greater incidences of these most common TEAEs occurred with rucaparib treatment compared with placebo, the TEAEs reported for the placebo group provide a general context of what events are prevalent in this patient population without treatment. The most common TEAEs that occurred in the placebo group were nausea (36.5%), combined asthenia/fatigue (43.9%), abdominal pain (25.9%), and constipation (23.8%).

The incidence of TEAEs in rucaparib and placebo patients observed in the updated safety data analysis, with a 31 December 2017 visit cut-off date, are comparable to the incidences of TEAEs observed at the primary analysis database lock (15 April 2017; Table 27).

Table 27: TEAEs reported in ≥ 20% of patients in any treatment group (safety population)

AE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)	
	Rucaparib (n=372)	Placebo (n=189)	Rucaparib (n=372)	Placebo (n=189)
At least one TEAE	372 (100)	182 (96.3)	372 (100)	182 (96.3)
Combined preferred terms				
Combined ALT/AST increased	126 (33.9)	7 (3.7)	129 (34.7)	8 (4.2)
Combined anaemia and/or low/decreased haemoglobin	139 (37.4)	11 (5.8)	145 (39.0)	10 (5.3)
Combined asthenia/fatigue	258 (69.4)	83 (43.9)	263 (70.7)	84 (44.4)
Combined thrombocytopenia and/or low/decreased platelets	104 (28.0)	5 (2.6)	109 (29.3)	5 (2.6)

AE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)	
	Rucaparib (n=372)	Placebo (n=189)	Rucaparib (n=372)	Placebo (n=189)
System organ class preferred term				
Blood and lymphatic system disorders	172 (46.2)	16 (8.5)	177 (47.6)	16 (8.5)
Anaemia	130 (34.9)	11 (5.8)	135 (36.3)	10 (5.3)
Gastrointestinal disorders	343 (92.2)	145 (76.7)	344 (92.5)	146 (77.2)
Abdominal pain	111 (29.8)	49 (25.9)	112 (30.1)	49 (25.9)
Constipation	136 (36.6)	45 (23.8)	141 (37.9)	46 (24.3)
Diarrhoea	118 (31.7)	41 (21.7)	121 (32.5)	41 (21.7)
Nausea	280 (75.3)	69 (36.5)	282 (75.8)	69 (36.5)
Vomiting	136 (36.6)	28 (14.8)	138 (37.1)	29 (15.3)
General disorders and administration site conditions	292 (78.5)	107 (56.6)	296 (79.6)	108 (57.1)
Asthenia	83 (22.3)	20 (10.6)	86 (23.1)	20 (10.6)
Fatigue	186 (50.0)	64 (33.9)	189 (50.8)	65 (34.4)
Infections and infestations	170 (45.7)	64 (33.9)	174 (46.8)	65 (34.4)
Investigations	209 (56.2)	43 (22.8)	214 (57.5)	43 (22.8)
Alanine aminotransferase increased	123 (33.1)	5 (2.6)	126 (33.9)	6 (3.2)
Aspartate aminotransferase increased	96 (25.8)	4 (2.1)	97 (26.1)	5 (2.6)
Metabolism and nutrition disorders	171 (46.0)	48 (25.4)	176 (47.3)	49 (25.9)
Decreased appetite	87 (23.4)	26 (13.8)	88 (23.7)	26 (13.8)
Musculoskeletal and connective tissue disorders	166 (44.6)	85 (45.0)	172 (46.2)	86 (45.5)
Nervous system disorders	241 (64.8)	66 (34.9)	244 (65.6)	67 (35.4)
Dysgeusia	146 (39.2)	13 (6.9)	148 (39.8)	13 (6.9)
Psychiatric disorders	106 (28.5)	37 (19.6)	107 (28.8)	38 (20.1)
Respiratory, thoracic and mediastinal disorders	141 (37.9)	42 (22.2)	144 (38.7)	42 (22.2)
Skin and subcutaneous tissue disorders	208 (55.9)	69 (36.5)	214 (57.5)	70 (37.0)
Vascular disorders	71 (19.1)	32 (16.9)	77 (20.7)	33 (17.5)

Key: AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment emergent adverse event.
Source: Coleman *et al*. 2017;[37] ARIEL3 CSR;[38] Summary of clinical safety - May 2018.[57]

Grade 3 or higher TEAEs

Table 28 summarises the Grade ≥3 TEAEs, regardless of causality, with incidence ≥5% in either treatment group at both the primary analysis database lock (15 April

2017) and the additional database lock for the updated safety data (31 December 2017).

As of 15 April 2017, 56.2% of patients in the rucaparib-treated group experienced a Grade ≥3 TEAE compared with 14.8% of placebo patients. For patients in the rucaparib group, four TEAEs that were Grade ≥3 had an incidence of >10%: combined anaemia/low or decreased haemoglobin (18.8%), anaemia (17.5%), combined increased alanine aminotransferase (ALT)/aspartate transaminase (AST) (10.5%) and increased ALT (10.2%).

The incidence of Grade ≥3 TEAEs in rucaparib and placebo patients observed in the updated safety data analysis, with a 31 December 2017 visit cut-off date, are comparable to the incidences of Grade ≥3 TEAEs observed at the primary analysis database lock (15 April 2017; Table 28).

Increases in ALT/AST are a known self-limiting effect of rucaparib treatment; therefore, management of these elevations was specified within the protocol. These observed elevations in ALT/AST were generally not accompanied by a concomitant elevation in bilirubin, and no cases met Hy's Law criteria for drug-induced liver injury. Despite the greater incidence in Grade ≥3 ALT/AST with rucaparib treatment, only two patients (0.5%) discontinued the study drug due to the event.

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

AE, n (%)	**Primary analysis data cut (15 April 2017)**		**Updated data cut (31 December 2017)**	
	Rucaparib (n=372)	**Placebo (n=189)**	**Rucaparib (n=372)**	**Placebo (n=189)**
At least one Grade 3* or higher TEAE	209 (56.2)	28 (14.8)	222 (59.7)	30 (15.9)
Combined preferred terms				
Combined ALT/AST increased	39 (10.5)	0 (0.0)	38 (10.2)	0 (0.0)
Combined anaemia and/or low/decreased haemoglobin	70 (18.8)	1 (0.5)	80 (21.5)	1 (0.5)
Combined asthenia/fatigue	25 (6.7)	5 (2.6)	26 (7.0)	5 (2.6)
Combined neutropenia and/or low/decreased ANC	25 (6.7)	2 (1.1)	29 (7.8)	2 (1.1)

Combined Thrombocytopenia and/or low/decreased platelets	19 (5.1)	0 (0.0)	20 (5.4)	0 (0.0)
System organ class Preferred term				
Blood and lymphatic system disorders	87 (23.4)	2 (1.1)	95 (25.5)	3 (1.6)
Anaemia	65 (17.5)	1 (0.5)	73 (19.6)	1 (0.5)
Neutropenia	18 (4.8)	1 (0.5)	19 (5.1)	1 (0.5)
Gastrointestinal disorders	47 (12.6)	12 (6.3)	49 (13.2)	12 (6.3)
General disorders and administration site conditions	29 (7.8)	6 (3.2)	31 (8.3)	6 (3.2)
Investigations	72 (19.4)	1 (0.5)	77 (20.7)	1 (0.5)
ALT increased	38 (10.2)	0 (0.0)	37 (9.9)	0 (0.0)
Metabolism and nutrition disorders	15 (4.0)	1 (0.5)	19 (5.1)	1 (0.5)

Key: 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;[37] ARIEL3 CSR;[38] Summary of clinical safety - May 2018.[57]

Treatment-related TEAEs

Treatment-related TEAEs and treatment-related Grade ≥3 TEAES are provided in Appendix L.

As of 15 April 2017, treatment-related TEAEs were reported for 96.8% and 73.5% of rucaparib and placebo patients, respectively. With the exception of constipation, diarrhoea, and abdominal pain, the events assessed as related to treatment were the same terms with similar/lower incidences as the most common TEAEs reported in Table 27 without causality assessment. As of 15 April 2017, 43.5% of patients in the rucaparib treated group, experienced a Grade ≥3 treatment-related TEAE compared with 4.8% of placebo patients. For patients in the rucaparib group, three TEAEs that were Grade ≥3 had an incidence of >10%: combined anaemia/low or decreased haemoglobin (18.5%), anaemia (17.2%) and combined increased ALT/AST (10.2%).

The incidence of treatment-related TEAEs and treatment-related Grade ≥3 TEAEs observed in the updated safety data analysis, with a 31 December 2017 visit cut-off date, are comparable to the incidences observed at the primary analysis database lock (15 April 2017).

Serious TEAEs and serious treatment-related TEAEs

At both the primary analysis database lock (15 April 2017) and the additional database lock for the updated safety data (31 December 2017), approximately 20% of patients in the rucaparib group and 10.6% of patients who were treated with placebo had at least one serious TEAE. Less than 10% in either treatment group had a serious TEAE assessed as related to study drug.

Serious TEAE and serious treatment-related TEAR data are provided in Appendix L.

As of 15 April 2017, a total of 16 patients (4.3%) treated with rucaparib had a serious TEAE of anaemia/low or decreased haemoglobin compared with one patient (0.5%) treated with placebo. All of the serious events of anaemia/low or decreased haemoglobin were assessed by the investigator as related to the study drug. Serious TEAEs of vomiting and pyrexia were each experienced by six patients treated with rucaparib; of these, two patients each (0.5%) had the event assessed as related to the study drug. Serious TEAEs of acute kidney injury were experienced by four patients in the rucaparib arm (1.1%), and no patients in placebo arm. Three of the four patients had potential alternative causes for acute kidney injury; there was limited information available the fourth patient. Febrile neutropenia was experienced by five patients (independent of the pyrexia cases) treated with rucaparib; of these, four patients (1.1%) had the event assessed as related to study drug. Similarly, four patients with a serious TEAE of thrombocytopenia/low or decreased platelets had the event assessed as related to the study drug. In contrast, no serious TEAEs of constipation or abdominal pain (five patients in the rucaparib group) were found to be related to study drug.

Deaths

As of the 15 April 2017 six patients (1.6%) in the rucaparib group and two patients (1.1%) in the placebo group had at least one TEAE with a fatal outcome. At the updated safety data cut-off date (31 December 2017), one further patient in the rucaparib group had at least one TEAE with a fatal outcome.

Two of the patients in the rucaparib group with a fatal TEAE developed acute myeloid leukaemia (AML) or myelodysplastic syndromes (MDS) evolving into AML, where a relationship to the study drug could not be ruled out. However, there are

many confounding risk factors in assessing drug relationships in the cases of MDS/AML.

Table 29: TEAEs with an outcome of death (safety population)

AE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)	
	Rucaparib (n=372)	**Placebo (n=189)**	**Rucaparib (n=372)**	**Placebo (n=189)**
At least one TEAE leading to death	6 (1.6)	2 (1.1)	7 (1.9)	2 (1.1)
Blood and lymphatic system disorders	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Histiocytosis haematophagic	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Cardiac disorders	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Cardiac arrest	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (1.1)	1 (0.5)	5 (1.3)	1 (0.5)
Acute myeloid leukaemia	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
B-cell unclassifiable lymphoma high grade	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Malignant neoplasm progression*	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Metastases to meninges	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)
Metastases to peritoneum*	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Myelodysplastic syndrome	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)
Pulmonary embolism	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)

Key: AE, adverse event; CSR, clinical study report; TEAE, treatment emergent adverse event.
Notes: *, This patient was summarised in the CSR as having died due to metastases to the peritoneum. The AE to which this event should have been coded was malignant neoplasm progression, which has been corrected for the updated safety data analysis.
Source: Coleman *et al*. 2017;[37] ARIEL3 CSR;[38] Summary of clinical safety - May 2018.[57]

TEAEs leading to treatment discontinuation

Table 30 summarises TEAEs that led to the discontinuation of the study drug, in two or more patients in any treatment group at both the primary analysis database lock (15 April 2017) and the additional database lock for the updated safety data (31 December 2017).

As of 15 April 2017, in the rucaparib group, 13.4% of patients had a TEAE the led to study drug discontinuation, compared with 1.6% in the placebo group. These data do

not include treatment emergent disease progressions. Three percent of patients (n=11) treated with rucaparib and no patients who received placebo discontinued the study drug due to a TEAE of anaemia/low or decreased haemoglobin. These results are consistent with the severity and seriousness of this event observed with rucaparib treatment (Table 28). Similarly, 2.7% of patients (n=10) in the rucaparib group discontinued the study drug due to TEAEs of thrombocytopenia and/or low/decreased platelets, and 1.6% due to asthenia/fatigue (n=6) in contrast to no patients in the placebo group. These results are consistent with the severity of these events for the rucaparib group (Table 28). Most of the events leading to study drug discontinuation were assessed as related to study treatment.

The incidence of TEAEs that led to study drug discontinuation in rucaparib and placebo patients in the updated safety data analysis, with a 31 December 2017 visit cut-off date, are comparable to the incidences of TEAEs that led to study drug discontinuation observed at the primary analysis database lock (15 April 2017; Table 30). Of note, the total discontinuations due to TEAE data for the updated safety analysis do include treatment emergent disease progressions.

Table 30: TEAEs that lead to discontinuation of the study drug in ≥2 patients in any treatment group (safety population)

AE, n (%)	**Primary analysis data cut (15 April 2017)**		**Updated data cut (31 December 2017)**	
	Rucaparib (n=372)	**Placebo (n=189)**	**Rucaparib (n=372)**	**Placebo (n=189)**
At least one TEAE leading to study drug discontinuation	50 (13.4)	3 (1.6)	61 (16.4)	4 (2.1)
Combined preferred terms				
Combined ALT/AST increased	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Combined anaemia and/or low/decreased haemoglobin	11 (3.0)	0 (0.0)	10 (2.7)	0 (0.0)
Combined asthenia/fatigue	6 (1.6)	0 (0.0)	6 (1.6)	0 (0.0)
Combined neutropenia and/or low/decreased ANC	2 (0.5)	0 (0.0)	4 (1.1)	0 (0.0)
Combined thrombocytopenia and/or low/decreased platelets	10 (2.7)	0 (0.0)	11 (3.0)	0 (0.0)
System organ class Preferred term				
Blood and lymphatic system disorders	21 (5.6)	0 (0.0)	21 (5.6)	0 (0.0)

AE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)	
	Rucaparib (n=372)	Placebo (n=189)	Rucaparib (n=372)	Placebo (n=189)
Anaemia	11 (3.0)	0 (0.0)	10 (2.7)	0 (0.0)
Febrile neutropenia	3 (0.8)	0 (0.0)	3 (0.8)	0 (0.0)
Neutropenia	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Thrombocytopenia	8 (2.2)	0 (0.0)	8 (2.2)	0 (0.0)
Cardiac disorders	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Gastrointestinal disorders	12 (3.2)	3 (1.6)	14 (3.8)	3 (1.6)
Nausea	9 (2.4)	1 (0.5)	10 (2.7)	1 (0.5)
Vomiting	5 (1.3)	1 (0.5)	6 (1.6)	1 (0.5)
General disorders and administration site conditions	6 (1.6)	0 (0.0)	6 (1.6)	0 (0.0)
Asthenia	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Fatigue	4 (1.1)	0 (0.0)	4 (1.1)	0 (0.0)
Investigations	7 (1.9)	0 (0.0)	10 (2.7)	0 (0.0)
ALT increased	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
AST increased	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Neutrophil count decreased	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Platelet count decreased	2 (0.5)	0 (0.0)	3 (0.8)	0 (0.0)
Weight decreased	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Nervous system disorders	2 (0.5)	0 (0.0)	3 (0.8)	0 (0.0)
Seizure	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)
Renal and urinary disorders	3 (0.8)	0 (0.0)	3 (0.8)	0 (0.0)
Acute kidney injury	2 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (0.5)	0 (0.0)	3 (0.8)	0 (0.0)

Key: AE, adverse events; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; TEAE, treatment emergent adverse event.
Source: Coleman *et al*. 2017;[37] ARIEL3 CSR;[38] Summary of clinical safety - May 2018.[57]

TEAEs resulting in dose reduction or interruption

TEAEs that led to dose reduction or interruption in ≥5% of patients, in any treatment group at both the primary analysis database lock (15 April 2017) and the additional database lock for the updated safety data (31 December 2017), are summarised in Table 31 and Table 32, respectively.

As of 15 April 2017, the incidence of TEAEs leading to dose reduction was greater for the rucaparib group (54.6%) as compared to the placebo group (4.2%). The most

commonly reported TEAEs leading to rucaparib dose reduction were combined anaemia/low or decreased haemoglobin (12.1%), combined ALT/AST increased (11.0%), combined thrombocytopenia and/or low/decreased platelets (10.5%), and nausea (9.9%). No TEAEs leading to dose reduction were reported in more than 5% of patients treated with placebo. The most commonly reported TEAE that led to a dose reduction in the placebo group was combined asthenia/fatigue in four patients (2.1%). Mostly, the TEAEs leading to dose reduction were considered by the investigator to be treatment related.

As of 15 April 2017, the incidence of TEAEs leading to treatment interruption was 63.7% in the rucaparib group and 10.1% in the placebo group. The most commonly reported TEAEs leading to rucaparib treatment interruption were combined thrombocytopenia and/or low/decreased platelets (17.2%), combined anaemia and/or low/decreased haemoglobin (13.7%), combined ALT/AST increased (10.5%), and nausea (10.2%). No TEAEs leading to treatment interruption were reported in more than 5% of patients treated with placebo. The most commonly reported TEAE leading to treatment interruption in the placebo group was combined asthenia/fatigue in six patients (3.2%). Mostly, the TEAEs leading to treatment interruption were considered by the investigator to be treatment related.

The incidence of TEAEs leading to dose reduction or treatment interruption in rucaparib and placebo patients, as of the 31 December 2017 visit cut-off date, are comparable to the incidences of TEAEs leading to dose reduction or treatment interruption observed at the primary analysis database lock (15 April 2017; Table 31 and Table 32, respectively).

The median time to first TEAE leading to dose modification (i.e. dose reduction; treatment interruption; dose reduction or treatment interruption; and dose reduction, treatment interruption, or study drug discontinuation) was, in general, shorter for patients who received rucaparib (approximately 1 month) as compared to patients who received placebo (approximately 2 to 3 months).

Table 31: TEAEs that led to dose reduction in ≥5% of patients in any treatment group (safety population)

AE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)	
	Rucaparib (n=372)	**Placebo (n=189)**	**Rucaparib (n=372)**	**Placebo (n=189)**
At least one TEAE leading to study drug dose reduction	203 (54.6)	8 (4.2)	206 (55.4)	8 (4.2)
Combined preferred terms				
Combined ALT/AST increased	41 (11.0)	0 (0.0)	41 (11.0)	0 (0.0)
Combined anaemia and/or low/decreased haemoglobin	45 (12.1)	0 (0.0)	47 (12.6)	0 (0.0)
Combined asthenia/fatigue	33 (8.9)	4 (2.1)	33 (8.9)	4 (2.1)
Combined thrombocytopenia and/or low/decreased platelets	39 (10.5)	0 (0.0)	40 (10.8)	0 (0.0)
System organ class Preferred term				
Blood and lymphatic system disorders	66 (17.7)	0 (0.0)	69 (18.5)	0 (0.0)
Anaemia	41 (11.0)	0 (0.0)	43 (11.6)	0 (0.0)
Thrombocytopenia	20 (5.4)	0 (0.0)	21 (5.6)	0 (0.0)
Gastrointestinal disorders	47 (12.6)	1 (0.5)	48 (12.9)	1 (0.5)
Nausea	37 (9.9)	1 (0.5)	37 (9.9)	1 (0.5)
General disorders and administration site conditions	33 (8.9)	6 (3.2)	33 (8.9)	6 (3.2)
Fatigue	25 (6.7)	4 (2.1)	24 (6.5)	4 (2.1)
Investigations	85 (22.8)	0 (0.0)	88 (23.7)	0 (0.0)
ALT increased	39 (10.5)	0 (0.0)	39 (10.5)	0 (0.0)
Platelet count decreased	20 (5.4)	0 (0.0)	20 (5.4)	0 (0.0)

Key: AE, adverse events; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; TEAE, treatment emergent adverse event.

Source: Coleman *et al*. 2017;[37] ARIEL3 CSR;[38] Summary of clinical safety - May 2018.[57]

Table 32: TEAEs that led to treatment interruption in ≥5% of patients in any treatment group (safety population)

AE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)	
	Rucaparib (n=372)	**Placebo (n=189)**	**Rucaparib (n=372)**	**Placebo (n=189)**
At least one TEAE leading to treatment interruption	237 (63.7)	19 (10.1)	243 (65.3)	19 (10.1)
Combined preferred terms				
Combined ALT/AST increased	39 (10.5)	0 (0.0)	38 (10.2)	0 (0.0)
Combined anaemia and/or low/decreased haemoglobin	51 (13.7)	1 (0.5)	56 (15.1)	1 (0.5)
Combined asthenia/fatigue	32 (8.6)	6 (3.2)	33 (8.9)	6 (3.2)
Combined neutropenia and/or low/decrease ANC	23 (6.2)	1 (0.5)	24 (6.5)	1 (0.5)
Combined thrombocytopenia and/or low/decreased platelets	64 (17.2)	0 (0.0)	64 (17.2)	0 (0.0)
System organ class Preferred term				
Blood and lymphatic system disorders	89 (23.9)	1 (0.5)	91 (24.5)	1 (0.5)
Anaemia	47 (12.6)	1 (0.5)	52 (14.0)	1 (0.5)
Thrombocytopenia	39 (10.5)	0 (0.0)	38 (10.2)	0 (0.0)
Gastrointestinal disorders	78 (21.0)	7 (3.7)	81 (21.8)	7 (3.7)
Nausea	38 (10.2)	2 (1.1)	38 (10.2)	2 (1.1)
Vomiting	32 (8.6)	2 (1.1)	32 (8.6)	2 (1.1)
General disorders and administration site conditions	42 (11.3)	7 (3.7)	43 (11.6)	7 (3.7)
Fatigue	23 (6.2)	6 (3.2)	24 (6.5)	6 (3.2)
Infection and infestations	22 (5.9)	5 (2.6)	24 (6.5)	5 (2.6)
Investigations	88 (23.7)	1 (0.5)	90 (24.2)	1 (0.5)
ALT increased	39 (10.5)	0 (0.0)	38 (10.2)	0 (0.0)
Platelet count decreased	26 (7.0)	0 (0.0)	27 (7.3)	0 (0.0)

Key: AE, adverse events; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; TEAE, treatment emergent adverse event.
Source: Coleman *et al*. 2017;[37] ARIEL3 CSR;[38] Summary of clinical safety - May 2018.[57]

Safety profile summary

Overall, rucaparib was generally well tolerated with AEs observed in the trial consistent with the known safety profile of rucaparib. There was no meaningful increase in mortality or morbidity in the rucaparib group compared with the placebo group. During the ARIEL3 study, the rucaparib treatment discontinuation rate due to

TEAEs was low at both the primary analysis database lock (14.2%; 15 April 2017) and at the additional database lock for the updated safety data analysis (16.4%; 31 December 2017), with TEAEs generally managed through dose modifications and supportive care. Importantly, very few deaths related to rucaparib treatment were observed (0.5%).

The side effect profile observed for rucaparib was generally in line with that observed in previous studies of maintenance treatment with PARPis, that is, gastrointestinal side effects, fatigue, asthenia, and myelosuppression. Observations from early PARPi studies raised some concerns about a potential risk of myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML) with this class of treatment but <1% of patients treated with rucaparib in ARIEL3 developed MDS/AML.

Some differences in PARPi safety profiles have been noted and are reflected in the Summary of Product Characteristics with specials warnings of photosensitivity with rucaparib, pneumonitis with olaparib, and hypertension, including hypertensive crisis with niraparib.[1, 36, 58] Differences in thrombocytopenia rates are also observed.

No other studies reported additional AEs for rucaparib in the maintenance setting, but the safety outcomes are similar to those reported with rucaparib use in the treatment setting with no new safety signals observed.

B.2.11. Ongoing studies

The ARIEL3 study is ongoing and will provide additional data for secondary endpoints including OS as the data mature.

B.2.12. Innovation

The ARIEL3 trial provides further evidence that PARPi maintenance treatment should be incorporated within the standard of care for people with platinum-sensitive OC, following a response to platinum-based chemotherapy in the relapsed setting.

Rucaparib was discovered and developed in the UK and should be made available to UK patients. In 1990, a collaboration between the Cancer Research Unit and the School of Chemistry at the University of Newcastle was established to make and test PARPis.[59] Rucaparib was subsequently identified in collaboration with Agouron and

Pfizer GRD, and with the help of the Cancer Research UK Centre for Drug Development, rucaparib went into Phase I trials in 2003, which stimulated a high levels of commercial interest in PARPis at multiple companies.[59] Rucaparib is now being developed and marketed by Clovis Oncology.

While the main health-related benefits of rucaparib maintenance treatment will be captured in the quality-adjusted life year (QALY) calculation presented in Section B.3, it should be acknowledged that ARIEL3 provides robust Phase III data for rucaparib with broad eligibility (including patients with endometrioid as well as serous EOC), without genomic selection, and a patient population closely resembling a clinical practice population, including patients with residual disease. This is further discussed in Section B.2.13, but as the first PARPi maintenance treatment to demonstrate further reduction in carcinoma burden in patients with a suboptimal response to initial treatment, rucaparib can be considered innovative in this setting.

In addition, rucaparib has administration benefits that will not be captured but could help to minimise the impact of treatment on patients' daily lives, that is, rucaparib reduces the number of tablets/capsules to be taken at each dose from six to two, and there are no restrictions on food intake relating to treatment absorption (Table 3).

B.2.13. Interpretation of clinical effectiveness and safety evidence

Principal findings from the available clinical evidence to support rucaparib

Rucaparib meets the primary aims of maintenance treatment in patients with relapsed platinum-sensitive OC, by prolonging the response to platinum-based chemotherapy and extending the chemotherapy-free interval and time to subsequent anti-cancer treatment. This efficacy was demonstrated regardless of BRCA status, supporting the use of rucaparib in a wide range of patients (see external validity). In the ITT population of the ARIEL3 study, rucaparib treatment significantly prolonged PFS (10.8 months versus 5.4 months; $p<0.0001$), chemotherapy-free interval (15.0 months versus 9.2 months; $p<0.0001$), and TFST (12.5 months versus 7.4 months; $p<0.0001$), compared with placebo. Furthermore, rucaparib substantially suppressed changes in CA-125 from baseline to Cycle 10, compared with placebo (256.6%

versus 1134.1%; p<0.0001); and both minimum and maximum changes in CA-125 were associated with improved PFS.

Rucaparib is the only PARPi, to date, that has been reported to prolong PFS in patients with residual bulky disease, which is representative of poorer prognosis. In the ITT population of the ARIEL3 study, rucaparib improved PFS as assessed by the investigator (8.2 months versus 2.9 months; p=0.0007) and PFS as assessed by BICR (8.3 months versus 3.0 months; p=0.0057), compared with placebo, in patients with residual bulky disease at baseline. Rucaparib is also the only PARPi, to date, that has been reported to reduce tumour burden in patients with residual measurable disease (tumour size >1cm), irrespective of BRCA status (there are some data for this outcome for olaparib but restricted to patients with a BRCA mutation[60]). In the ITT population of the ARIEL3 study, a significantly higher proportion of patients with residual measurable disease at baseline achieved a confirmed overall response when treated with rucaparib compared with placebo (18.4% versus 7.6%; p=0.0069). These outcomes are of particular importance in the maintenance setting, as the risk of relapse is higher in such patients (see Section B.1.3).

Rucaparib was generally well tolerated with TEAEs observed in the ARIEL3 study consistent with the known safety profile of rucaparib, and no new safety signals observed. TEAEs that did occur were generally expected *a priori* and manageable with dose modifications and supportive care. Furthermore, low rates of discontinuations due to TEAEs (14.2%), and very few deaths related to rucaparib treatment, were reported (0.5%). While common TEAEs align across the drug class, differences in the safety profiles of PARPi maintenance treatments are noted.

Maintenance of HRQL was observed with rucaparib treatment in ARIEL3. This lack of detrimental impact is particularly pertinent in a patient group which has undergone at least two rounds of potentially toxic chemotherapy as this can negatively impact HRQL. In the real world setting, you would expect prolonged response to platinum-based chemotherapy to have a positive impact on patients daily lives. This is observed in post-hoc QA-PFS and Q-TWiST analysis with significant benefits in favour of rucaparib observed when the patient perspective is modelled over time until progression.

No meaningful differences were observed in ITC analyses comparing rucaparib to olaparib, suggesting that rucaparib provides at least similar clinical benefits to current PARPi maintenance treatment but in a broader patient group and with reduced administration burden and a safety profile that differs from the safety profile of other PARPi maintenance treatments. If rucaparib is made available in NHS England, such characteristics should help further advance the incorporation of PARPi maintenance treatment within the standard of care for people with platinum-sensitive relapsed OC.

Internal validity

ARIEL3 was a well-designed, multicentre, randomised, double-blind, placebo-controlled, Phase III study providing comparative evidence of rucaparib versus placebo (representative of routine surveillance). The ARIEL3 study was conducted in line with Good Clinical Practice guidelines, with steps taken to minimise the risk of bias. An independent data monitoring committee was established to provide independent oversight of safety and efficacy considerations and study conduct. The overall risk of bias in the ARIEL3 study is considered to be low, and any potential biases are against rucaparib rather than in its favour. For example, one potential source of bias is the possible use of subsequent PARPi treatment in placebo-treated patients post-progression. This may have an impact on the final OS results, as the use of post-progression PARPi treatment may mask the true treatment effect of rucaparib versus placebo.

A limitation of the ARIEL3 study is that it does not provide head-to-head data with comparator treatments outside of routine surveillance; this is reflective of the treatment landscape at the time of trial design (when no active maintenance treatments were established standard of care in clinical practice and PARPi treatments were being developed in parallel). In the absence of head-to-head trial data, an ITC analysis, in accordance with NICE technical support guidance, has been conducted to provide an estimate of rucaparib compared with olaparib in the relevant patient population (people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy).

One potentially unexpected result was the longer PFS time estimates when a BICR assessment was conducted versus PFS assessment by the investigator in the rucaparib arm. According to ARIEL3 study protocol, scans were sent for BICR until progression or death as assessed by the investigator, therefore, there was a higher censoring rate in BICR analyses (with no further scans sent for BICR once the investigator had assessed progression) that could be contributing to the differences observed. A significant improvement in PFS was observed with rucaparib treatment, regardless of the assessment method. This observation (higher median PFS by BICR as compared to investigator assessment) has also been made in other clinical studies of PARPi maintenance treatments within the relapsed OC setting. [42-44]

External validity

The ARIEL3 trial was a multicentre study conducted in 87 centres in 11 countries and provides head-to-head data with placebo, representative of routine surveillance. Of the patients with OC included in this study, 67 were enrolled and treated from 10 sites in the UK. The study population enrolled was unselected with regard to the molecular characteristics of the tumour such that the ITT population provides a true ITT analysis of all randomised patients, but pre-defined analyses also provide data for HRD subgroups.

Indeed, the ARIEL3 study is the most inclusive PARPi maintenance treatment trial to date, also including patients with measurable and bulky residual disease at initiation of maintenance treatment. Importantly (and as demonstrated in previous sections), the efficacy observed with rucaparib in the ARIEL3 study was demonstrated in the unselected patient population, that is, regardless of the molecular characteristics of the tumour (HRD and BRCA status) and residual disease at baseline, supporting the use of rucaparib as a maintenance treatment for all platinum-sensitive patients.

Overall, the ARIEL3 study population is therefore representative of the wide range of patients presenting for treatment in NHS England. In the ARIEL3 study, the median age of OC patients was 61, which is similar to the median age of observed for patients in UK clinical practice (55–60 years)[4] and the majority of patients had EOC (83.5%), similar to the observed UK population (90%).[5] While clinical consultation suggested the trial population is likely to be generally younger and fitter than real-

world patients (as observed in the vast majority of clinical trials), it was confirmed that ARIEL3 patients are representative of UK patients and that Clovis were correct to include those patients with residual disease.[56]

The primary efficacy endpoint of the ARIEL3 study was investigator-assessed PFS. The main aim of treatment in the maintenance setting is to prolong response to chemotherapy; therefore, PFS is considered an appropriate primary endpoint, and is widely accepted and used for clinical studies and regulatory approval in this setting. Investigator assessment is also consistent with clinical practice in NHS England. Secondary efficacy endpoints and exploratory endpoints assessed further aims of maintenance treatment, and provide data for all outcomes considered of relevance to the scope of this appraisal by expert commentators and consultees.

Although not observed in the short-term HRQL data collected during the ARIEL3 study, in the real-world setting, prolonged response to platinum-based chemotherapy (as demonstrated by a statistically significant extension in PFS) is expected to have a positive impact, that is, an extended period of symptom-free disease may allow patients to return to some sort of normal living. Furthermore, improvements in chemotherapy free-interval and time to next treatment (as observed in the ARIEL3 study) are likely to mean an extended period of chemotherapy-free living, which will reduce the risk of potentially deleterious side effects of OC treatment. Improvements in both PFS and chemotherapy-free interval also allow patients to be considered for re-treatment with platinum-based chemotherapy at relapse, thus facilitating more effective subsequent treatment lines.

Rucaparib as an end-of-life therapy

While rucaparib does not strictly meet the typical criteria for consideration as an end-of-life therapy, it is intended to treat patients with an aggressive and incurable cancer associated with an overall poor prognosis. Although the life expectancy of patients with advanced OC can exceed 24 months from diagnosis, patients with tumours that become resistant to platinum-based chemotherapy are not expected to live beyond a year, so it is imperative for their overall prognosis to introduce maintenance treatments to the clinical pathway of care that can prolong disease control with platinum treatment. Rucaparib meets that need.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

- In appendix G, describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology appraisal).
- See section 3.1 of the user guide for full details of the information required in appendix G.

A systematic literature review (SLR) was originally performed on 12 October 2017 to identify published cost-effectiveness studies relevant to this appraisal. Update searches were conducted on 3 December 2018.

Electronic databases Embase® (via embase.com), MEDLINE® (via embase.com and PubMed), EconLit, and NHS Economic Evaluation Database (EED) (via the Cochrane Library) were searched.

Appendix G provides full details of the search strategy, inclusion and exclusion of articles, critical appraisal, and results. The searches identified 859 papers and abstracts. After removing duplicates, 772 were screened, of which 38 full-text publications were reviewed. Eighteen full-text publications and three grey literature records were considered relevant. Eight cost-effectiveness analyses (CEAs)[61-68], eight budget impact analyses[69-76] and one utility study[77] were identified. The eight CEAs are summarised in Table 33.

Table 33: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Secord et al.[61]	2013	Semi-Markov model with decision tree nodes – BRCA test, PARP treatment, pre-progression, progression, adverse events	Platinum-sensitive, recurrent, high-grade, serous OC	N/A	Global olaparib: $70,300 BRCA1/2 testing followed by olaparib: $30,478 Observation: $18,960	Global olaparib vs observation: $234,128 per progression-free year of life saved (PF-LYS) BRCA1/2 testing vs observation: $193,442 per PF-LYS
Smith; et al.[63]	2015	Two decision analysis models	Platinum-sensitive, recurrent, high-grade, serous OC with germline BRCA 1/2 mutation	N/A	Olaparib maintenance: $169.2 million Observation: $5.5 million	$258,864 per PF-LYS
			Platinum-sensitive, recurrent, high-grade, serous OC with wild-type BRCA mutation	N/A	Olaparib maintenance: $444.2 million Observation: $22.1 million	$600,552 per PF-LYS
Mylonas et al.[62]	2016	Markov model adapted for Greece	BRCA-mutated platinum-sensitive recurrent OC	Olaparib QALYs 0.89 greater than 'watch and wait'	Lifetime costs; Olaparib: €85,716 Watch and Wait: €12,144	€82,799 per QALY
Chin et al.[65]	2018	Partition-survival	BRCA-mutated platinum-sensitive, recurrent OC	The incremental QALYs for rucaparib versus placebo were 0.73.	Rucaparib vs placebo: $264,989	Rucaparib vs placebo: $361,535 per QALY
Fisher et al.[78, 79]	2018	Decision analysis	Platinum-sensitive, recurrent OC	Niraparib vs routine surveillance N/A	Niraparib vs olaparib non-gBRCAmut: -$57,575	Niraparib vs routine surveillance

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				Niraparib versus olaparib gBRCAmut: similar QALYS non-gBRCAmut: incremental QALYs of 1.437	gBRCAmut: -$60,400 Niraparib vs rucaparib Non-gBRCAmut: -$117,916 gBRCAmut: -$261,950	non-gBRCAmut: $94,186 gBRCAmut: $58,508 Niraparib vs olaparib non-gBRCAmut: niraparib dominates gBRCAmut: niraparib dominates
Liu et al.[66]	2017	Decision analysis	Platinum-sensitive, recurrent OC	N/A	Total costs; Observation: $1 million Olaparib: $251 million Niraparib: $286 million Rucaparib: $200 million	BRCA1/2 mutations; Olaparib vs observation: $195,788/PF-LYS Niraparib vs observation: $196,117/PF-LYS Rucaparib vs observation: $290,245/PF-LYS Somatic HRD; Niraparib vs observation: $205,171/PF-LYS Rucaparib vs observation: $496,157/PF-LYS Wild-type; Niraparib vs observation: $321,799/PF-LYS
Zhong et al.[67, 80]	2018	Decision tree analysis	Platinum-sensitive, recurrent OC	Total progression-free QALYs overall population:	All patients; Olaparib vs placebo: $122,000	All patients Olaparib vs placebo: $287,000/PF-LYS

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				Placebo: 0.27 Olaparib: 0.60 Niraparib: 0.73	Niraparib vs placebo: $14,800 gBRCA mutations; Olaparib vs placebo: $800 Niraparib vs placebo: $254,700 Without gBRCA mutations; Olaparib vs placebo: $98,500 Niraparib vs placebo: $17,500	Niraparib vs placebo: $235,000/PF-LYS Niraparib vs olaparib: $93,000/PF-LYS Olaparib vs niraparib and placebo: extendedly dominated gBRCA mutations; Olaparib vs placebo: $226,000/PF-LYS Niraparib vs placebo: $197,000/PF-LYS Olaparib vs niraparib: dominated Without gBRCA mutations; Olaparib vs placebo: $328,000/PF-LYS Niraparib vs placebo: $253,000/PF-LYS Niraparib vs olaparib: $111,000/PF-LYS
Wolford et al.[68]	2018	Markov	Platinum-sensitive, recurrent OC	N/A	Total PARP costs prior to progression: $471,989	BRCA-deficient patients; Pembrolizumab vs niraparib: $20,032/LMG Pembrolizumab vs rucaparib: $18,444/LMG

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						Pembrolizumab vs olaparib: $17,520/LMG

Key: BRCA, breast cancer gene; gBRCA, germline breast cancer gene; gBRCAmut, germline breast cancer gene mutation; ICER, incremental cost-effectiveness ratio; LMG, life month gained; OC, ovarian cancer; PARP, poly ADP ribose polymerase; PF-LYS, progression-free year of life saved; QALY, quality-adjusted life year.

B.3.2. Economic analysis

Patient population

As described in Section B.1.2 positive Committee for Medicinal Products for Human Use (CHMP) opinion was granted on a Type-II variation of European Medicines Agency (EMA) marketing authorisation of rucaparib on 13 December 2018, for use as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. European Commission marketing authorisation was granted on 23 January 2019. The economic analysis evaluates the cost effectiveness of rucaparib in this patient group, consistent with the stated decision problem and final scope.

The key clinical data available for this submission are from the ARIEL3 trial, described in detail in Section B.2. These data, from a robustly designed, controlled study, were used to inform the economic comparison of rucaparib versus routine surveillance, assuming that placebo outcomes reflect routine surveillance in the UK.

The *de novo* cost-effectiveness model includes two populations, based on the current clinical pathway for maintenance treatment of ovarian cancer (Table 34). The primary population of interest was the total randomised population (the ITT population) in ARIEL3. The BRCA 3L+ population is also included based on the final scope, to allow comparison with olaparib, as this treatment is currently only reimbursed for patients with BRCA mutation who have received three or more prior lines of platinum-containing regimens in the UK.

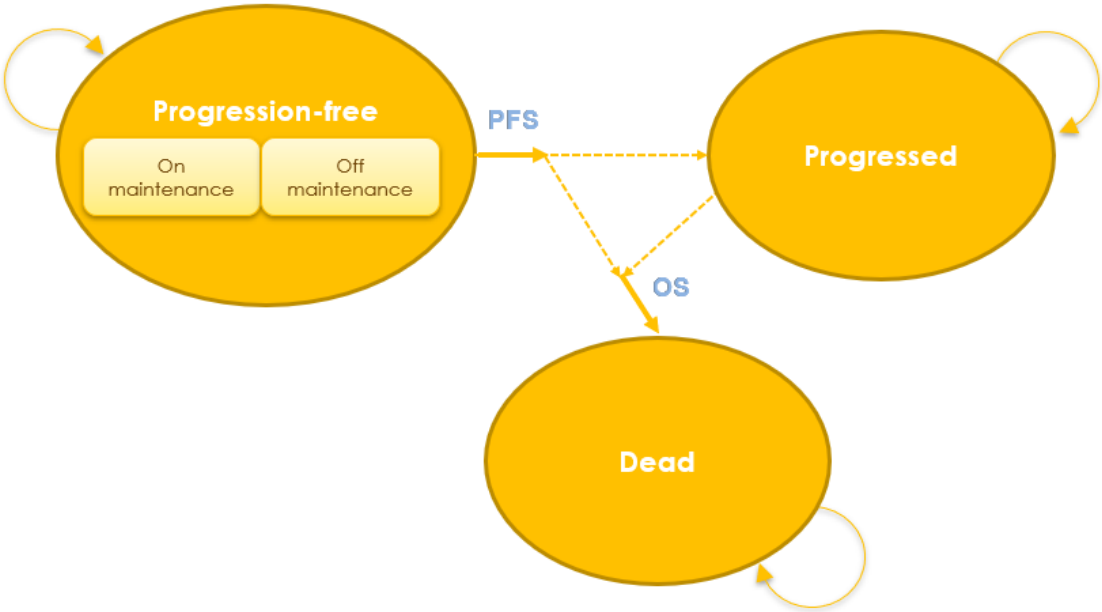
Table 34: Populations included in the *de novo* cost-effectiveness analysis

Population	Description
ITT 2L+ MTN	'All-comers' patients who had undergone two or more prior platinum-containing regimens and were able to receive maintenance treatment, including patients with BRCA-mutated disease and non-BRCA-mutated disease.
BRCA 3L+ MTN	Patients with BRCA-mutated disease who had undergone three or more prior platinum-containing regimens and were able to receive maintenance treatment.
Key: 2L+, two or more prior lines; 3L+, third- or later-line; BRCA, breast cancer gene; ITT, intention-to-treat; MTN, maintenance.	

Model structure

A *de novo* economic model was constructed in Microsoft Excel® to evaluate the cost effectiveness of rucaparib. Its structure and possible transitions are represented in Figure 7.

Figure 7: Structure of the cost-effectiveness model



Key: OS, overall survival; PFS, progression-free survival.

The *de novo* cost-effectiveness model used a partitioned survival analysis structure, selected for its ability to capture the main determinants of health and cost outcomes in recurrent OC in the different populations of interest. This model structure has been used in previous relevant health technology assessments (see below in this section) and is a widely accepted approach in oncology indications.[81] While the model structure is simple, it is flexible enough to extrapolate survival using various methods and can incorporate relative efficacy in numerous ways.

The model has three main health states: 'Progression-free' (where all patients enter the model), 'Progressed' and 'Dead'. The Progression-free health state is divided into 'On maintenance' and 'Off maintenance'.

The benefit of each intervention is captured and differentiated through impact on PFS and OS, described in further detail in Section B.3.3. The cost impact of

subsequent therapies is considered in the model within the Progressed state, described in further detail in Section B.3.5.

The Progression-free health state includes patients who are alive and whose disease has not yet progressed. Thus, the proportion of patients in the Progression-free state is represented by the PFS curve at that point in time. Upon moving to the next model cycle, patients may remain progression free and continue receiving maintenance treatment, remain progression free but discontinue maintenance treatment before disease progression, progress (and receive subsequent therapy) or die.

The Progressed disease state consists of patients who are alive but have progressed. The proportion of the cohort in this health state at any given time is calculated as the difference between the PFS and OS curves. Once progressed, patients cannot return to the Progression-free health state. Patients in the Progressed state may receive an initial treatment-dependent mix of subsequent therapy. Subsequent therapy only affects costs in the progressed health state.

The model structure is in line with previous relevant NICE appraisals. For the appraisals of olaparib (TA381) and niraparib (TA528), and the ongoing appraisal of olaparib in its expanded marketing authorisation (ID1296), the Evidence Review Group (ERG) preferred a partitioned survival model.[33, 34, 82] Models identified in the SLR described in Section B.3.1 had alternative structures, but given the recent appraisals, a partitioned survival model was deemed most relevant for this decision problem. A leading expert clinician confirmed that the model was appropriate to reflect key aspects of the disease. See Section B.3.10 for further details of the validation process.

The economic models used in the bevacizumab appraisal (TA285), and the appraisal of several chemotherapy agents (topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin, and gemcitabine; TA389) were also studied. Table 35 summarises and justifies other key features of the economic analysis alongside the corresponding features of NICE appraisals TA285, TA381, TA389 and TA528.[33, 34, 83, 84] The table illustrates how the approach has considered previous relevant technology appraisals and the Guide to the Methods of Technology Appraisal.[85]

Table 35: Features of the economic analysis

	Previous appraisals				Current appraisal	
Factor	**TA285[83]**	**TA381[33]**	**TA389[84]**	**TA528[34]**	**Chosen values**	**Justification**
Time horizon	10 years	15 years	15 years	Lifetime	30 years	Assumed long enough to capture health and cost consequences over the entire patient lifetime of the populations of interest. At the end of the model time horizon, 3.3% of patients remain alive in the ITT population, and <0.1% remain alive in the BRCA 3L+ population.
Treatment waning effect?	Not applied	Not applied	Not applied	Not applied	Not applied	Waning of treatment effect is not considered relevant for PARP inhibitors, in line with previous appraisals.
Source of utilities	EQ-5D utilities from the OVA-301 trial with a recurrent ovarian cancer population (taken from TA222)	Mapped FACT-O data from Study 19 to EQ-5D	EQ-5D utilities from the OVA-301 trial with a recurrent ovarian cancer population (used in TA222)	Treatment-specific health-state utility values, EQ-5D-5L for niraparib and BSC, and TA381 for olaparib	ARIEL3 EQ-5D-3L analysis	Patient-level data from the ARIEL3 trial are available for the populations of interest, therefore the trial data have been used. This is in line with preferences stated within the NICE reference case (REF reference case)
Source of costs	Drug costs: BNF/CMU/eMIT; other: NHS reference costs/Unit Costs of Health and Social Care	Outpatient visit: £127; blood test: £3; CT scan: £90. No administration costs as regular follow-up	Drug costs: BNF; other: NHS reference costs/Unit Costs of	Not specified	Drug costs: BNF/eMIT; other costs: NHS reference costs/Unit Costs of	Standard cost sources have been used, consistent with previous appraisals

	Previous appraisals				Current appraisal	
Factor	**TA285[83]**	**TA381[33]**	**TA389[84]**	**TA528[34]**	**Chosen values**	**Justification**
		assumed. Subsequent treatment: eMIT and BNF	Health and Social Care		Health and Social Care	

Key: BNF, British National Formulary; BSC, best supportive care; CMU, Commercial Medicines Unit; CT, computed tomography; eMIT, electronic market information tool; EQ-5D-5L, five-level EQ-5D; FACT-O, Functional Assessment of Cancer Therapy – Ovarian; PARP, poly ADP ribose polymerase; TA, technology appraisal.

The model time horizon was set to 30 years. Patients with advanced OC have a shorter life expectancy than the general population, and the median age of the patients in the ITT population in the ARIEL3 trial was 62 years. Therefore, 30 years was assumed to be long enough to capture the long-term clinical and economic impacts of maintenance therapy over the entire patient lifetime.[86] A scenario was tested in which the model used a time horizon of 50 years, described in Section B.3.8.

The model cycle length is 1 month, corresponding to the treatment cycle length in the ARIEL3 trial.[86] Health benefit and cost calculations were half-cycle corrected by averaging the number of patients at the start and end of each cycle. The acquisition and administration costs of rucaparib and olaparib were assumed to be incurred at the beginning of each cycle, therefore half-cycle correction was not applied in these cost categories. Both health and cost outcomes were discounted at a rate of 3.5% per annum, consistent with the NICE reference case.[85]

No treatment waning effect was assumed, in line with previous relevant technology appraisals (shown in Table 35). To provide utility values for each health state, the three-level EQ-5D (EQ-5D-3L) data from the ARIEL3 trial were used and a UK tariff was applied (described in further detail in Section B.3.4). Previous relevant technology appraisals have also used EQ-5D utility values from trials and/or mapped data to the EQ-5D (shown in Table 35).

Most costs in the economic model came from standard cost sources, in line with the NICE reference case and previous appraisals. Drug costs were based on the British National Formulary (BNF)[87] and electronic market information tool (eMIT)[88] databases, and administration and resource use costs were based on NHS reference costs[89] and the Unit Costs of Health and Social Care[90].

Intervention technology and comparators

In line with the final scope, rucaparib was compared against the standard of care, routine surveillance, within the ITT population, as there is no active maintenance treatment currently routinely commissioned. NICE has recommended olaparib as maintenance treatment for patients with BRCA mutations who have received three or

more prior lines of therapy; therefore a pairwise comparison to olaparib was carried out in the BRCA 3L+ population only.

Of note, niraparib is included in the Cancer Drugs Fund (CDF) as maintenance treatment for patients with germline BRCA mutation who have received two prior lines of therapy, and patients without germline BRCA mutation who have received two or more prior lines. However, as it is not routinely commissioned, it is not regarded a comparator for rucaparib, in line with the final scope.

Dosing and administration frequencies for all treatments are in line with their respective marketing authorisations. The olaparib marketing authorisation recently received Type-II variation for a tablet formulation, in addition to the previous capsule formulation. The NICE technology appraisal for the updated formulation is still ongoing (ID1296); as such, the comparison to olaparib within the cost-effectiveness analysis is to the capsule formulation within the BRCA 3L+ population, in line with the final scope for this appraisal.[1, 33]

B.3.3. Clinical parameters and variables

The pivotal study used to inform the cost-effectiveness analysis was ARIEL3, as described in detail in Section B.2.6.

The following clinical outcomes were assessed:

- Investigator-assessed PFS
- Independent review committee PFS
- OS
- Time to discontinuation (TTD)
- HRQL (described in Section B.3.4)
- TEAEs (described in Section B.3.4)

The data for most of these outcomes are incomplete. Given this, and the need to take a lifetime perspective for modelling, parametric survival analysis was undertaken to inform key clinical parameters in the cost-effectiveness analysis. Due to the immaturity of OS data from ARIEL3, OS data from Study 19 were utilised in the model base case.

Following methods guidance from NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 18, the remainder of this section sets out the methodology and results of parametric survival analyses to capture and extrapolate PFS, OS and TTD over a lifetime horizon, and describes the incorporation of indirect comparison results for the comparison with olaparib.[55, 81] Of note, independent review committee PFS is not included within the model, as investigator-assessed PFS was the primary endpoint within ARIEL3, and clinical expert opinion indicated this endpoint better reflects clinical practice within the UK.

As described in Section B.2.9, an NMA and MAIC were performed to compare rucaparib and olaparib in the BRCA 3L+ population, as no head-to-head trials of the two treatments exist. As the comparisons showed no conclusive evidence of direction of effect between rucaparib and olaparib, the model base case assumes equivalence of PFS and OS for the two treatments. This assumption was validated by two UK clinical experts in ovarian cancer. Sensitivity analyses have also been

conducted, using the output of the NMA and MAIC. These are described throughout this section and results are presented in Section B.3.8.

Investigator-assessed progression-free survival

In ARIEL3, investigator-assessed PFS was calculated as 1 plus the number of days from randomisation to disease progression (as determined by the investigator according to RECIST v1.1 criteria) or death due to any cause, whichever occurred first. Patients without a documented event of progression or death were censored on the date of their last scan or date of randomisation if no tumour assessments had been performed.

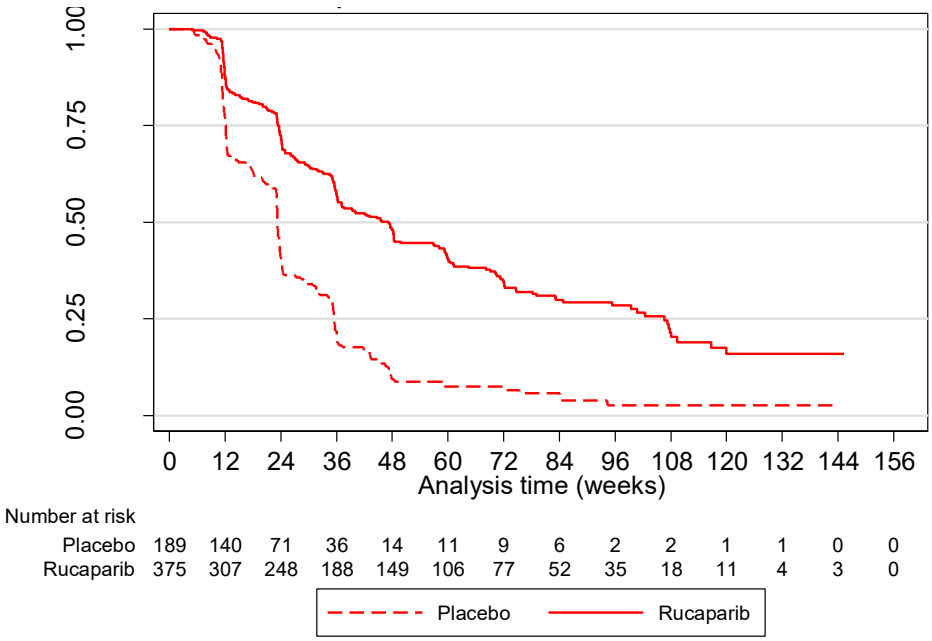
Parametric survival curves were fitted to the time-to-event data available from ARIEL3. For this and all other endpoints, distributions fitted included exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma in line with the NICE reference case.[85]

The statistical distributions were fitted to the data using treatment (active treatment versus placebo) as a predictor as well as using separate models. Separate models were chosen, if there was evidence that the assumption of proportional hazards for the effect of treatment did not hold or if predicted and observed data did not match well. The process of selecting the best fitting distribution involved both statistical fit to the observed data and clinical plausibility of the extrapolated outcomes.

ITT 2L+ population

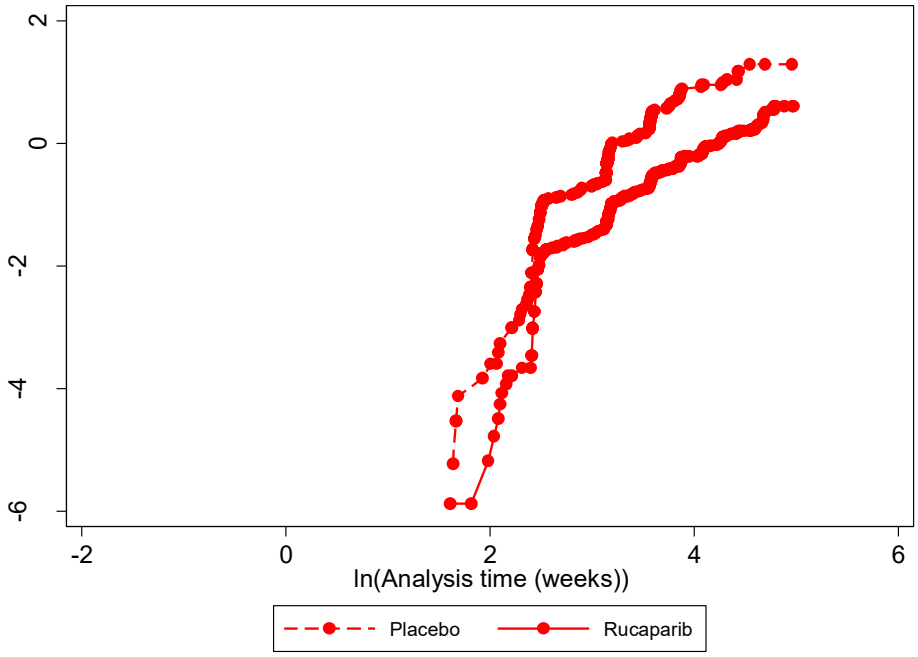
Figure 8 shows the KM curve for investigator-assessed PFS in the ARIEL3 trial, displaying both active treatment and placebo arms in the ITT 2L+ population. Proportional hazards were tested in a log-cumulative hazard plot, shown in Figure 9. Separate models were fit to the data; an overview of all curve fits is presented in Figure 10 and Figure 11. Table 36 presents the observed median investigator-assessed PFS in weeks from ARIEL3, in addition to the median and mean as predicted by each fitted parametric survival model. Table 37 presents the Akaike information criterion (AIC) and Bayesian information criterion (BIC).

Figure 8: Kaplan–Meier investigator-assessed progression-free survival estimate in the ITT population – rucaparib and placebo



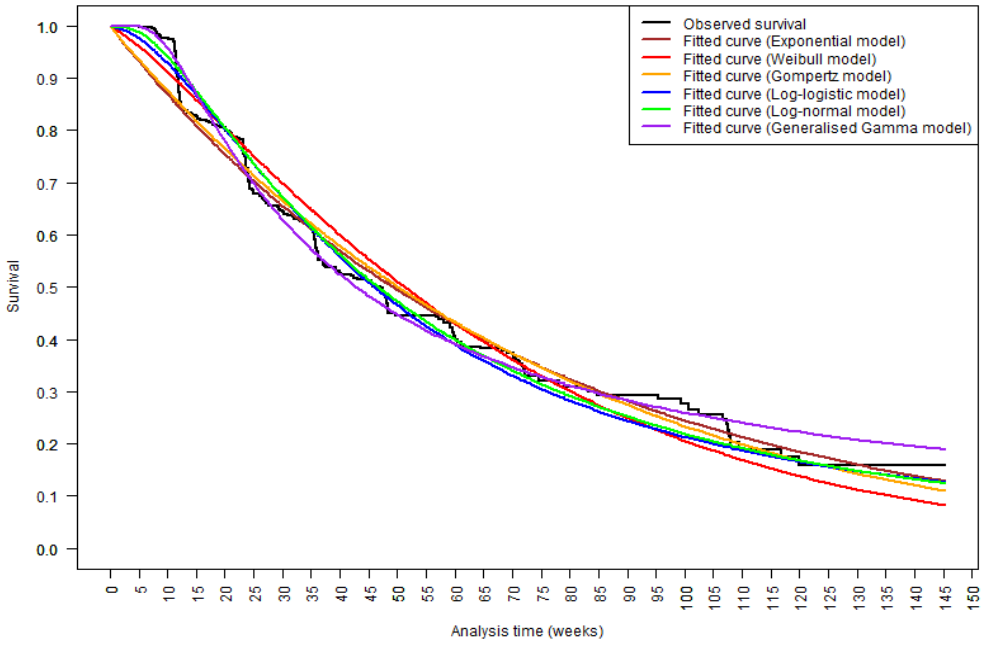
Key: ITT, intention-to-treat.

Figure 9: Log-cumulative hazard plot of investigator-assessed progression-free survival in the ITT population – rucaparib and placebo



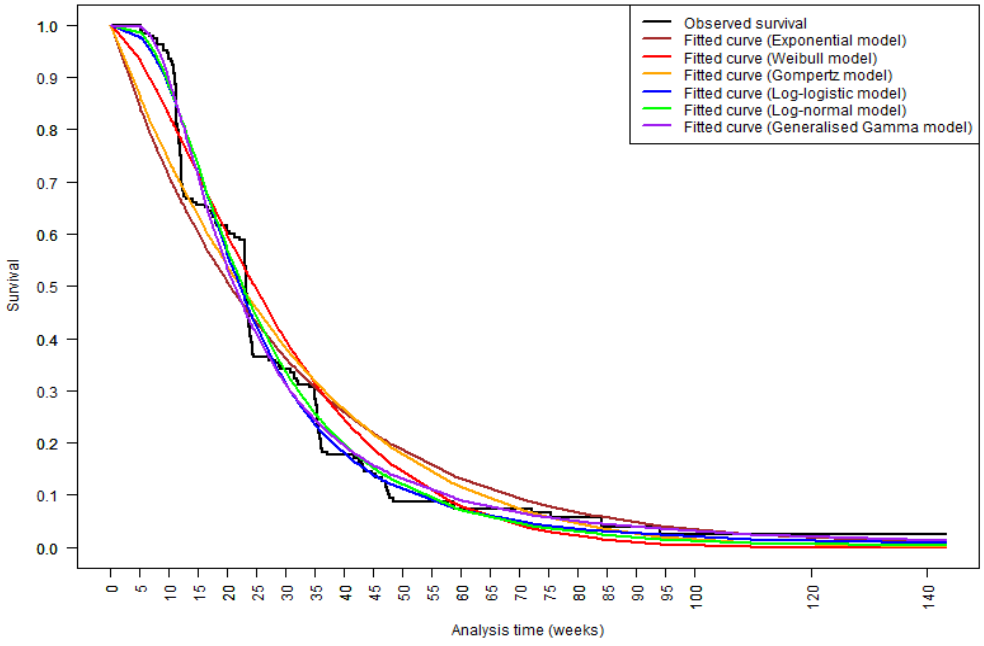
Key: ITT, intention-to-treat.

Figure 10: Overview of all parametric curve fits to the rucaparib investigator-assessed PFS KM data from the ARIEL3 ITT population



Key: ITT, intention-to-treat, KM, Kaplan–Meier; PFS, progression-free survival.

Figure 11: Overview of all parametric curve fits to the placebo investigator-assessed PFS KM data from the ARIEL3 ITT population



Key: ITT, intention-to-treat, KM, Kaplan–Meier; PFS, progression-free survival.

Table 36: Predicted mean and median number of weeks of investigator-assessed PFS in ARIEL3 in the ITT population – rucaparib and placebo

Treatment arm and extrapolation		Observed median	Predicted	
			Median	Mean
Rucaparib	Exponential	47.14	49.22	71.01
	Weibull		51.25	64.46
	Gompertz		50.16	67.13
	Log-logistic		46.00	89.94
	Log-normal		46.67	75.76
	Generalised gamma		42.83	Not estimable
Placebo	Exponential	23.29	20.56	29.66
	Weibull		24.70	28.76
	Gompertz		22.32	28.77
	Log-logistic		22.18	28.87
	Log-normal		22.67	28.37
	Generalised gamma		21.31	30.71
Key: ITT, intention-to-treat; PFS, progression-free survival.				

Table 37: Statistical fit of all investigator-assessed PFS parametric curve fits within ITT population – rucaparib and placebo

	AIC	BIC
Placebo		
Exponential	458.10	461.34
Weibull	422.99	429.48
Gompertz	455.23	461.71
Log-logistic	379.85	386.33
Log-normal	377.07	383.56
Generalised gamma	371.05	380.78
Rucaparib		
Exponential	901.5	905.5
Weibull	889.4	897.3
Gompertz	902.8	910.7
Log-logistic	864.2	872.0
Log-normal	850.2	858.1
Generalised gamma	836.7	848.5

The statistical fit of the parametric curves shown in Table 37 indicates that the log-normal and generalised gamma curves best fitted the data. Two leading UK clinical experts confirmed the log-normal curve had the most clinically plausible fit; as such this was selected as the base curve for the model. The second and third best-fitting curves (generalised gamma and log-logistic) were tested in scenario analyses, the results of which are presented in section B.3.8.

BRCA 3L+ population

Figure 6 shows the KM curves for investigator-assessed PFS in the ARIEL3 trial, displaying both active treatment and placebo arms in the BRCA 3L+ population. Proportional hazards were tested in a log-cumulative hazard plot, shown in Figure 13. Separate models were fitted by arm; an overview of all curve fits is shown in Figure 14 and Figure 15. Table 38 presents the observed median investigator-assessed PFS in weeks from ARIEL3, in addition to the median and mean as predicted by each fitted parametric survival model. Table 39 presents the AIC and BIC.

Figure 1: Kaplan-Meier investigator-assessed progression-free survival estimate in the 3L+ BRCA population in ARIEL 3 – rucaparib and placebo

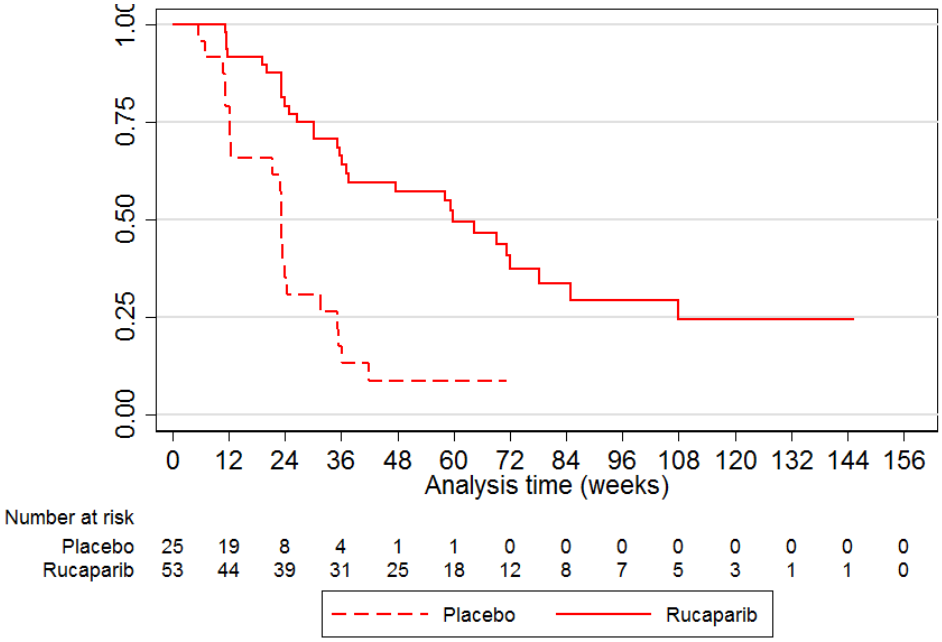


Figure 13: Log-cumulative hazard plot of investigator-assessed progression-free survival in the BRCA 3L+ population in ARIEL3 – rucaparib and placebo

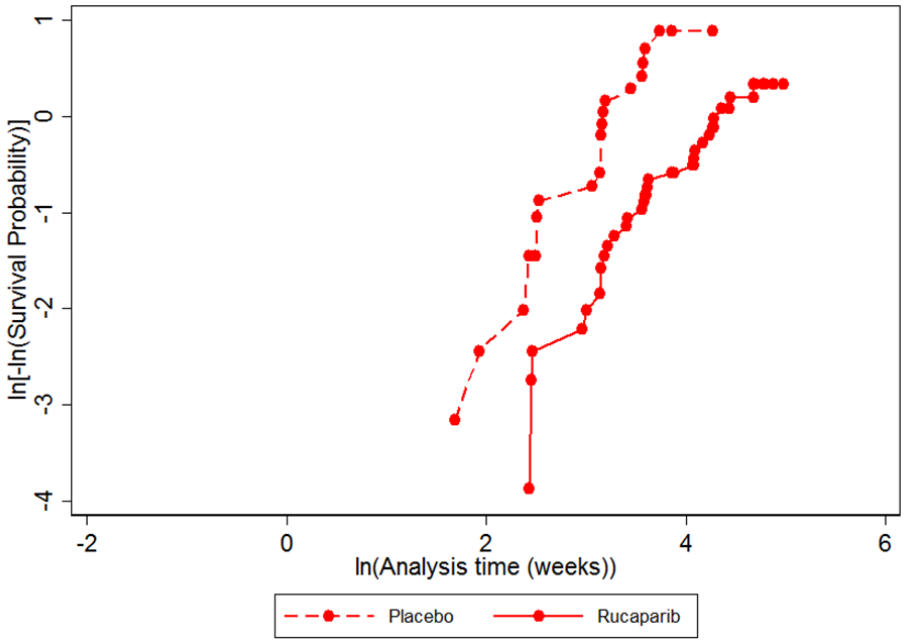
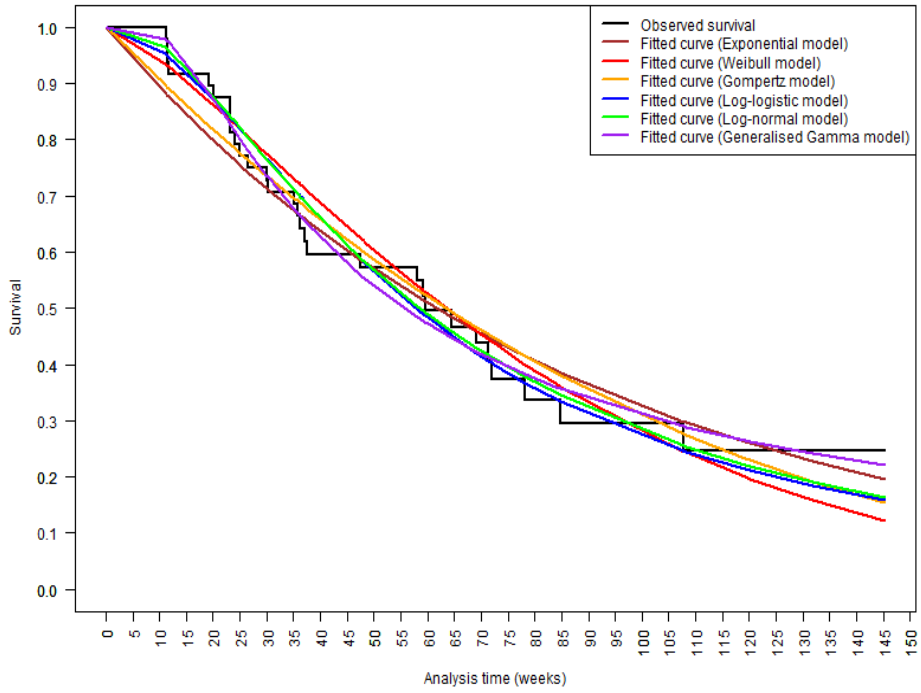


Figure 14: Overview of all parametric curve fits to the rucaparib investigator-assessed PFS KM data from the ARIEL3 3L+ BRCA population



Key: 3L+, third- or later-line; BRCA, breast cancer gene; KM, Kaplan–Meier; PFS, progression-free survival.

Figure 15: Overview of all parametric curve fits to the placebo investigator-assessed PFS KM data from the ARIEL3 3L+ BRCA population

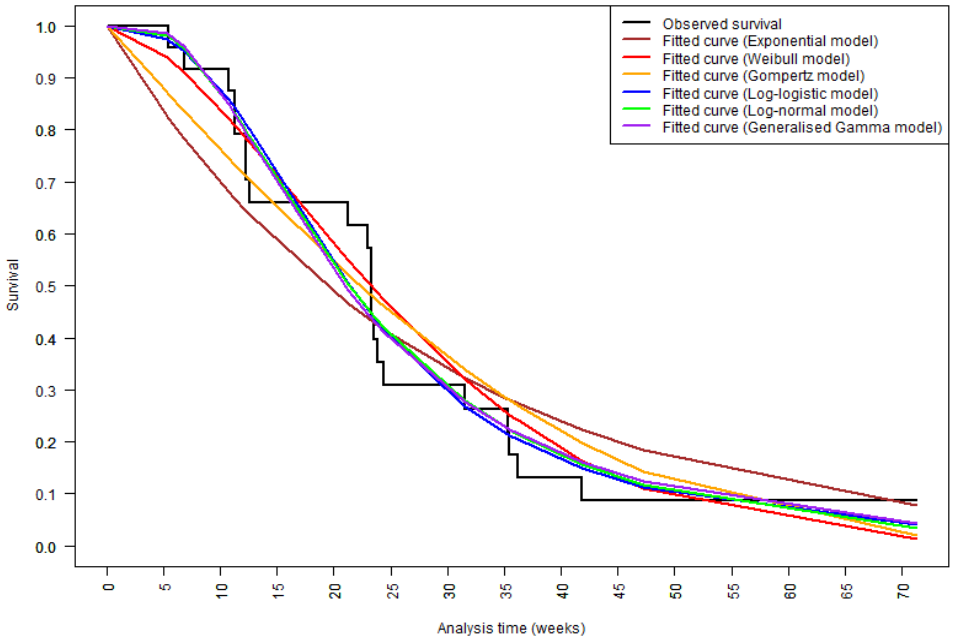


Table 38: Predicted mean and median number of weeks of investigator-assessed PFS in ARIEL3 in the 3L+ BRCA population – rucaparib and placebo

Treatment arm and extrapolation		Observed median	Predicted	
			Median	Mean
Rucaparib	Exponential	59.71	61.75	89.08
	Weibull		63.51	76.71
	Gompertz		63.49	78.75
	Log-logistic		57.87	102.11
	Log-normal		58.66	90.07
	Generalised gamma		55.59	613.21
Placebo	Exponential	23.29	19.31	27.86
	Weibull		23.28	26.07
	Gompertz		22.34	25.79
	Log-logistic		21.46	27.68
	Log-normal		21.37	26.66
	Generalised gamma		20.98	27.28
Key: BRCA, breast cancer gene; ITT, intention-to-treat; PFS, progression-free survival.				

Table 39: Statistical fit of all investigator-assessed PFS parametric curve fits within BRCA 3L+ population – rucaparib and placebo

	AIC	BIC

Placebo		
Exponential	60.83	62.05
Weibull	55.94	58.38
Gompertz	60.60	63.04
Log-logistic	52.36	54.80
Log-normal	52.35	54.79
Generalised gamma	54.25	57.90
Rucaparib		
Exponential	119.05	121.02
Weibull	117.68	121.62
Gompertz	120.61	124.55
Log-logistic	114.17	118.11
Log-normal	112.60	116.54
Generalised gamma	112.97	118.88
Key: 3L+, third- or later-line; AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intention-to-treat, PFS, progression-free survival; BRCA, breast cancer gene; PFS, progression-free survival.		

The statistical fit of the parametric curves shown in Table 39 indicates that the log-normal and generalised gamma curves best fitted the data. A leading UK clinical expert confirmed the log-normal curve had the most clinically plausible fit; as such this was selected as the base curve for the model. The second and third best-fitting curves (generalised gamma and log-logistic) were tested in scenario analyses, the results of which are presented in Section B.3.8.

As stated earlier in this section and described in Section B.2.9, the comparisons to olaparib showed no conclusive evidence on the direction of effect between the treatments. As such, the base case comparison to olaparib assumes equivalence of PFS, using ARIEL3 PFS to represent both treatments, which was validated with two UK clinical experts, who noted they would not expect the treatments to differ in terms of efficacy. This assumption is extensively tested in scenario analysis, the details of which are presented in Table 40, with results presented in Section B.3.8. Notably, the HRs presented are the inverse of those presented in Section B.2.9, due to the method of application within the model. One of the scenarios tests PFS equivalence using Study 19, using pseudo-IPD from published data. The process of fitting parametric curves to these data is described in Appendix M.1.

Table 40: PFS comparison scenarios (olaparib versus rucaparib)

Scenario	Equivalence?	HR (CI)	Source within document

Olaparib PFS predicted by NMA	No	0.85 (0.38, 1.89)	B.2.9
Olaparib PFS predicted by MAIC (Study 19)	No	0.49 (0.17, 1.46)	B.2.9
Olaparib PFS predicted by MAIC (SOLO2)	No	1.23 (0.55, 2.74)	B.2.9
Olaparib PFS predicted by MAIC (pooled analysis)	No	0.89 (0.47, 1.71)	B.2.9
PFS based on olaparib Study 19 curve	Yes	N/A	Appendix M
Key: CI, confidence interval; HR, hazard ratio; MAIC, matched-adjusted indirect comparison; N/A, not applicable; NMA, network meta-analysis; PFS, progression-free survival			

Time to treatment discontinuation

Three approaches for modelling time on maintenance treatment were incorporated in the *de novo* cost-effectiveness model, based on the availability of data for rucaparib and olaparib. Information about time on maintenance with rucaparib was available directly from ARIEL3 and is available in the *de novo* cost-effectiveness model as a time to discontinuation or death (TTDD) KM curve with parametric models fitted. This is used as the base case approach for the ITT population. TTDD data for olaparib in the form of a KM curve and/or parametric models were not available; as such, two alternative approaches are included in the model for a fair comparison with olaparib in the BRCA 3L+ population. The proportion of patients discontinuing treatment due to AEs was available to derive constant discontinuation rates for olaparib and rucaparib; this approach is used as the base case in the BRCA 3L+ population. Additionally, a third option tested in scenario analysis only assumes that patients receive maintenance treatment until progression, upon which treatment is discontinued. As routine surveillance is not considered an active treatment option and has no associated treatment cost (see Section B.3.5), discontinuation from routine surveillance is not considered in the model. The three options for modelling discontinuation are summarised in Table 41:

Table 41: Options for modelling TTDD within the model

Approach to time on treatment	Intervention(s) for which approach is an option	Source(s)
TTDD curve	Rucaparib	ARIEL3[38]
Constant rate based on discontinuation due to AEs	Rucaparib	ARIEL3[38]
	Olaparib (BRCA 3L+ only)	Study 19[33]
Treatment until progression	Rucaparib	ARIEL3[38]
	Olaparib (BRCA 3L+ only)	Study 19[33]

Approach to time on treatment	Intervention(s) for which approach is an option	Source(s)
Key: AE, adverse event; BRCA, breast cancer gene; TTDD, Time to discontinuation or death.		

ARIEL3 TTDD curve

ITT 2L+ population

Figure 16 shows the KM curve for TTDD in the ARIEL3 trial, displaying both active treatment and placebo arms in the ITT 2L+ population. Proportional hazards were tested in a log-cumulative hazard plot, shown in Figure 17. Curves were fitted to the rucaparib arm only, as described above. An overview of all curve fits is presented in Figure 18. Table 42 presents the observed median TTDD in weeks from ARIEL3, in addition to the median and mean as predicted by each fitted parametric survival model. Table 43 presents the AIC and BIC.

Figure 16: Kaplan–Meier time to discontinuation or death estimate in the intention-to-treat population – rucaparib and placebo

Figure 17: Log-cumulative hazard plot of time to discontinuation or death in the intention-to-treat population – rucaparib and placebo

Figure 18: Overview of all parametric curve fits to the rucaparib time to discontinuation or death KM data from the ARIEL3 intention-to-treat population

Table 42: Predicted mean and median number of weeks of time to discontinuation or death in ARIEL3 in the intention-to-treat population - rucaparib

Model	Observed Median (weeks)	Predicted Median (weeks)	Predicted Mean (weeks)
Exponential			
Weibull			
Gompertz			
Log-logistic			
Log-normal			
Generalised gamma			

Table 43: Statistical fit of all time to discontinuation or death parametric curve fits within intention-to-treat population - rucaparib

Model	AIC	BIC
Exponential	1104.70	1108.63
Weibull	1105.88	1113.73
Gompertz	1104.10	1111.96
Log-logistic	1082.63	1090.49
Log-normal	1096.30	1104.16
Generalised gamma	1091.71	1103.49

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; ITT, intention-to-treat, PFS, progression-free survival; BRCA, breast cancer gene; PFS, progression-free survival.

The statistical fit of the parametric curves in Table 43 indicates that the log-logistic and generalised gamma curves best fitted the data. A leading UK clinical expert confirmed the log-logistic curve had the most clinically plausible fit; as such this was selected as the base curve for the model. Generalised gamma was tested in a scenario analysis, the results of which are presented in section B.3.8.

BRCA 3L+ population

Figure 19 shows the KM curve for TTDD in the ARIEL3 trial, displaying both active treatment and placebo arms in the ITT 2L+ population. The rucaparib hazards were tested in a log-cumulative hazard plot, shown in Figure 20. Curves were fitted to the rucaparib arm only, as described above. An overview of all curve fits is presented in Figure 21. Table 44 presents the AIC and BIC for each fitted curve, the observed median TTDD within the ARIEL3 BRCA 3L+ population, in addition to the median and mean TTDD as predicted by each fitted parametric survival model.

Figure 19: Kaplan–Meier time to discontinuation or death estimate in the BRCA 3L+ population – rucaparib and placebo

Figure 20: Log-cumulative hazard plot of time to discontinuation or death in the BRCA 3L+ population – rucaparib and placebo

Figure 21: Overview of all parametric curve fits to the rucaparib time to discontinuation or death KM data from the ARIEL3 BRCA 3L+ population

Table 44: Exploratory analysis of fitting results for rucaparib time to discontinuation or death: BRCA 3L+ MTN

Model	AIC	BIC	Observed Median (weeks)	Predicted Median (weeks)	Predicted Mean (weeks)
Exponential	167.59	169.56	[redacted]	[redacted]	[redacted]
Weibull	169.32	173.27		[redacted]	[redacted]
Gompertz	169.31	173.25		[redacted]	[redacted]
Log-logistic	171.00	174.94		[redacted]	[redacted]
Log-normal	175.92	179.86		[redacted]	[redacted]
Generalised gamma	171.29	177.20		[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; MTN, maintenance; OS, overall survival

The AIC and BIC information presented in Table 44 indicate that the exponential and Weibull curves have the best statistical fit to the data, and the exponential and Gompertz curves best predict the median TTDD. Therefore, the exponential curve was selected for use in scenario analysis.

Constant discontinuation rates

In the base case for the BRCA 3L+ population, constant rates for olaparib and rucaparib were used based on discontinuation due to AEs. The proportion of patients discontinuing due to AEs reported in each corresponding trial was used to calculate a constant rate over the duration of exposure to treatment, and subsequently a cycle probability of discontinuation using the exponential formula, given in Equation 1.

Equation 1: Exponential formula

With probability (P) over time (T), the instantaneous rate (r) is:

$$r = -[\ln(1 - P)]/T$$

From r, probability (p) over time period (t) is:

$$p = 1 - \exp(-r * t)$$

The proportions of discontinuing patients from ARIEL3 and Study 19 and corresponding cycle probabilities of discontinuation are presented in Table 45, and are applied to all patients in the Progression-free On maintenance model health state. Of note, the rate for olaparib in the ITT population is included, although olaparib is not a comparator within this population; this is to inform the base case OS approach, described in further detail below in this section (page 122).

Table 45: Time on treatment based on trial discontinuation rates

Intervention	Trial	Proportion of patients discontinuing due to AEs	Follow-up period (weeks)	Calculated probability of discontinuation per model cycle
ITT population				
Rucaparib	ARIEL3[38]	[redacted]	[redacted]	[redacted]
Olaparib	Study 19[33]	4.4%	64	0.31%
BRCA 3L+ population				
Rucaparib	ARIEL3[38]	[redacted]	[redacted]	[redacted]
Olaparib	Study 19[33]	6.8%	72	0.42%
Key: AE, adverse event.				

Treatment until progression

This approach assumes that patients continue active treatment until progression. As such, the approach assumes that there is no early discontinuation of maintenance due to toxicity or any other reasons. PFS curves described earlier in this section (pages 107 to 115) are used to power time to discontinuation using this approach. This approach is tested in a scenario analysis only, within Section B.3.8.

Overall survival

As described in Section B.2.6, OS data from ARIEL3 are currently too immature to produce a robust survival analysis. Although the OS data are immature, it is a critical outcome for estimating the cost effectiveness of rucaparib. Therefore, three alternative approaches for modelling OS in the economic model were considered:

1. Assuming post-progression survival (PPS) outcomes from Study 19 (ITT population)
2. Assuming equal OS to olaparib using Study 19 data (BRCA 3L+ population)
3. Using a ratio of PFS to OS, to benchmark against previous appraisals (both populations)

Using the first approach, health and cost outcomes are separated into pre-progression and post-progression. For rucaparib and routine surveillance, pre-progression outcomes come from ARIEL3 PFS data, as described earlier in this section. Post-progression outcomes are estimated from a partitioned survival model based on the mature PFS and OS curves of olaparib and placebo from Study 19. The difference between the Study 19 PFS and OS curves is used to calculate post-progression outcomes for olaparib and routine surveillance. This approach was developed to follow ERG advice from TA528.[34] Conversely, for a similar comparison to previous appraisals, a scenario analysis is presented using a ratio of PFS to OS. The approach within this submission aimed to take on board criticisms from previous appraisals by avoiding the use of a means-based model. The strengths and limitations of each approach are discussed in detail at the end of this section (page 136).

Assuming post-progression outcomes from Study 19 (ITT population)

Step 1: Calculation of pre-progression outcomes

Pre-progression outcomes were calculated within a partitioned survival model using ARIEL3 PFS and time on treatment data for rucaparib and placebo. PFS and time on treatment data are described earlier in this section (pages 107 to 115 and pages 115 to 122, respectively). The data were modelled separately for the rucaparib and routine surveillance arms, and pre-progression outcomes were calculated while patients remained in the Progression-free model health states. The outcomes generated within this part of the model are:

- Progression-free life years
- QALYs in Progression-free health state
- Drug acquisition and administration costs of maintenance treatment
- Monitoring costs in Progression free health state
- Management of AEs

Of note, only pre-progression outcomes of the partitioned survival model were kept; any OS assumptions do not impact the outcomes.

Step 2: Calculation of post-progression outcomes

A full partitioned survival model was produced using PFS, OS and discontinuation survival data for olaparib and placebo from Study 19. As for pre-progression outcomes, the olaparib and routine surveillance arms were modelled separately using the relevant data, with all post-progression outcomes calculated from the post-progression phase of this model. The outcome measures derived are:

- Progressed life years
- QALYs in Progressed disease health state
- Monitoring costs in Progressed health state
- Subsequent therapy costs
- One-off costs

Although mature, survival data from Study 19 were incomplete. Therefore, parametric curves were fit to the PFS and OS data. The data and associated curve fitting process are described in turn, below.

ITT population: PFS curve fits

Figure 22 shows the KM curves for investigator-assessed PFS in the Study 19 trial, displaying both active treatment and placebo arms in the ITT population. Proportional hazards were tested in a log-cumulative hazard plot, shown in Figure 23. Separate curves were fit to the olaparib and placebo arms, and resulting curve fits for olaparib and placebo are presented in Figure 24 and Figure 25, respectively.

Figure 22: Kaplan–Meier investigator-assessed progression-free survival estimate in the ITT population from Study 19 – olaparib and placebo

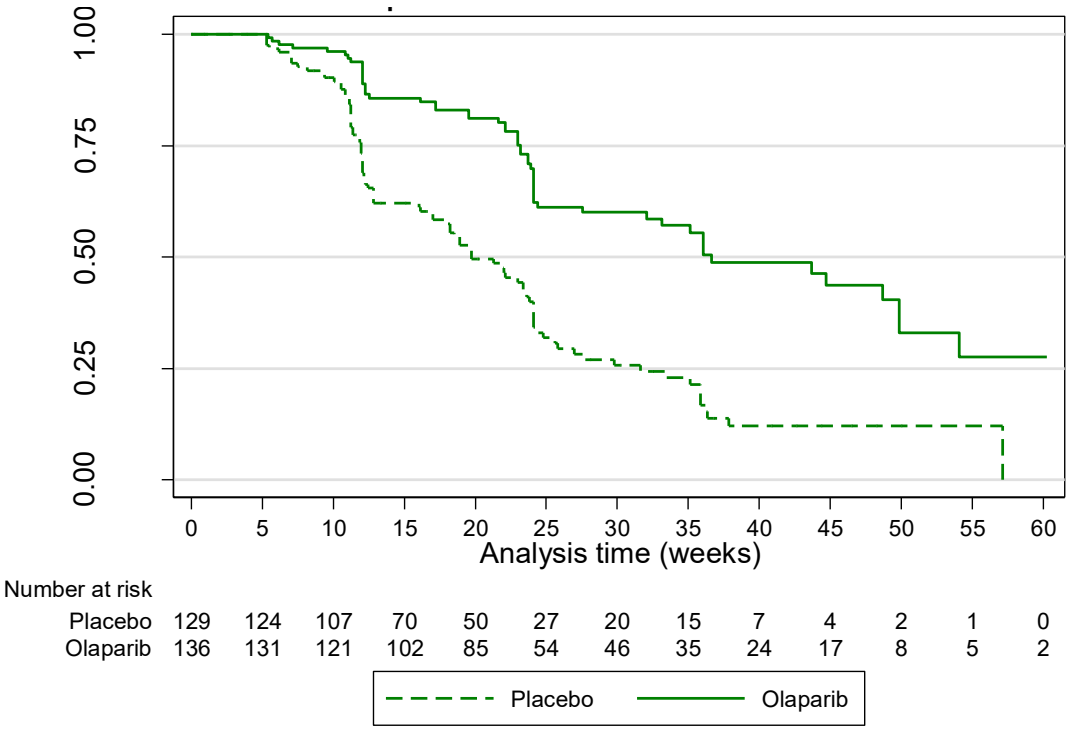


Figure 23: Log-cumulative hazard plot of investigator-assessed progression-free survival in the ITT population from Study 19 – olaparib and placebo

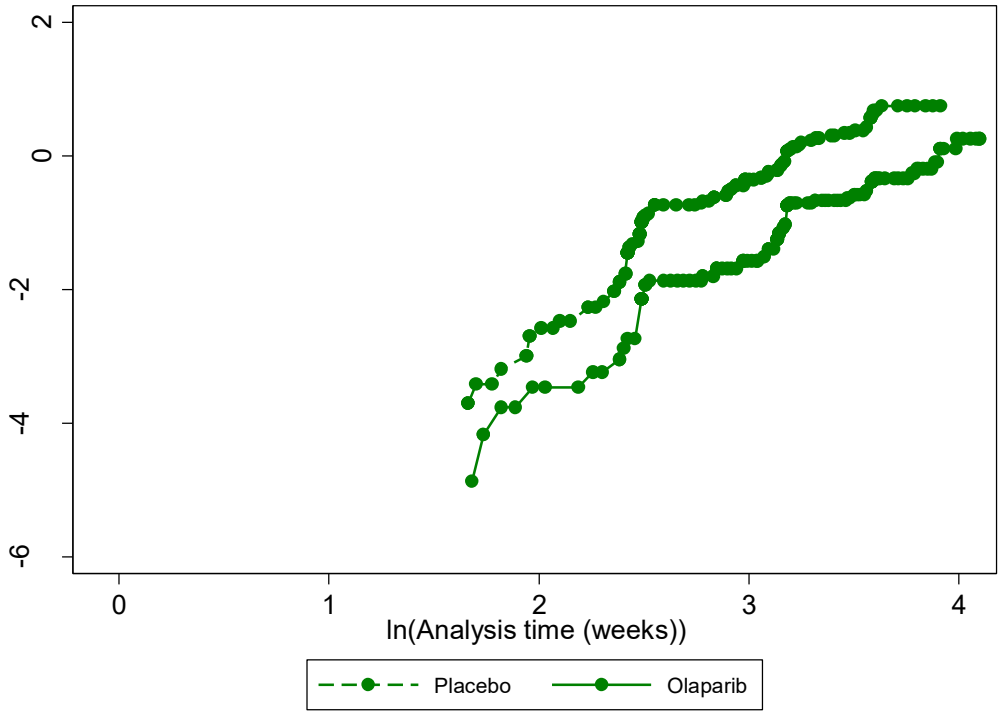


Figure 24: Overview of all parametric curve fits to the olaparib investigator-assessed PFS KM data from the Study 19 ITT population

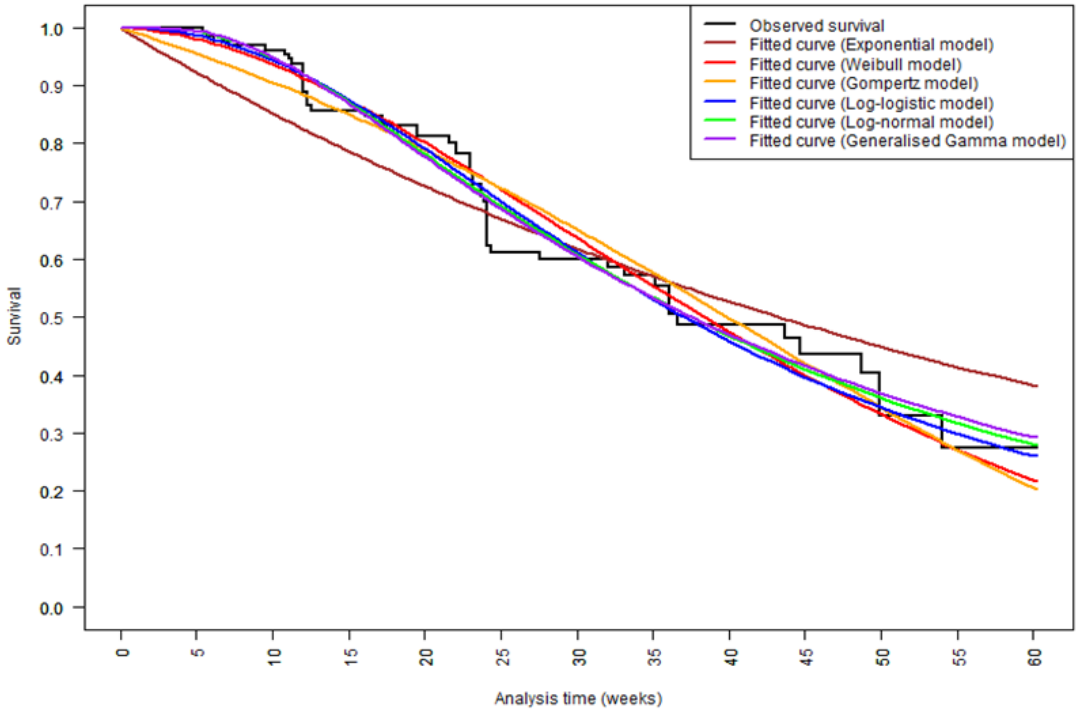


Figure 25: Overview of all parametric curve fits to the placebo investigator-assessed PFS KM data from the Study 19 ITT population

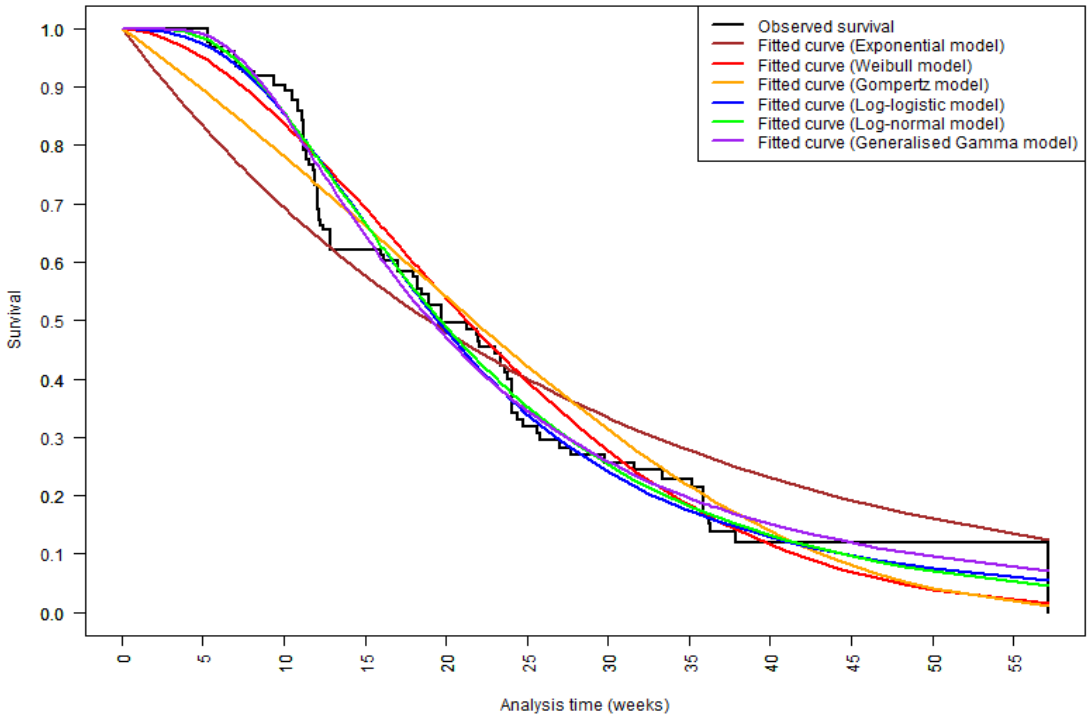


Table 46: Predicted mean and median number of weeks of PFS in the Study 19 ITT population – olaparib and placebo

Treatment arm and extrapolation		Observed median	Predicted	
			Median	Mean
Olaparib	Exponential	36.64	43.32	62.49
	Weibull		38.37	42.11
	Gompertz		39.94	40.35
	Log-logistic		37.06	54.29
	Log-normal		37.50	51.98
	Generalised gamma		37.56	56.55
Placebo	Exponential	19.72	18.92	27.29
	Weibull		21.29	23.21
	Gompertz		21.69	23.04
	Log-logistic		19.47	24.88
	Log-normal		19.66	24.07
	Generalised gamma		19.05	26.06
Key: ITT, intention-to-treat; PFS, progression-free survival.				

Table 47: Statistical fit of all PFS parametric curve fits within the Study 19 ITT population – olaparib and placebo

Model	AIC	BIC
Placebo		
Exponential	521.34	528.50
Weibull	462.64	473.38
Gompertz	491.51	502.25
Log-logistic	450.58	461.32
Log-normal	446.52	457.25
Generalised gamma	448.40	462.72
Olaparib		
Exponential	242.16	245.08
Weibull	223.06	228.89
Gompertz	231.93	237.75
Log-logistic	220.21	226.03
Log-normal	218.25	224.07
Generalised gamma	220.13	228.87

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; ITT, intention-to-treat; PFS, progression-free survival.

The statistical fit of the parametric curves shown in Table 47 indicates that the log-normal and generalised gamma curves best fitted the data. A leading UK clinical expert confirmed the log-normal curve had the most clinically plausible fit; as such this was selected as the base curve for the model. While the impact of PFS distribution choice is not explored within a scenario analysis, the wider assumptions of this OS approach are explored in section B.3.8.

ITT population: OS curve fits

Figure 26 shows the KM curve for investigator-assessed PFS in the Study 19 trial, displaying both active treatment and placebo arms in the ITT population. Proportional hazards were tested in a log-cumulative hazard plot, presented in Figure 27, and suggest a clear change in the hazard of olaparib over time, unlikely to be captured within standard parametric curves. As such, consistent with ERG preferences from the ongoing olaparib appraisal (ID1296), a 1-knot spline model has been chosen as the base case approach, using reconstructed individual patient OS data from Study 19 and using the Royston-Parmar method as per DSU guidance from TSD 14.[81] Additionally, standard parametric curves were fitted to the data for

use in scenario analyses. Table 48 presents the observed median OS from Study 19 in weeks, in addition to the median and mean as predicted by each fitted standard parametric survival model. Table 49 presents the AIC and BIC.

Figure 26: Kaplan–Meier overall survival estimate in the ITT population from Study 19 – olaparib and placebo

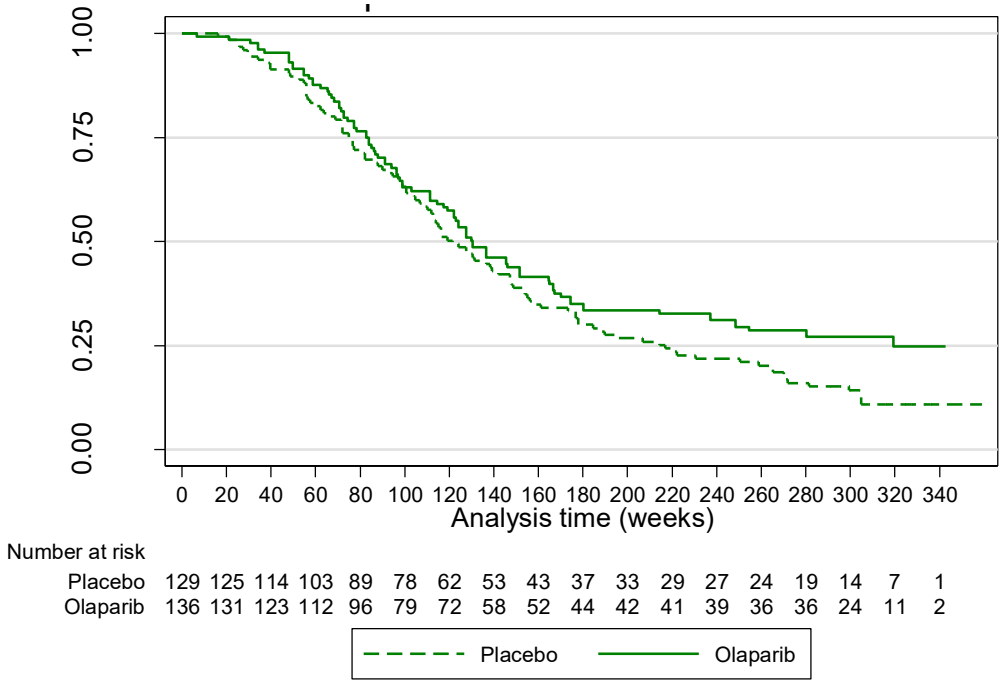


Figure 27: Log-cumulative hazard plot of overall survival in the Study 19 ITT population – olaparib and placebo

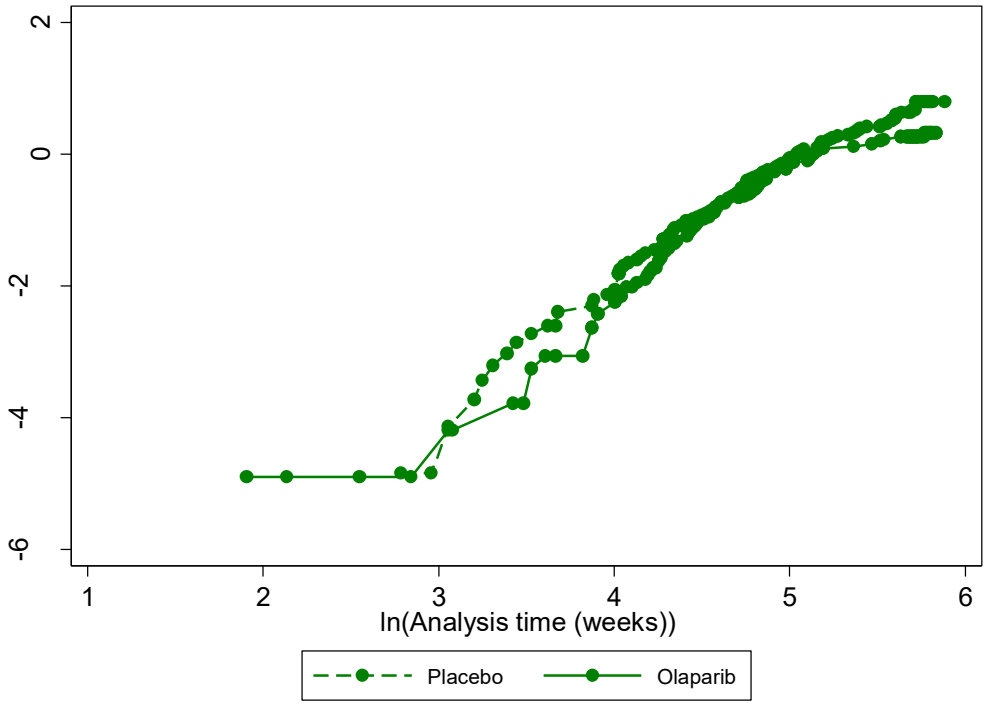


Table 48: Predicted mean and median number of weeks of overall survival in Study 19 ITT population

Treatment arm and extrapolation		Observed median	Predicted	
			Median	Mean
Olaparib	Exponential	130.22	159.02	229.42
	Weibull		168.44	207.43
	Gompertz		160.63	222.51
	Log-logistic		148.98	253.13
	Log-normal		154.88	237.39
	Generalised gamma		151.83	270.79
Placebo	Exponential	120.98	118.54	171.02
	Weibull		138.66	160.58
	Gompertz		136.67	157.91
	Log-logistic		125.80	181.52
	Log-normal		125.82	171.09
	Generalised gamma		125.57	171.67
Key: ITT, intention-to-treat.				

Table 49: Statistical fit of all OS parametric curve fits within Study 19 ITT population – olaparib and placebo

	AIC	BIC
Placebo		
Exponential	327.03	329.89
Weibull	307.09	312.81
Gompertz	320.29	326.01
Log-logistic	296.76	302.48
Log-normal	295.88	301.60
Generalised gamma	297.87	306.45
Olaparib		
Exponential	344.50	347.41
Weibull	338.80	344.62
Gompertz	346.43	352.26
Log-logistic	321.12	326.95
Log-normal	321.13	326.95
Generalised gamma	321.94	330.68

The predicted medians within Table 48 demonstrate that all standard parametric curves over-predict the median survival time of olaparib, further signalling the need for a more flexible modelling approach. Of the standard curve fits, Table 49 indicates that the statistical fit of the log-logistic and Weibull curves best fitted the data. As such, these curves were selected for scenario analysis. The KM data and distributions used in the model (1-knot spline, log-logistic, Weibull) are shown for olaparib and placebo in Figure 28 and Figure 29, respectively.

Figure 28: Overview of parametric curve fits (1-knot spline, log-logistic, Weibull) to olaparib overall survival KM data from the Study 19 ITT population

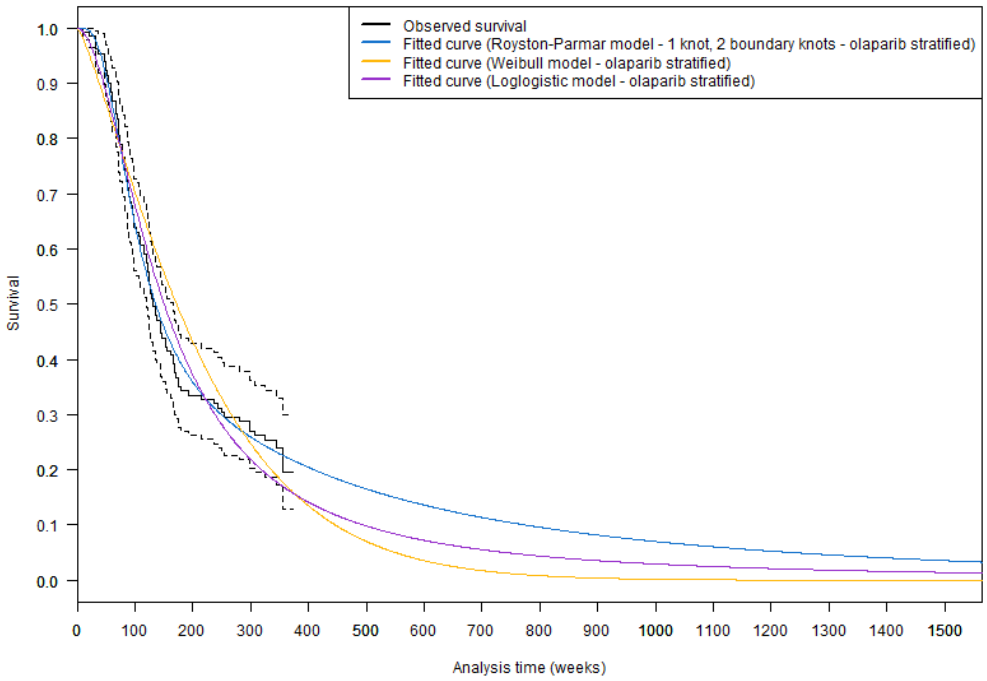
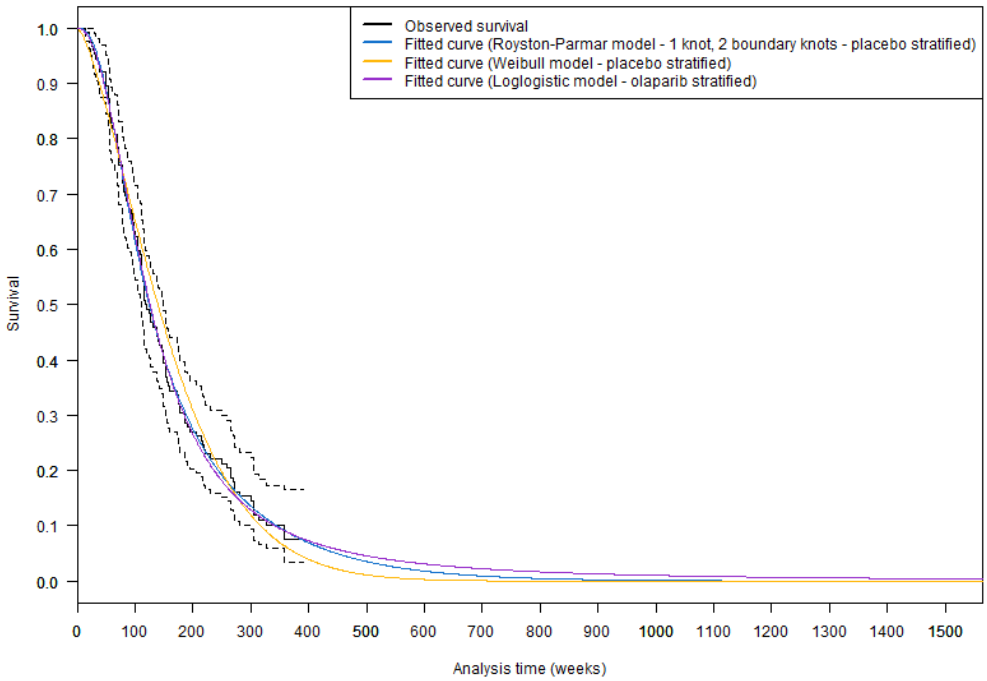


Figure 29: Overview of parametric curve fits (1-knot spline, log-logistic, Weibull) to placebo overall survival KM data from the Study 19 ITT population



Note: within this portion of the model, subsequent therapy costs were sourced from ARIEL3 data as described in Section B.3.5. The potential impact of this is discussed

below. TTD was set to constant discontinuation and was based on Study 19 numbers for olaparib, as described earlier in this section (page 120 to page 121).

Step 3: Calculation of overall outcomes

The pre-progression outcomes from Step 1 and the post-progression outcomes from Step 2 are tabulated and combined to obtain overall outcomes for active treatment and routine surveillance.

Assuming equal overall survival to olaparib using Study 19 data (BRCA 3L+ population)

Figure 30 shows the KM curve for OS in Study 19, displaying both the olaparib and placebo arms in the BRCA 3L+ population. Proportional hazards were tested in a log-cumulative hazard plot, shown in Figure 31, and indicate no step-change in the hazard for olaparib over time. An overview of all curve fits is presented in Figure 32. Table 50 presents the observed median investigator-assessed PFS for olaparib in weeks from Study 19, in addition to the median and mean as predicted by each parametric model. Table 51 presents the AIC and BIC.

Figure 30: Kaplan-Meier investigator-assessed overall survival estimate in the 3L+ BRCA population in Study 19 – olaparib and placebo

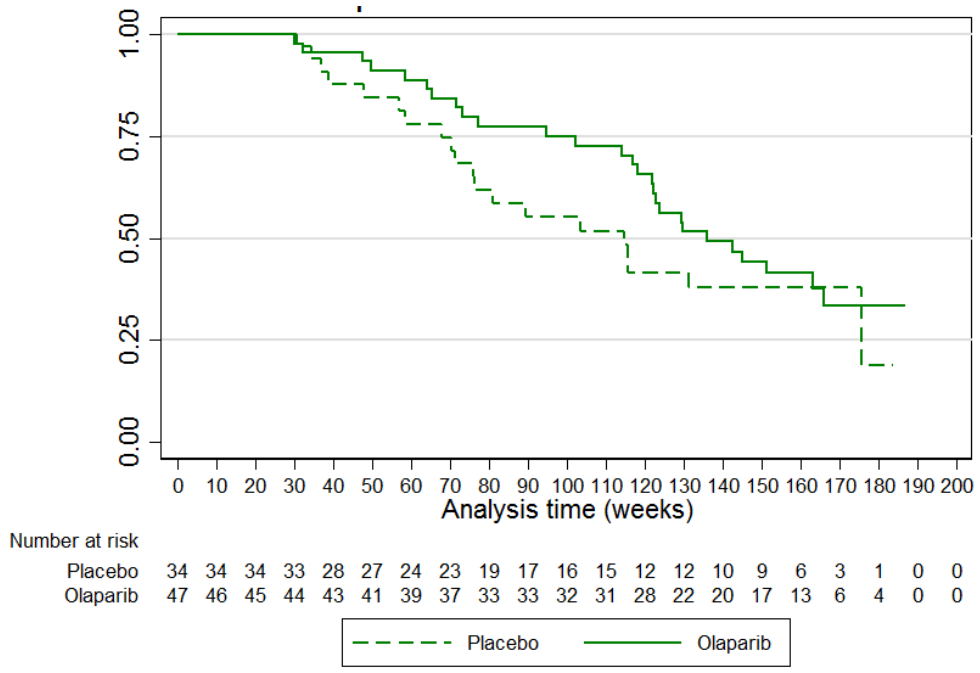


Figure 31: Log-cumulative hazard plot of investigator-assessed overall survival in the BRCA 3L+ population in Study 19 – olaparib and placebo

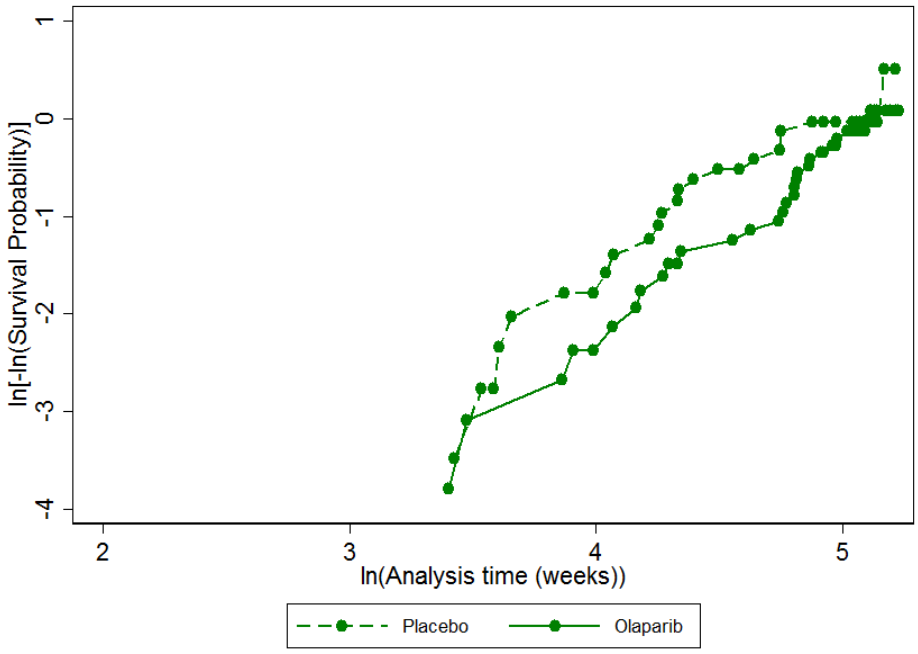


Figure 32: Overview of all parametric curve fits to the olaparib overall survival data from the Study 19 BRCA 3L+ population

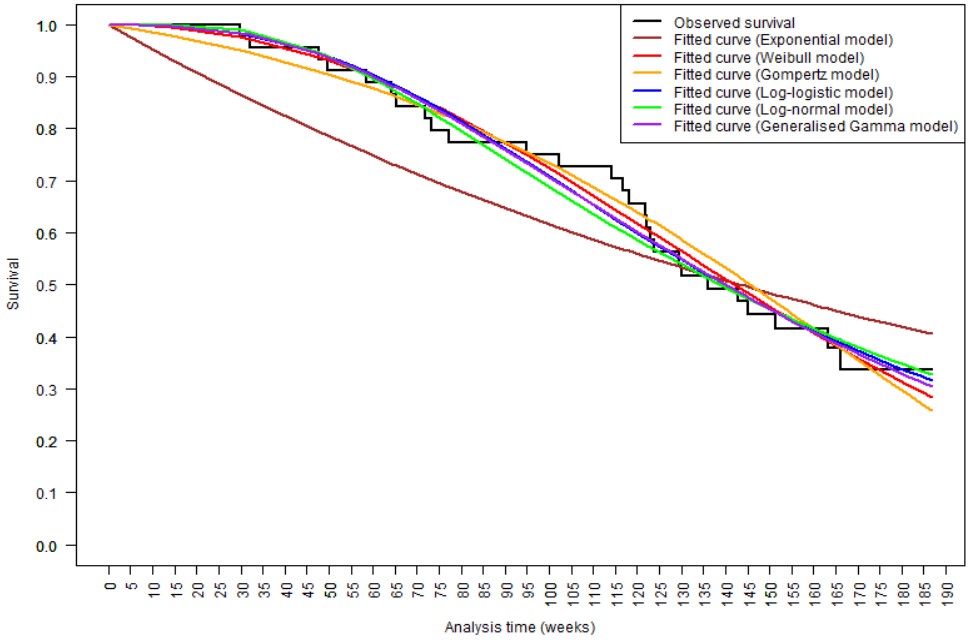


Table 50: Predicted mean and median number of weeks of overall survival in Study 19 BRCA 3L+ population – olaparib

Treatment arm and extrapolation		Observed median (weeks)	Predicted	
			Median	Mean
Olaparib	Exponential	136.11	143.39	206.88
	Weibull		142.07	148.93
	Gompertz		145.51	141.28
	Log-logistic		139.78	178.64
	Log-normal		138.80	173.18
	Generalised gamma		140.09	157.09
Key: 3L+, three or more prior lines; BRCA, breast cancer gene; PFS, progression-free survival.				

Table 51: Statistical fit of all overall survival parametric curve fits within Study 19 BRCA 3L+ population – olaparib

	AIC	BIC
Exponential	99.00	100.85
Weibull	85.21	88.91
Gompertz	87.99	91.69
Log-logistic	85.19	88.89
Log-normal	85.28	88.98
Generalised gamma	86.90	92.45

Using a PFS:OS ratio

For consistency and benchmarking with previous appraisals, a second OS approach is included as a scenario analysis, in which the incremental OS gains for rucaparib and olaparib versus routine surveillance were assumed to be proportional to the incremental mean PFS gains. This is broadly based on and can be considered an extension of concepts used in TA528[34]. The OS of rucaparib and olaparib were modelled based on mature OS data for the routine surveillance arm in Study 19. The ratio of the mean PFS gain, of rucaparib/olaparib versus placebo, to the mean OS gain versus placebo, is a user modifiable input. Based on feedback from NICE, both a conservative 1:1 ratio and 1:2 ratio were tested. Further details of implementation are provided below.

The calculation of OS curves for each active treatment involved the following steps:

1. The PFS for rucaparib, olaparib and routine surveillance were predicted by PFS curves as described earlier within this section (pages 107-115).
2. For rucaparib and olaparib, the mean PFS benefit versus routine surveillance was calculated as the difference in undiscounted mean progression-free life years.
3. The mean OS gain between rucaparib or olaparib vs routine surveillance was calculated by multiplying the mean progression-free life year difference using a ratio, assumed to be equal to 1 such that mean OS gain is equal to mean PFS gain.
4. The mean OS gain was then added to the undiscounted mean life year estimates for routine surveillance (based on mature Study 19 OS data).
5. The parametric curve for OS routine surveillance was selected as described above (pages 128-132).
6. A calibration step was undertaken. Under the assumption of proportionality of hazards between rucaparib/olaparib and routine surveillance, the OS of active treatments and routine surveillance was assumed to be related via a hazard ratio (HR):

$$OS_{active\ treatment} = (OS_{routine\ surveillance})^{HR}$$

7. Using the goal-seek function in Excel, the calibration method identifies a hazard ratio such that, when applied to routine surveillance OS from Study 19, the resulting estimated mean total LY for active treatment was equal to the one calculated in Step 4. Note that by estimating a HR, a full parametric OS curve was estimated, allowing accrual of costs and benefits as well as discounting appropriately.

Table 52 summarises the input requirements for this approach to OS.

Table 52. Inputs for the calculation of OS using the mean PFS difference between routine surveillance and rucaparib

Element	Rucaparib	Olaparib	Routine surveillance
PFS	Parametric models from ARIEL3 investigator-assessed PFS	Applying HR (NMA) on rucaparib parametric models	Applying HR on rucaparib parametric models or parametric models from ARIEL3 investigator-assessed PFS
OS	Calculated	Calculated	Parametric models from Study 19 OS
Proportionality constant	User-defined variable		NA

Strengths and limitations of the approaches to modelling OS

Assuming post-progression outcomes from Study 19

This approach has been developed to take on ERG advice from TA528 suggesting an equal risk of death post-progression would be a suitable approach to OS. Using full PFS and OS curves from Study 19 was deemed to allow for the best approximation of rucaparib having equal post-progression survival to olaparib in the ITT population, without adapting to a Markovian structure.

There are some limitations to this approach. Due to difference in PFS estimates from Study 19 and ARIEL3, the discounting from the post-progression outcomes will be slightly out of line with the pre-progression outcome. However, given the absence of patient level data from Study 19, this is the nearest approximation to correct discounting possible. In addition, a limitation of the method as currently implemented is that ARIEL3 subsequent therapy data are used in the post-progression portion of the model, but Study 19 health outcomes are used. There were fewer switches to active treatment in Study 19 than in ARIEL3, and as such there is a potential disconnect between the patients used to generate costs and outcomes, which may bias the model results. Despite this, using the shares of subsequent therapies received by patients in ARIEL3 was deemed more appropriate than Study 19 when considering the cost of subsequent lines of therapy following maintenance with rucaparib.

Regarding the simpler approach in the BRCA 3L+ population, using Study 19 OS outcomes directly was deemed suitable as rucaparib and olaparib are assumed to

have equal PFS and OS. Given this assumption, the two treatments have equal post-progression outcomes without the adjustment step used for the ITT population.

PFS:OS ratio

The PFS:OS ratio method used in this submission aims to improve on similar approaches in previous submissions (TA538, ID1296). Use of full parametric survival curves avoids use of a means-based approach, thus avoiding oversimplification of costs and QALYs (notably, by taking the non-linearity of survival curves into account). The use of a PFS:OS ratio has previously been criticised, therefore this method is presented as scenario analysis only, to allow for benchmarking versus previous appraisals.

B.3.4. Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

Data from the ARIEL3 trial (15 April 2017 cut-off) were used to analyse HRQL and derive health state utilities.

The analysis population consisted of all randomised patients (the ITT population). By design, all patients in the ITT population had received two or more prior lines of platinum chemotherapy.

HRQL data were elicited in ARIEL3 using the patient-reported EQ-5D-3L questionnaire at pre-defined time points. The EQ-5D-3L, a generic preference-based measure of HRQL, is the preferred HRQL measure according to the NICE reference case.[85] Patient responses to EQ-5D-3L questionnaires were collected at screening, on Day 1 of every treatment cycle, at treatment discontinuation, and at the 28-day follow-up visit after treatment discontinuation. In intermediate time points, the EQ-5D-3L score is unknown.

EQ-5D-3L patient responses were converted to utility index scores using the published UK national tariff. For each visit, EQ-5D-3L index scores were summarised as means and 95% confidence intervals (CIs) (see Table 53). Results in Table 53 show that average quality of life was stable over time on treatment for all patients, and for the subset of patients who were progression free.

To calculate the decrement in utility associated with having progressed disease, a mixed-effects linear regression model was fitted using all available EQ-5D-3L measurements. A random intercept for each patient was included in the model to account for the clustering of multiple observations for each patient. The regression models were adjusted for an indicator for progression, defined as '0' if EQ-5D-3L was measured before progression, '1' if the EQ-5D-3L was measured at or after progression, and 'missing' if the EQ-5D-3L was measured after patients were censored with respect to their PFS. Under the assumption that baseline utility while progression free does not depend on treatment, treatment was not included as an explanatory variable in the model. This assumption was validated by a clinical expert in the UK. The mean utility value among progression-free ARIEL3 patients was 0.830 (95% CI 0.817 to 0.843). The regression coefficient for progression was -0.074 (95%CI -0.088 to -0.060, $p<0.0005$), which can be interpreted as the disutility due to progression relative to the mean utility of progression-free patients.

In administering and analysing the EQ-5D-3L, the approach taken to utility modelling was consistent with the NICE reference case. The analysis derived appropriate inputs for the economic model: mean utility values for both main health states (progression free and progressed disease).

Figure 33: Mean EQ-5D-3L scores and 95% confidence intervals for both treatment arms of ARIEL3 combined

Key: EQ-5D-3L, three-level EQ-5D.

Table 53: Summary of EQ-5D-3L utility scores for both treatment arms of ARIEL3 combined including all observations and observations before progression

Treatment	All patients			Progression-free patients		
Visit	N	Mean EQ-5D-3L (SD)	95% CI	N	Mean EQ-5D-3L (SD)	95% CI
Cycle 1						
Cycle 2						
Cycle 3						
Cycle 4						
Cycle 5						
Cycle 6						
Cycle 7						
Cycle 8						
Cycle 9						
Cycle 10						

Treatment	All patients			Progression-free patients		
Visit	**N**	**Mean EQ-5D-3L (SD)**	**95% CI**	**N**	**Mean EQ-5D-3L (SD)**	**95% CI**
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28 days follow up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: CI, confidence interval; EQ-5D-3L, three-level EQ-5D; N, number; SD, standard deviation.						

Mapping

No mapping between outcome measures was used. The UK tariff was applied to EQ-5D-3L data to calculate utility index scores using standardised methodology.

Health-related quality-of-life studies

Alongside the search for published cost-effectiveness studies, an SLR was conducted. The SLR identified any HRQL studies or utility data for patients with *de novo* locally advanced or metastatic OC, fallopian tube or primary peritoneal carcinomas who have platinum-sensitive disease, have had two or more prior lines of chemotherapies, and have responded to prior platinum therapy. The study selection methods and results of the HRQL review are shown in Appendix H.

All six of the clinical trials identified in the clinical evidence review reported the impact of interventions on HRQL outcomes, but one olaparib trial did not evaluate these outcomes, as the authors considered the open-label nature of the trial a source of bias.[61-63, 69, 70, 77] Reporting levels varied between publications, which limits the comparability of these results. Olaparib was shown to lead to a statistically significant improvement in quality-adjusted PFS and time without symptoms of disease or toxicity (Q)TWIST versus placebo in the BRCA population. Patients in the olaparib arm also had significantly longer quality-adjusted PFS. Overall, no publications reported a significant negative impact on patient HRQL for any maintenance therapy in platinum-sensitive advanced or metastatic OC. The only clinical study reporting EQ-5D outcomes was the NOVA trial publication, which provided EQ-5D-5L utilities (assessed with a US value set), for BRCA patients at baseline, at the end of treatment and post-progression.[42]

From the economic SLR, only one UK study, Hettle et al. 2015 was identified that reported EQ-5D-3L utility data.[77] This study mapped FACT-G and FACT-O from patients with platinum-sensitive recurrent OC to the EQ-5D-3L using an ordinary least squares algorithm. The utility results were presented for the ITT and BRCA-mutated populations at screening (mean 0.802 [standard error (SE) 0.009] versus 0.787 [0.013], respectively), at scheduled routine assessments (0.786 [0.008] versus 0.768 [0.013], respectively) and at unscheduled assessments (0.720 [0.015] versus 0.708 [0.024], respectively). Although the utilities cannot be directly compared to those from ARIEL3 data due to differences in reporting, the utilities for all patients were similar between the two studies, with descriptive measurements across all cycles of between [redacted] for the ARIEL3 trial (Table 53) and 0.82 and 0.72 for the Hettle et al. publication.[77]

No other utility values were reported, but HRQL outcomes from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 and QLQ-OV28), FACT-O, Trial Outcome Index and FOSI-8 were reported in the other studies found in the clinical evidence review.[48, 49]

Adverse reactions

Grade 3 and above AEs were considered in the economic modelling, as these are assumed to require hospitalisation and therefore pose the greatest burden to the healthcare system and patients' quality of life. AEs were initially included if they affected >5% of patients in any treatment arm in ARIEL3. The list of AEs was expanded to include 3 additional AEs: nausea & vomiting was suggested for inclusion with a UK clinical expert, and hypertension and thrombocytopenia were added for consistency with TA528.[34]

Due to the low rate of AEs in ARIEL3 (described in Section B.2.10), disutilities due to AEs (anaemia, fatigue, hypertension, increased ALT/AST, nausea, neutropenia, thrombocytopenia and vomiting) were not investigated using ARIEL3 data. Instead, disutility estimates were obtained from published literature.

The mean duration of AEs was calculated using data from ARIEL2 (11 April 2017 data-cut), thus utilising all available information relevant for the decision problem. ARIEL2 was an international, multicentre, two-part, Phase II, open-label study

assessing the safety and efficacy of rucaparib as treatment in platinum-sensitive high-grade ovarian carcinoma. It is assumed that the average length of AE episodes in ARIEL2 can be generalised to the maintenance indication (see Table 54).

Table 54: Mean duration of adverse events applied in the economic model

	Mean duration (days)	Source
Combined ALT/AST	[redacted]	ARIEL2 statistical analyses – data on file[39, 91]
Anaemia	[redacted]	
Fatigue/asthenia	[redacted]	
Neutropenia	[redacted]	
Thrombocytopenia	[redacted]	
Nausea/vomiting	[redacted]	
Hypertension	[redacted]	
Key: AST, aspartate transaminase; ALT, alanine aminotransferase.		

In the base case, AE disutilities were excluded from the economic model as health state utility values are taken from ARIEL3 and as such, it was deemed that the health-state utility values already captured any detrimental effects of AEs. AE disutilities were included within a scenario analysis to explore this assumption. The impact of this is assessed in Section B.3.8.

AE disutility impacts were applied by combining the risk of AEs while on maintenance treatment with duration of symptoms to estimate the monthly QALYs lost. The risks for rucaparib and routine surveillance were taken from ARIEL3 data, while the risks for olaparib were taken from its CHMP assessment report.[86, 92] The resulting monthly risks of each AE, by treatment, are provided in Table 55.

Table 55: Adverse event risk per month on treatment

Adverse event	Rucaparib	Olaparib	Routine surveillance
Combined ALT/AST	[redacted]	0.00%	[redacted]
Anaemia	[redacted]	0.36%	[redacted]
Fatigue/asthenia	[redacted]	0.52%	[redacted]
Neutropenia	[redacted]	0.41%	[redacted]
Thrombocytopenia	[redacted]	0.00%	[redacted]
Nausea/vomiting	[redacted]	0.31%	[redacted]
Hypertension	[redacted]	0.00%	[redacted]
Key: ALT, alanine aminotransferase; AST, aspartate transaminase. **Source:** Rucaparib and routine surveillance, ARIEL3 data[38]; olaparib, CHMP assessment report[92].			

Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of utility values used in the cost-effectiveness analysis is provided in Table 56. Health state utilities were sourced directly from the EQ-5D-3L analysis of the ARIEL3 trial. Use of ARIEL3 data for health state utilities is considered preferable as it allows for consistency with efficacy data used in the submission. AE disutilities, which were only applied within scenario analysis, and their sources are provided in Appendix M. Another scenario is tested using health state utility values from TA528; these are also described in Appendix M.

Table 56: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Progression free	[redacted]	[redacted]	Section B.3.4, page 137	Use of ARIEL3 data allows for robust estimates of utility in an appropriate patient population. Analyses also showed a consistent utility score over time for patients in the progression-free health-state.
Progressed disease	[redacted]	[redacted]	Section B.3.4, page 137	The same patient population (ARIEL3 all ITT patients) was used to derive a decrement for progressed disease. Use of ARIEL3 data allows for robust estimates of utility in an appropriate patient population, and consistency with progression-free utility.

Key: ALT, alanine aminotransferase; AST, aspartate transaminase; ITT, intention-to-treat.

The health-state utilities used in the model were similar to those identified in literature searching (Appendix H). Further clinical validation of utilities was not conducted.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

In appendix I describe how relevant cost and healthcare resource data were identified.

The SLR used to identify published cost-effectiveness studies had a secondary aim: to capture relevant cost and healthcare resource use data (see Appendix I for further details). Two studies captured cost and resource use data from a US perspective.[61, 63] However, relevant data for England were not identified. Due to the lack of relevant data in the systematic review, commonly used and accepted national UK tariffs were used to inform costing estimates in the model so that they were more applicable to clinical practice in England.

Intervention and comparators' costs and resource use

Rucaparib

The list price for rucaparib is £3,652.00 per pack of 60 tablets. Assuming a use of four tablets a day (two tablets twice daily), the total drug acquisition cost for the intervention is £7,227.89 per month. Inclusive of the submitted commercial discount, the NHS England acquisition cost for one month of rucaparib treatment is [redacted].

Comparators

As routine surveillance does not constitute any active treatment other than standard monitoring, there is no acquisition cost associated with this within the model. The list price of olaparib is £3,550.00 per pack of 448 capsules.[87] Assuming a use of 16 tablets a day (eight tablets twice daily) the total drug acquisition cost for olaparib is £3,859.04 per month.[87]

Administration costs

The administration cost of each regimen was dependent on the route of administration, according to costs provided in the NHS Schedule of Reference Costs (see Table 57).[89] While the maintenance active therapies are applied orally, numerous subsequent therapies are administered intravenously (IV). Oral therapies have an administration cost in the base case, assumed monthly. Infusion drugs are assumed to have an administration cost on each day of administration, according to the duration of administration.

Table 57. Administration costs

Item	Description	Unit Cost (£)
Initial oral administration cost	Deliver Exclusively Oral Chemotherapy	163.82
Initial infusion administration cost	Deliver simple chemotherapy at first attendance; Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle	173.99
Deliver more complex chemotherapy	Deliver simple chemotherapy at first attendance; Overall time of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle.	264.56
Deliver complex chemotherapy, including prolonged infusion treatment	Deliver complex chemotherapy at first attendance; Overall time of 60 minutes nurse time and over two hours chair time for the delivery of a complete cycle	269.86
Subsequent elements of a chemotherapy cycle	Deliver Subsequent Elements of a Chemotherapy Cycle	205.09

Subsequent therapies

The cost of subsequent therapy was applied to patients as a one-off cost upon progression. The cost was a weighted average of patients receiving a mix of regimens. Within the model, the average cost was applied to the newly progressed cohort for each intervention assessed at each model cycle. The costs are summarised in Table 58, and calculations feeding into this are described in full detail within Appendix M.2.

Table 58. One-off subsequent therapies cost by treatment arm

Treatment	Subsequent therapies cost
Active treatments (rucaparib and olaparib)	£ 5,465.52
Routine surveillance	£ 16,776.05

Health-state unit costs and resource use

The literature review did not provide suitable resource use costs for inclusion within the model structure. As such, resource use was estimated via clinical opinion, with the associated costs identified from standard NHS cost sources. The resulting per-cycle cost by health state is shown in Table 59, and full details of the process for generating these costs are provided in Appendix M.3.

Table 59: Per-cycle diagnostic and monitoring costs by health state

Health state	Total cost
Progression-free (on maintenance)	£ 284.90
Progression-free (off maintenance)	£ 74.36
Progressed disease	£ 536.67

Adverse reaction unit costs and resource use

For consistency across appraisals, adverse event management costs were taken from TA528, which in turn were based on cost categorisations from TA381.[34]. These values were taken from 2015-16 NHS reference costs. The only AE cost not sourced in this way is ALT/AST; as part of preparation for this appraisal, validation with a UK clinical expert advised that standard treatment for this AE is monitoring via a liver function test. For ALT/AST, the cost of testing was therefore sourced from 2016-17 NHS reference costs. The costs for all AEs and the associated sources are summarised in Table 60.

Table 60: List of adverse reactions and summary of costs in the economic model

Adverse event	Average cost per patient episode	Reference
Combined ALT/AST	£7.89	NHS Reference Costs 2016-2017: DAPS04 - Clinical Biochemistry - Hepatic function panel including: Albumin; Bilirubin, total; Bilirubin, direct; Phosphatase, alkaline; Protein, total; Transferase, alanine amino (ALT); Transferase, aspartate amino (AST) [89]
Anaemia	£681.92	NICE TA528, Committee Papers p. 205
Fatigue/asthenia	£353.06	NICE TA528, Committee Papers p. 205
Neutropenia	£506.47	NICE TA528, Committee Papers p. 205
Thrombocytopenia	£578.47	NICE TA528, Committee Papers p. 205
Nausea/vomiting	£471.09	NICE TA528, Committee Papers p. 205
Hypertension	£590.55	NICE TA528, Committee Papers p. 205
Key: ALT, alanine aminotransferase; AST, aspartate transaminase.		

Miscellaneous unit costs and resource use

The one-off cost of BRCA testing (£795.00), applied to all model arms in the first model cycle, was taken from costs provided by the UK Genetic Testing Network as part of the Sheffield RGC Postnatal Diagnosis Routine.[93]

The one-off cost of death (£3,692.00) was taken from the technology appraisal of niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA528).[34]

B.3.6. Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

Table 61: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
Survival parameters			
Progression-free survival – rucaparib – ARIEL 3 - ITT population – Log-normal	Intercept: 3.843 ln(sigma): -0.016	| | Intercept | Log(sigma) | | Intercept | 0.0033 | 0.0007 | | Log(sigma) | 0.0007 | 0.0024 |	Section B.3.3
Progression-free survival – routine surveillance – ARIEL 3 - ITT population – Log-normal	Intercept: 3.121 ln(sigma): -0.401	| | Intercept | Log(sigma) | | Intercept | 0.0025 | 0.0001 | | Log(sigma) | 0.0001 | 0.0031 |	
Progression-free survival – olaparib – Study 19 - ITT population – Log-normal	Intercept: 3.624 ln(sigma): -0.213	| | Intercept | Log(sigma) | | Intercept | 0.0090 | 0.0045 | | Log(sigma) | 0.0045 | 0.0099 |	
Progression-free survival – routine surveillance – Study 19 - ITT population – Log-normal	Intercept: 2.979 ln(sigma): -0.453	| | Intercept | Log(sigma) | | Intercept | 0.0038 | 0.0009 | | Log(sigma) | 0.0009 | 0.0059 |	
Progression-free survival – rucaparib – ARIEL 3 - BRCA 3L+ population – Log-normal	Intercept: 4.072 ln(sigma): -0.077	| | Intercept | Log(sigma) | | Intercept | 0.0222 | 0.0059 | | Log(sigma) | 0.0059 | 0.0186 |	
Overall survival – olaparib – Study 19 -	Beta 1: 4.181	| | Beta 1 | Beta 2 | Intercept | | Beta 1 | 0.4018 | 0.0436 | -1.5726 |	Section B.3.3

<table>
<tr><th>Variable</th><th>Value</th><th>Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models</th><th>Reference</th></tr>
<tr><td>ITT population – Royston-Parmar model</td><td>Beta 2: 0.350
Intercept: -17.800</td><td><table><tr><td>Beta 2</td><td>0.0436</td><td>0.0048</td><td>-0.1688</td></tr><tr><td>Intercept</td><td>-1.5726</td><td>-0.1688</td><td>6.1882</td></tr></table></td><td></td></tr>
<tr><td>Overall survival – routine surveillance – Study 19 – ITT population – Royston-Parmar model</td><td>Beta 1: 2.648
Beta 2: 0.237
Intercept: -12.344</td><td><table><tr><td></td><td>Beta 1</td><td>Beta 2</td><td>Intercept</td></tr><tr><td>Beta 1</td><td>0.1747</td><td>0.0305</td><td>-0.7315</td></tr><tr><td>Beta 2</td><td>0.0305</td><td>0.0057</td><td>-0.1250</td></tr><tr><td>Intercept</td><td>-0.7315</td><td>-0.1250</td><td>3.0899</td></tr></table></td><td></td></tr>
<tr><td>Overall survival – olaparib – Study 19 – BRCA 3L+ population – Log-normal</td><td>Intercept: 4.933
ln(sigma): -0.408</td><td><table><tr><td></td><td>Intercept</td><td>Log(sigma)</td></tr><tr><td>Intercept</td><td>0.0126</td><td>0.0051</td></tr><tr><td>Log(sigma)</td><td>0.0051</td><td>0.0212</td></tr></table></td><td></td></tr>
<tr><td>Time to discontinuation or death – rucaparib – ARIEL 3 - ITT population – Log-normal</td><td>Intercept: [redacted]
ln(sigma): [redacted]</td><td><table><tr><td></td><td>Intercept</td><td>Log(sigma)</td></tr><tr><td>Intercept</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Log(sigma)</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Section B.3.3</td></tr>
<tr><td colspan="4">Adverse events</td></tr>
<tr><td>ARIEL 3 – rucaparib arm - Proportion of patients discontinuing</td><td>[redacted]</td><td>[redacted]</td><td>Section B.3.3</td></tr>
<tr><td>Study 19 – olaparib arm - Proportion of patients discontinuing</td><td>6.8%</td><td>Beta(5,69)</td><td></td></tr>
<tr><td>ARIEL 3 – rucaparib arm – Follow up period (weeks)</td><td>56</td><td>Normal(56.09,11.22)</td><td></td></tr>
<tr><td>Study 19 – olaparib arm - Follow up period (weeks)</td><td>72</td><td>Normal (72.20,14.44)</td><td></td></tr>
<tr><td>Rucaparib – ARIEL 3 - patient numbers</td><td>372</td><td>-</td><td>Section B.3.3</td></tr>
<tr><td>Routine Surveillance – ARIEL 3 - patient numbers</td><td>189</td><td>-</td><td></td></tr>
<tr><td>Olaparib – Study 19 - patient numbers</td><td>136</td><td>-</td><td></td></tr>
<tr><td>Rucaparib – ARIEL 3 – average treatment duration (weeks)</td><td>[redacted]</td><td>[redacted]</td><td>Section B.3.3</td></tr>
<tr><td>Routine Surveillance – ARIEL 3 - average</td><td>27.8</td><td>Normal(27.83,5.57)</td><td></td></tr>
</table>

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
treatment duration (weeks)			
Olaparib – Study 19 - average treatment duration (weeks)	63.5	Normal(63.53,12.71)	
Rucaparib – ARIEL 3 – AE risk for combined ALT/AST	[redacted]	[redacted]	Section B.3.4
Rucaparib – ARIEL 3 – AE risk for anaemia	[redacted]	[redacted]	
Rucaparib – ARIEL 3 – AE risk for fatigue/asthenia	[redacted]	[redacted]	
Rucaparib – ARIEL 3 – AE risk for neutropenia	[redacted]	[redacted]	
Rucaparib – ARIEL 3 – AE risk for thrombocytopenia	[redacted]	[redacted]	
Rucaparib – ARIEL 3 – AE risk for nausea/vomiting	[redacted]	[redacted]	
Rucaparib – ARIEL 3 – AE risk for hypertension	[redacted]	[redacted]	
Routine surveillance – ARIEL 3 – AE risk for combined ALT/AST	[redacted]	[redacted]	Section B.3.4
Routine surveillance – ARIEL 3 – AE risk for anaemia	[redacted]	[redacted]	
Routine surveillance – ARIEL 3 – AE risk for fatigue/asthenia	[redacted]	[redacted]	
Routine surveillance – ARIEL 3 – AE risk for neutropenia	[redacted]	[redacted]	
Routine surveillance – ARIEL 3 – AE risk for thrombocytopenia	[redacted]	[redacted]	
Routine surveillance – ARIEL 3 – AE risk for nausea/vomiting	[redacted]	[redacted]	
Routine surveillance – ARIEL 3 – AE risk for hypertension	[redacted]	[redacted]	
Olaparib – STUDY 19 – AE risk for combined ALT/AST	0.00	Beta(0,189)	Section B.3.4

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
Olaparib – STUDY 19 – AE risk for anaemia	0.01	Beta(0.95,188.06)	
Olaparib – STUDY 19 – AE risk for fatigue/asthenia	0.02	Beta(3.02,185.98)	
Olaparib – STUDY 19 – AE risk for neutropenia	0.01	Beta(0.95,188.06)	
Olaparib – STUDY 19 – AE risk for thrombocytopenia	0.00	Beta(0,189)	
Olaparib – STUDY 19 – AE risk for nausea/vomiting	0.00	Beta(0,189)	
Olaparib – STUDY 19 – AE risk for hypertension	0.01	Beta(0.95,188.06)	
Duration of combined ALT/AST (days)	[redacted]	[redacted]	Section B.3.4
Duration of anaemia (days)	[redacted]	[redacted]	
Duration of fatigue/asthenia (days)	[redacted]	[redacted]	
Duration of neutropenia (days)	[redacted]	[redacted]	
Duration of thrombocytopenia (days)	[redacted]	[redacted]	
Duration of nausea/vomiting (days)	[redacted]	[redacted]	
Duration of hypertension (days)	[redacted]	[redacted]	
AE Management - unit cost: Combined ALT/AST	£600.00	gamma(25,24)	Section B.3.5
AE Management - unit cost: Anaemia	£681.92	gamma(25,27.28)	
AE Management - unit cost: Fatigue/asthenia	£353.06	gamma(25,14.12)	
AE Management - unit cost: Neutropenia	£506.47	gamma(25,20.26)	
AE Management - unit cost: Thrombocytopenia	£578.47	gamma(25,23.14)	
AE Management - unit cost: Nausea/vomiting	£471.09	gamma(25,18.84)	
AE Management - unit cost: Hypertension	£590.55	gamma(25,23.62)	
Utilities			

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
Mean health state utility value: progression-free health state	[redacted]	Normal[redacted]	Section B.3.4
Mean health state utility value: progressed disease health state	[redacted]	Normal[redacted]	
Drug acquisition costs			
Pack cost, rucaparib	£3,562	gamma(25,142.48)	Section B.3.5
Pack cost, routine surveillance	£3,550	gamma(25,142)	
Pack cost, olaparib	£0	gamma(0,0)	
Discount applied to drug acquisition cost, rucaparib	[redacted]	-	Section B.3.5
Discount applied to drug acquisition cost, olaparib	0%	-	
Administration costs			
Initial oral administration cost	£163.82	gamma(25,6.55)	Section B.3.5
Initial infusion administration cost	£173.99	gamma(25,6.96)	
Deliver more complex chemotherapy	£264.56	gamma(25,10.58)	
Deliver complex chemotherapy, including prolonged infusion treatment	£269.86	gamma(25,10.79)	
Subsequent elements of a chemotherapy cycle	£205.09	gamma(25,8.2)	
Resource use			
Progression-free (on maintenance)	£ 284.90	Individual components varied (Resource use; unit cost)	Section B.3.5, Appendix M
Progression-free (off maintenance)	£ 74.36	Individual components varied (Resource use, unit cost)	
Progressed disease	£ 536.67	Individual components varied (Resource use; unit cost)	
One-off costs			
BRCA mutation test cost	£795.00	gamma(25,31.8)	Section B.3.5
Terminal care cost	£3692.00	gamma(25,147.68)	
Subsequent treatment			
Subsequent treatment cost: Active arms	£ 5,425.70	Individual aspects varied (proportion of patients receiving treatment, treatment duration and cost)	Section B.3.5, Appendix M
Subsequent treatment cost: Routine surveillance	£ 11,719.10	Individual aspects varied (proportion of patients receiving treatment, treatment duration and cost)	

Variable	Value	Measurement of uncertainty and distribution: Distribution (CI); variance-covariance matrices reported for survival models	Reference
Key: 3L+, third- or later-line; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; BRCA, breast cancer gene; CA123, cancer antigen 125; CI, confidence interval; CT, computed tomography; ITT, intention to treat; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PARPi; poly (ADP ribose) polymerase inhibitor; PET, positron emission tomography. **Note**, for brevity, inputs with value 0 and CI (0,0) were removed from this table.			

Assumptions

The assumptions of the economic analysis and their justifications are detailed in Table 62. The modelling approach makes the best use of available data to inform the decision problem, in line with the NICE reference case and guidance on methods of appraisal. In the absence of data, assumptions were designed to minimise potential bias in the analysis. Any bias identified in these assumptions has been listed in Table 62.

Table 62: Summary of assumptions of the economic analysis

#	Assumption	Likely direction of bias	Justification
1	The economic model health states capture the elements of the disease and care pathway that are important for patient health outcomes and NHS/PSS costs.	No bias expected	Sections A.10, B.3.2
2	Placebo within ARIEL3 is reflective of routine surveillance in UK	No bias expected	Section B.2
3	Within the BRCA 3L+ population, rucaparib and olaparib can be assumed to have equivalent PFS and OS	No bias expected	Section B.3.3
4	The lower proportion partial versus complete responders at baseline in ARIEL3 versus Study 19 is not relevant to cost-effectiveness	Against rucaparib	Section B.2
5	Within the ITT population, rucaparib can be assumed have equivalent PPS as olaparib in Study 19, and routine surveillance can be assumed to have equivalent PPS as placebo in Study 19	Direction of bias unknown	Section B.3.3
6	Patients who receive treatment with a maintenance PARP inhibitor will not receive a subsequent PARP inhibitor	No bias expected	Section B.3.5
7	Subsequent therapy adjustments: • Any patients receiving a PARP inhibitor after routine surveillance would receive olaparib (and no other PARP inhibitor), for costing purposes only • Off-label use of subsequent therapies from ARIEL3 does not occur in UK practice	No bias expected	Section B.3.5
8	30 years is sufficiently long enough to capture all relevant outcomes	No bias expected	Section B.3.2
9	No waning effect for PARP inhibitors	No bias expected	Section B.3.2

#	Assumption	Likely direction of bias	Justification
10	Patient utility is affected by disease progression status only, and captured by the patient reported EQ-5D-3L data reported in ARIEL3	No bias expected	Section B.3.4
11	Baseline utility while progression free does not depend on treatment	No bias expected	Section B.3.4
12	Health state utilities capture impact of AEs on HRQL	No bias expected	Section B.3.4
14	AE durations from ARIEL2 can be generalised to maintenance indication, and are not treatment-specific	No bias expected	Section B.3.4
15	Oral therapies have an associated monthly administration cost	Against rucaparib (ITT population) / No bias expected (BRCA 3L+ population)	Section B.3.5
16	Vial sharing allowed	No bias expected	Section B.3.5
17	Relative dose intensity of rucaparib and olaparib assumed to be 100%	Against rucaparib	Section B.3.5

B.3.7. Base-case results

Base-case incremental cost-effectiveness analysis results

Table 63 and Table 64 display the cost-effectiveness results for rucaparib for the ITT population and the BRCA 3L+ population, respectively. The manufacturer has submitted a Patient Access Scheme comprising a simple commercial discount of [redacted], which is subject to approval. All results presented here are inclusive of the proposed discount.

Rucaparib is estimated to offer a high per-patient benefit in the ITT population, providing over one year of additional life and an additional [redacted] QALYs, versus routine surveillance. The estimated incremental cost-effectiveness ratio (ICER) for rucaparib is £50,429 per QALY gained. Within the BRCA 3L+ population, rucaparib is dominated by olaparib, inherent from the assumption of equal PFS and OS to olaparib.

Disaggregated cost-effectiveness results and comparison to trial outcomes are presented in Appendix J.

Table 63: Base-case results, ITT population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Routine surveillance	[redacted]	3.060	[redacted]				
Rucaparib	[redacted]	4.919	[redacted]	[redacted]	1.859	[redacted]	50,429

Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.

Table 64: Base-case results, BRCA 3L+ population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Olaparib	[redacted]	3.091	[redacted]				
Rucaparib	[redacted]	3.091	[redacted]	[redacted]	0.000	[redacted]	Rucaparib dominated

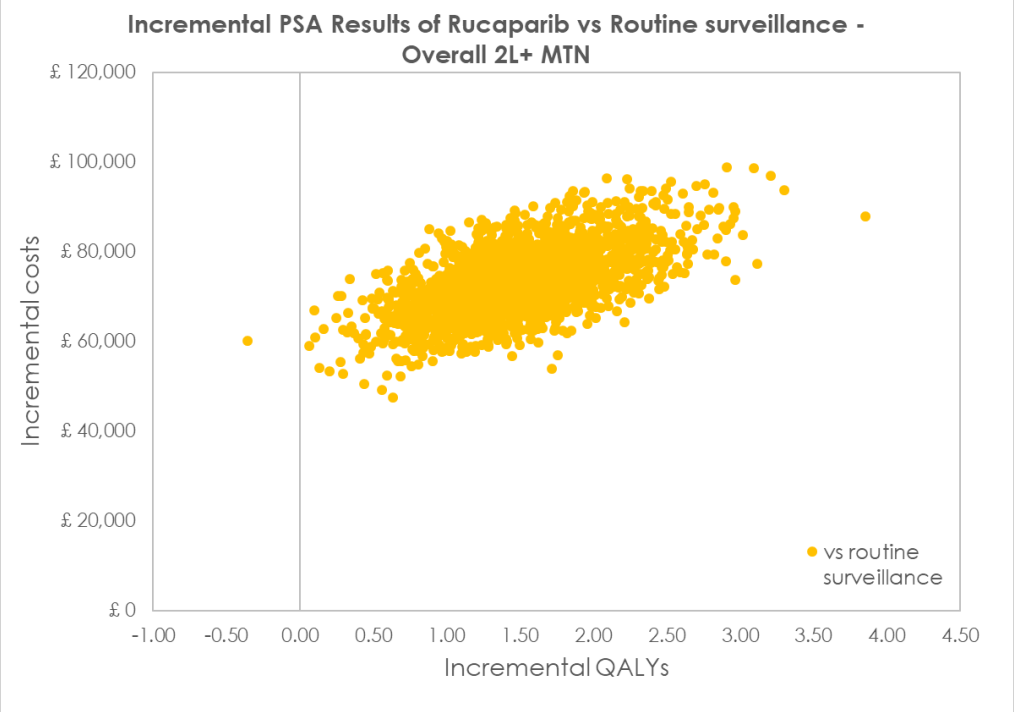
Key: 3L+, third- or later-line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MTN, maintenance treatment; QALY, quality-adjusted life year.

B.3.8. Sensitivity analyses

Probabilistic sensitivity analysis

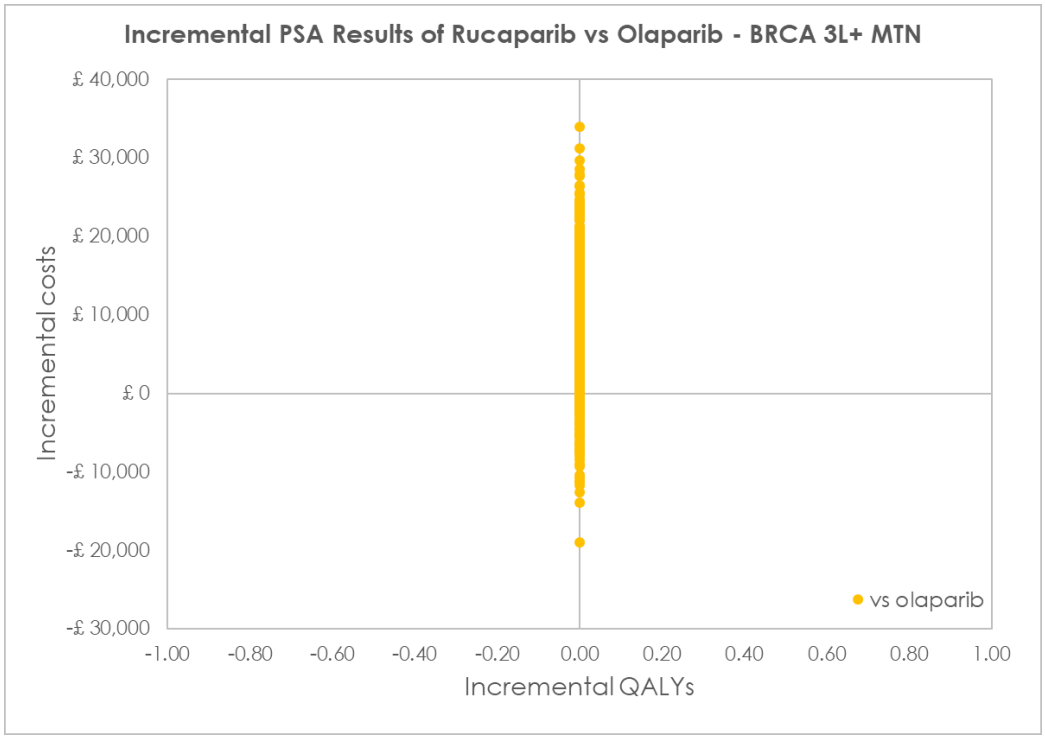
Probabilistic sensitivity analysis (PSA) was undertaken using 2,000 iterations, varying inputs according to their distributions as outlined in Table 61. Figure 34 to Figure 37 show the PSA scatterplots and cost-effectiveness acceptability curves for the ITT and BRCA 3L+ populations, respectively. Mean PSA results are very consistent with the deterministic analysis, as shown in Table 65 and Table 66.

Figure 34: PSA scatterplot, ITT population



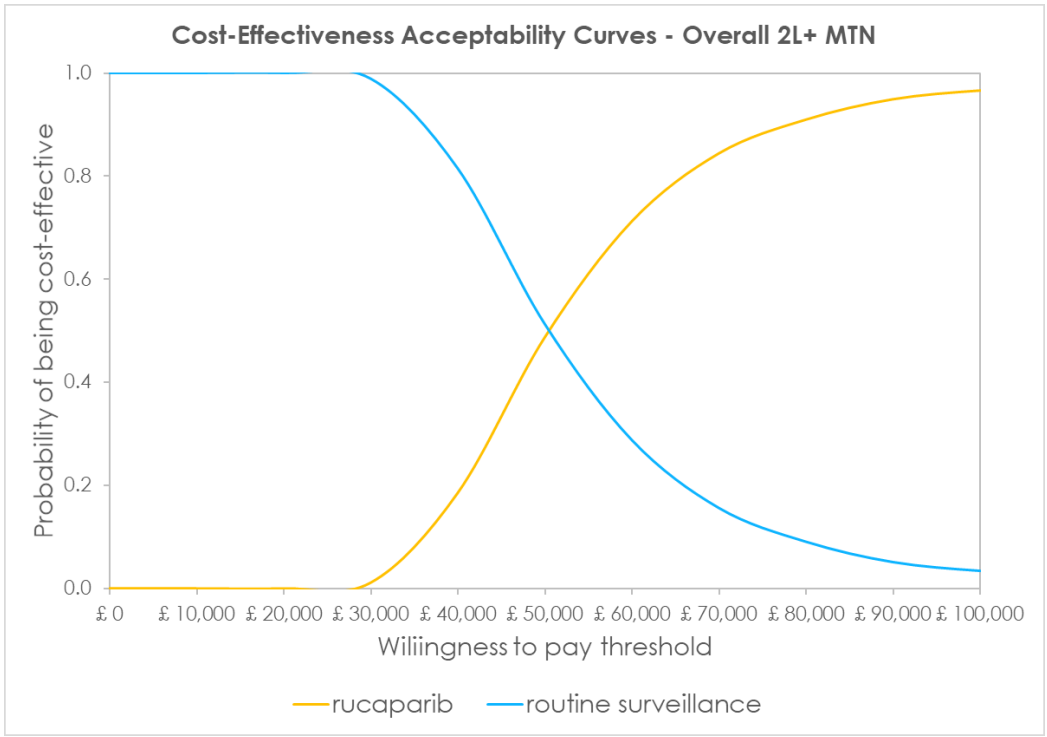
Key: ITT, intention-to-treat; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 35: PSA scatterplot, BRCA 3L+ MTN population



Key: 3L+, third- or later-line; BRCA, breast cancer gene; MTN, maintenance treatment; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 36: Cost-effectiveness acceptability curve, ITT population



Key: ITT, intention-to-treat; QALY, quality-adjusted life year.

Figure 37: Cost-effectiveness acceptability curve, BRCA 3L+ MTN population

Key: 3L+, third- or later-line; BRCA, breast cancer gene; MTN, maintenance treatment; QALY, quality-adjusted life year.

Table 65: Mean PSA results, ITT population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Routine surveillance	[redacted]	3.092	[redacted]				
Rucaparib	[redacted]	4.968	[redacted]	[redacted]	1.876	[redacted]	49,584

Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Table 66: Mean PSA results, BRCA 3L+ MTN

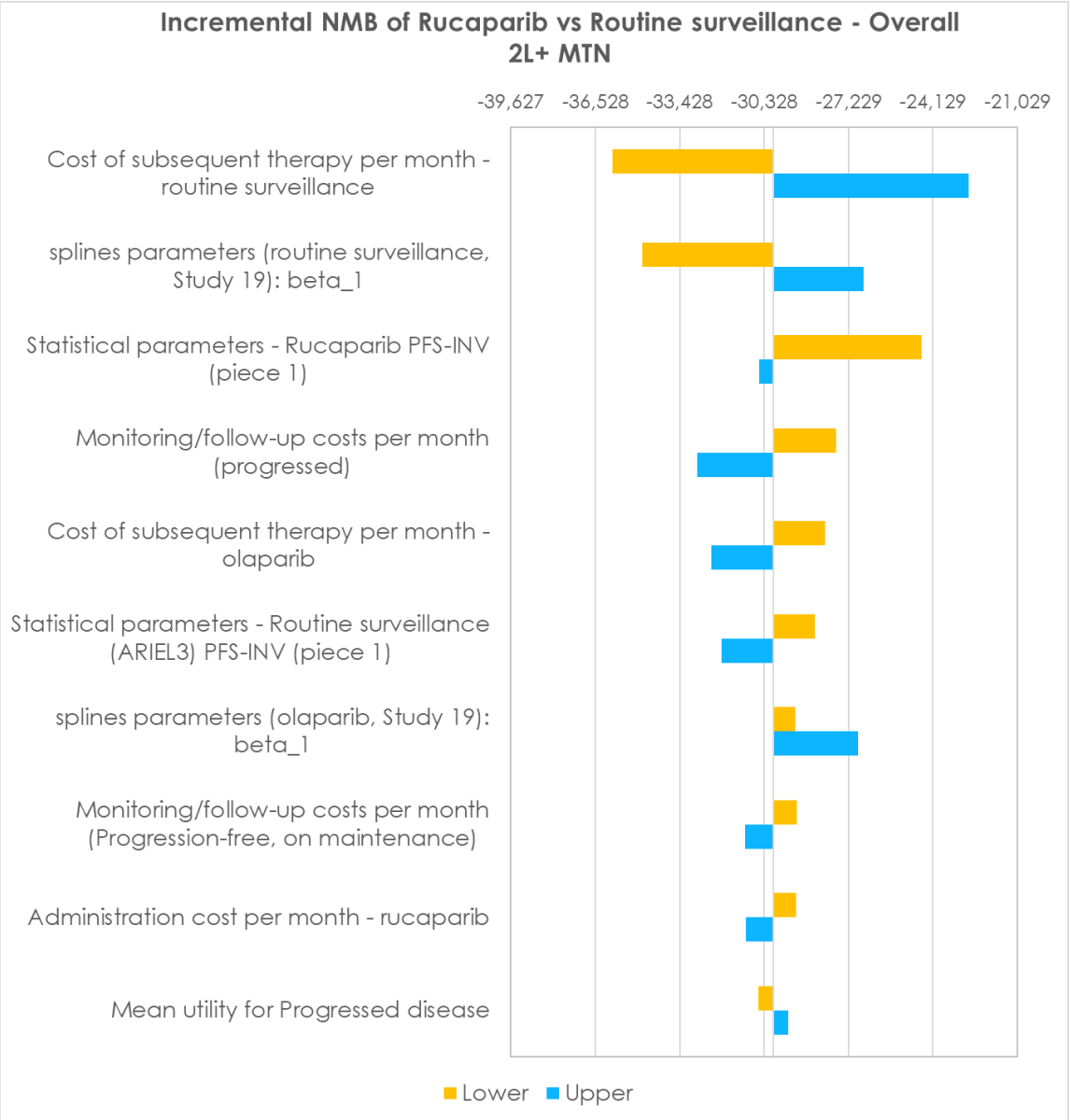
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Olaparib	[redacted]	3.135	[redacted]				
Rucaparib	[redacted]	3.135	[redacted]	[redacted]	0	[redacted]	Rucaparib dominated

Key: 3L+, third- or later-line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MTN, maintenance treatment; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Deterministic sensitivity analysis

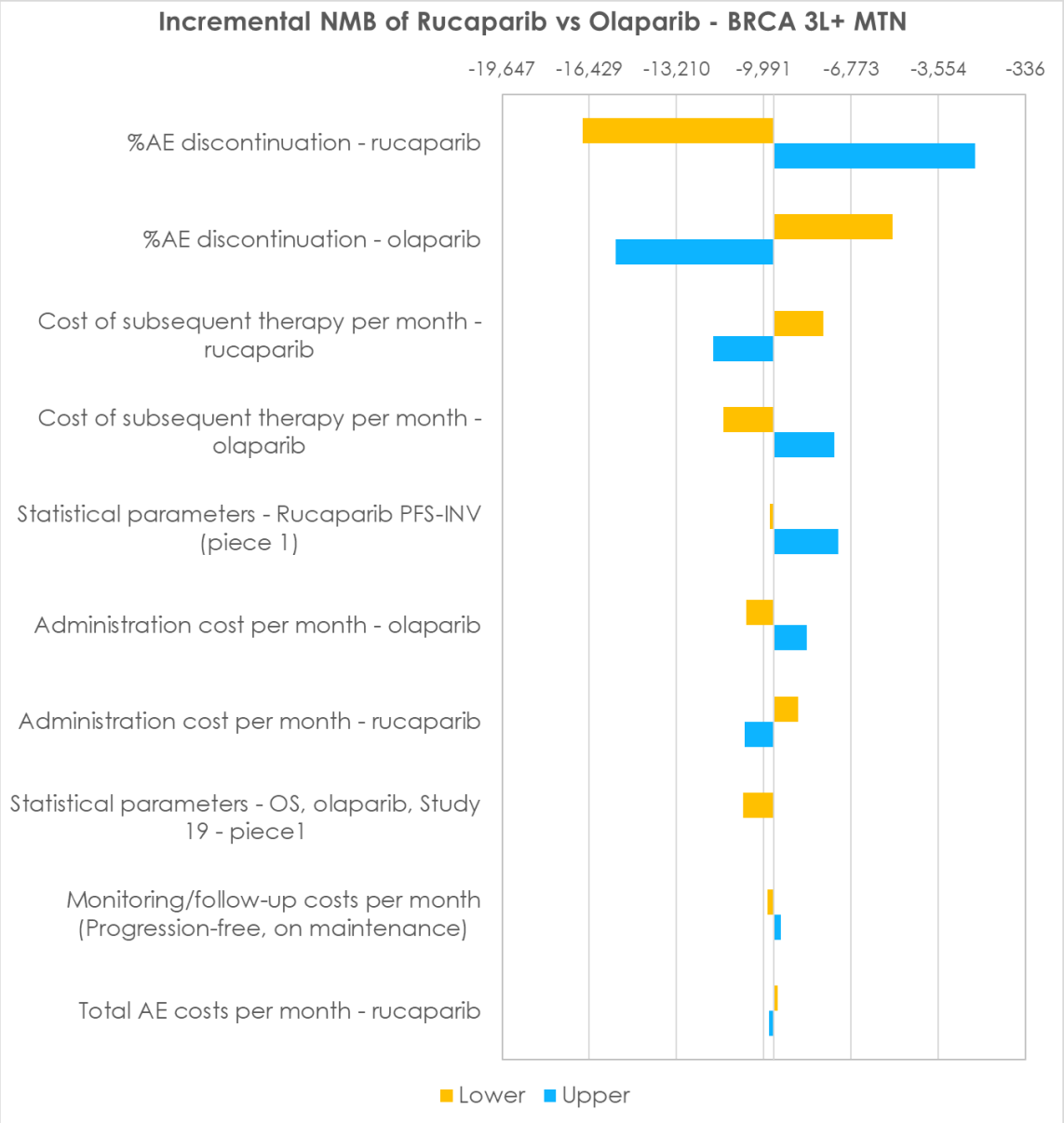
Figure 38 and Figure 39 display tornado diagrams of the 10 most influential parameters from the one-way sensitivity analysis in each population, in terms of impact on net monetary benefit using a willingness-to pay threshold of £30,000. Each parameter was varied to its upper and lower bound as described in Table 61. Consistently, the key drivers of the model included those influencing subsequent therapy and relative survival (OS hazard ratio). Within the BRCA 3L+ population, discontinuation rates for rucaparib and olaparib are most influential parameters; this is expected given that the treatments are assumed to differ only in cost.

Figure 38: One-way sensitivity analysis, ITT population



Key: AE, adverse event; HR, hazard ratio; INV, investigator assessed; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

Figure 39: One-way sensitivity analysis, BRCA 3L+ MTN population



Key: 3L+, third- or later-line; AE, adverse event; BRCA, breast cancer gene; HR, hazard ratio; INV, investigator assessed; ITT, intention-to-treat; MTN, maintenance treatment; OS, overall survival; PFS, progression-free survival.

Scenario analysis

Scenario analyses are shown in Table 67, and indicate that the model is mostly robust to each scenario. The scenarios which have increase the ITT population ICER

the most are the PFS:OS ratio scenarios. As described in Section B.3.3, these scenarios are included purely to benchmark against previous appraisals. Use of standard parametric curves for OS also increases the ITT ICER; aside from this, no other scenarios substantially differ from the base case ICER.

Table 67: Key scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER	
			ITT	**BRCA 3L+**
Base case			**£50,429**	**Rucaparib dominated**
OS: other approaches	Second-best parametric fits for OS: Log-logistic	Understand parameter uncertainty in base choice curve	£ 70,650	Rucaparib dominated
	Third-best parametric fits for OS: Weibull		£ 78,035	Rucaparib dominated
PFS: Other curves	Second-best parametric fits for PFS: Generalised gamma	Understand parameter uncertainty in base choice curve	£ 41,221	Rucaparib dominated
	Third-best parametric fits for PFS: Log-logistic		£ 52,964	Rucaparib dominated
TTDD: other approaches	Overall 2L+ MTN: Second-best parametric fits for rucaparib TTDD: Gompertz	Understand parameter uncertainty in base choice curve	£ 48,821	N/A
	Overall 2L+ MTN discontinuation rule: Constant discontinuation rate per cycle for rucaparib		£ 42,962	N/A
	BRCA 3L+ MTN discontinuation rule: TTDD curves for rucaparib: Exponential	Understand structural uncertainty in base choice approach	N/A	Rucaparib dominated
	Discontinuation rule - Treat until progression for all interventions	Understand structural uncertainty in base choice approach	£ 56,126	Rucaparib dominated
ITT OS method: PFS:OS approach	Overall 2L+ MTN: PFS-OS ratio = 1, routine surveillance PFS: Lognormal	Understand structural uncertainty in base choice approach	£ 108,668	N/A
	Overall 2L+ MTN: PFS-OS ratio = 2, routine surveillance PFS: Lognormal		£ 62,507	N/A
	PFS-OS ratio = 1, routine surveillance PFS: based on HR		£ 108,330	Less costly, less effective

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER	
	PFS-OS ratio = 2, routine surveillance PFS: based on HR		£ 62,330	Less costly, less effective
BRCA 3L+ comparison to olaparib: other PFS comparative estimates	BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by NMA estimates for relative efficacy (equivalence in OS only)	Understand uncertainty around comparative effectiveness versus olaparib	N/A	Less costly, less effective
	BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (Study 19) estimates for relative efficacy (equivalence in OS only)		N/A	Less costly, less effective
	BRCA 3L+ MTN: OS equivalence, Olaparib PFS predicted by MAIC (SOLO2) estimates for relative efficacy (equivalence in OS only)		N/A	£ 934,728
	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
AEs: apply disutilities	Alternative AE assumption: Apply AE disutilities but do not accrue AE costs	Understand uncertainty around assumption that impact of AEs is captured within	£ 50,283	Rucaparib dominated
	Alternative AE assumption: Do not apply AE disutilities and do not accrue AE costs		£ 50,193	Rucaparib dominated
Alternative AE costs	Alternative AE costs based on feedback from UK clinical expert	Understand uncertainty around resource use assumptions for AE treatment within model base case	£ 50,210	Rucaparib dominated
Alternative RU estimates	Alternative frequency of RU based on feedback from UK clinical expert	Understand uncertainty around resource use estimates	£ 49,700	Rucaparib dominated

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER	
		within model base case		
Longer time horizon	Extend time horizon to 50 years	Time horizon consistent with previous appraisals	£ 48,265	Rucaparib dominated
No discounting	No discounting for costs and health outcomes	Undiscounted results	£ 39,647	Rucaparib dominated
Assume wastage	Do not allow vial sharing (assume wastage) - IV/SC drugs	Understand the impact of vial sharing	£ 50,490	Rucaparib dominated
Assume no cost of BRCA mutation test	Exclude one-off cost of BRCA mutation test at the beginning of the time horizon	Understand the impact of the BRCA mutation test on CE results	£ 50,429	Rucaparib dominated
No administration costs	Do not apply administration cost of maintenance and subsequent therapies	Understand the impact of administration costs on CE results	£ 48,968	Rucaparib dominated
Alternative utilities (TA528)	PF and PD mean utility values reported in the niraparib NICE submission [TA528]; PF: 0.831, PD: 0.799	Test for consistency with previous appraisals	£ 48,954	Rucaparib dominated
Alternative subsequent therapy shares	Shares for subsequent therapy costs unadjusted for non-UK treatments (all patients, ARIEL3)	Understand uncertainty around the exclusion of non-UK treatments, to understand the potential impact of off-label use	£ 51,498	Rucaparib dominated
Apply RDI for maintenance therapies	Apply relative dose intensity from ARIEL2 for rucaparib and Study 19 for olaparib	Understand uncertainty around assumption of 100% RDI	£ 47,794	Rucaparib dominated

Key: 2L+, second and later line; 3L+, third and later line; AE, adverse event; BRCA, breast cancer gene; ITT, intention to treat; MTN, maintenance; N/A, not applicable; NMA, network meta-analysis; MAIC, matching-adjusted indirect comparison, OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; RDI, relative dose intensity; RU, resource use; TTDD, time to discontinuation or death.

Summary of sensitivity analyses results

Sensitivity analysis results showed the base case results to be robust to uncertainty around most input parameters. However, survival assumptions are clearly important for cost-effectiveness results; the use of a PFS:OS ratio led to different absolute and incremental benefit estimates for rucaparib versus routine surveillance and olaparib. The probabilistic results remain very similar to deterministic results, indicating that the model is robust to this aspect of uncertainty.

While there is clear inherent uncertainty around the clinical- and cost-effectiveness of rucaparib within this patient group, care has been taken to investigate the different clinical data available, while taking a transparent approach in illustrating the uncertainty around results. Overall, the sensitivity and scenario analyses explored indicate that under a range of assumptions and across different datasets, rucaparib promises a substantial health benefit to routine surveillance, and very similar benefit to olaparib within the BRCA 3L+ population when results of indirect treatment comparisons are used.

B.3.9. Subgroup analysis

Analysis of additional specific subgroups from ARIEL3 was not undertaken.

B.3.10. Validation

Validation of cost-effectiveness analysis

Internal validation was ensured via a comprehensive and rigorous quality check, performed by an internal peer reviewer not involved in the original implementation of the model. This included validating the logical structure of the model, mathematical formulas, sequences of calculations and the values of numbers supplied as model inputs. Any unexpected model behaviour, implementation and typing errors were all identified by this review.

External validation was sought from UK clinicians. An initial round of validation was conducted in 2018, comprising of the below elements:

- Cost-effectiveness model structure and approach

Clinicians confirmed that the approach adequately captures treatment patterns, resource utilisation and the impact of treatment on patients' quality of life, in accordance with current clinical practice for maintenance treatment of adult patients with advanced ovarian cancer in England and Wales.

- Prognostic factors and treatment effect modifiers

  An extensive list of potential prognostic factors and treatment effect modifiers were discussed with expert clinicians. Rigorous efforts were made to distinguish between the two types of variables to inform the MAIC analyses.

- Parametric survival analyses

  Expert opinion was sought for validation of the choice of parametric distribution including the shape of parametric curves for OS, PFS and TTDD and long-term extrapolations. Predicted PFS and TTDD curves based on ARIEL3 and OS curves based on Study 19 for the BRCA 3L+ and ITT populations were presented to clinical experts in the UK, who were asked to confirm whether the long-term estimates of OS reflected their experience in clinical practice. The outcomes from discussions were considered alongside the statistical goodness-of-fit as measured by AIC and BIC values for the final parametric curve selections.

- Equivalence in PARPi efficacy

  Of the two clinicians that were interviewed, both expected to see equivalence in efficacy across PARP inhibitors (rucaparib, olaparib and niraparib). One clinician suggested that potential differences might only be seen in terms of their toxicity profiles. Statements from clinicians informed the efficacy assumptions applied in the base case analysis.

- PARPi dosing and dose interruptions

  Clinicians administered olaparib per the recommended dose of 800 mg per day. Comments from one clinical expert indicated that dose interruption and dose reductions were not common in their practice and that adverse events and treatment toxicity were rarely a reason to stop PARPi maintenance.

- Resource use inputs

Clinical experts estimated one-off resource use at progression, subsequent treatment use following progression, adverse events on PARPi maintenance, hospital-related costs after progression following PARPi maintenance, and best supportive care composition for patients with advanced ovarian cancer.

In January 2019, curves used within the model were validated with another leading UK clinician; the responses from this guided final curve choice decisions.[56]

Attempts were made to compare clinical outcomes of the model to clinical outcomes of previous technology appraisals. Many inputs from recent appraisals of relevance (TA381, TA528, ID1296) have been marked commercial in confidence.[33, 34, 82] However, overall LYs from TA381 were available, and are very similar to the olaparib/rucaparib LYs from the BRCA 3L+ model population (3.32 LYs within TA381 compared to 3.09 within the model).

B.3.11. Interpretation and conclusions of economic evidence

As described throughout Section B.3, the methods and approaches used to evaluate the cost effectiveness of rucaparib as maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy are based on the best currently-available evidence, from both ARIEL3 and comparator clinical trials.

The main strength of this economic evaluation compared to previous appraisals in this disease setting is that it attempts to maximise the use of OS data in an appropriate way, taking on board ERG and NICE committee comments from previous relevant appraisals to understand and present informative estimates of the likely benefit of rucaparib maintenance treatment within this patient group. Because the OS data for rucaparib is currently so immature, this has entailed using external (non-rucaparib) OS data sources, namely Study 19. The base case comparison to routine surveillance uses a novel approach to assuming equal post-progression survival to treatments in Study 19, in a way which allows for appropriate discounting and avoids use of a means-based model. Similarly, the comparison to olaparib

considers the results of several indirect comparisons, using as much available data as possible in a pragmatic attempt to contextualise the relative clinical and cost-effectiveness of rucaparib. The majority of scenarios presented within the ITT population do not materially affect the ICER.

In assuming equivalent efficacy of rucaparib to olaparib, a conservative approach was taken to modelling the treatment benefits of rucaparib observed in ARIEL3. The economic evaluation does not factor in the lower proportion of patients with a complete response to last prior therapy seen in ARIEL3 compared to the olaparib studies. Another potential benefit of rucaparib within the BRCA 3L+ population not captured within this evaluation is the benefit for patients of receiving an oral therapy with reduced pill burden and no restriction on food intake which could help minimise the impact of treatment on patients' daily lives. Furthermore, the ARIEL3 study is the most inclusive PARPi maintenance treatment trial to date, providing data relevant to patients presenting in UK practice, including those with residual disease at baseline and irrespective of the molecular characteristics of the tumour. In omitting these potential benefits of rucaparib, the economic evaluation presents a conservative estimate of the benefit to patients of rucaparib maintenance treatment.

The main weaknesses of the economic evidence presented is the lack of OS data for rucaparib mature enough to support decision making. This is a common theme across relevant appraisals, and we have demonstrably attempted to present sensible approaches to modelling this key model outcome for fair and transparent appraisal of a decision problem that affects a patient group with an overall poor prognosis and where there is outstanding unmet need.

Throughout the development of this submission, a rigorous and comprehensive approach has been taken to exploring alternative modelling methodologies and scenarios, in an attempt to thoroughly and transparently explore the uncertainty around key model aspects, such as survival assumptions. The range of ICERs within the ITT population from different OS approaches and assumptions indicate that while rucaparib maintains a clear clinical benefit, the exact magnitude of this benefit is uncertain at the present time. As such, this variation further indicates that rucaparib would benefit from further data collection within the CDF.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

Clarification questions

February 2019

File name	Version	Contains confidential information	Date
ID 1485 Rucaparib ERG clarification questions to PM for company_22 March 2019_REDACTED	**Version 2**	**Yes(REDACTED)**	**22.03.2019**

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Notes for company

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Question	Response Date	Status	Notes
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A2	22 March 2019	Response Submitted	
A3	22 March 2019	Response Submitted	
A4	22 March 2019	Response Submitted	
A5	12 March 2019	Response Submitted	
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Section A: Clarification on effectiveness data

A1. Priority Question: Please provide data (mean, median, number of events, HR, KM-curve) for OS, PFS (INV), and TTD for ARIEL3, separately for

a) **Non-BRCA**

b) **BRCA 2L (second line only)**

Response: Data are provided for these groups as requested but please note that the design of the ARIEL3 trial does not align to this request and does not provide robust analysis for these subgroups. ARIEL3 prospectively evaluated PFS by RECIST, as assessed by the investigator, in **molecularly defined HRD subgroups**, not by non-BRCA or BRCA 2L subgroups - these were not predefined analysis populations within the statistical analysis plan. Further analyses have therefore been conducted to meet this request, but their post-hoc nature, combined with the small patient numbers and low event rates - particularly in the OS data where censoring was needed for nearly 85% of patients in the BRCA 2L group and over 75% of patients in the non-BRCA group - warrant significant caution to be applied when interpreting these data.

Clovis Oncology acknowledges that the ERG believes these subgroups better reflect what happens in the NHS currently compared to the prospectively defined subgroups in the ARIEL 3 trial. However, in addition to the concerns raised regarding the robustness of these post-hoc analyses, Clovis Oncology also believes that these subgroups do not currently reflect or guide treatment decisions in NHS England outside of the BRCA 3L+ population.

The non-BRCA and BRCA subgroups have been characterised in the NOVA clinical trial of niraparib (and even then, the BRCA group only included patients with germline BRCA mutations and thus the ‘non-BRCA’ group contained patients with somatic BRCA mutations), but niraparib is not available through routine commissioning in England and therefore was not identified as a relevant comparator within the scope for this appraisal

Genetic testing for germline BRCA (BRCA1 and BRCA2) is widely established in England, and is vital for the identification of harmful mutations in the genes that

predispose individuals, or their relatives, to cancer (ovarian and/or breast cancer).[1] However, treatment decisions in current routine clinical practice are not informed by the results of this testing, outside of the BRCA 3L+ setting, and in fact, patients in the non-BRCA and BRCA 2L subgroups receive the same routine surveillance following completion of platinum-based chemotherapy in the relapsed setting regardless of mutational status. Furthermore, somatic BRCA testing is not widely available in England and therefore this subgroup is not fully identifiable in the NHS currently.

Clovis Oncology therefore believes the analysis for the ITT population of the ARIEL3 trial is the most robust, and of the most clinical relevance to the decision problem.

Table 1: Summary of OS, PFS INV and TTD – post-hoc analyses

	Non-BRCA		BRCA 2L	
	Rucaparib (n=245)	PBO (n=123)	Rucaparib (n=77)	PBO (n=41)
Overall survival				
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
Restricted mean OS, weeks (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival				
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
Restricted mean PFS, weeks (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Time to treatment discontinuation				
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median TTD, weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	
Restricted mean TTD, weeks (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Key: 2L, second line; BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; INV, investigator; OS, overall survival; PBO, placebo; PFS, progression-free survival; SE, standard error; TTD, time to treatment discontinuation.

Figure 1: Kaplan–Meier estimates of PFS INV – non BRCA – post-hoc analyses

Key: BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 2: Kaplan–Meier estimates of TTD – non BRCA – post-hoc analyses

Key: BRCA, breast cancer gene; INV, investigator; TTD, time to treatment discontinuation.

Figure 3: Kaplan–Meier estimates of PFS INV – BRCA 2L – post-hoc analyses

Key: 2L, second line; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 4: Kaplan–Meier estimates of TTD – BRCA 2L – post-hoc analyses

Key: 2L, second line; BRCA, breast cancer gene; INV, investigator; TTD, time to treatment discontinuation.

A2. Priority Question: Please provide baseline characteristics of patients in ARIEL3 and Study 19 for the following subgroups:

a) **Non-BRCA**

b) **BRCA 2L**

Response: Selected baseline characteristics (based on those considered potential effect modifiers in the ITC) are provided for the non-BRCA groups of ARIEL3 and Study 19 in Table 2. Data for the BRCA 2L group are provided for ARIEL3 and SOLO2 as data for this group are not available from Study 19.

Table 2: Selected baseline characteristics – post-hoc analyses

	Non-BRCA				BRCA 2L			
	ARIEL 3		Study 19		ARIEL 3		SOLO 2	
	Rucaparib (n=245)	Placebo (n=123)	Olaparib (n=57)	Placebo (n=61)	Rucaparib (n=77)	Placebo (n=41)	Olaparib (n=110)	Placebo (n=62)
Age, median years	[redacted]	[redacted]	62	63	[redacted]	[redacted]	56	55
Race, white %	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
BMI, mean	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
Time since diagnosis, mean years	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
Metastatic sites <3, %	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
ECOG ≥1, %	[redacted]	[redacted]	19.3	24.6	[redacted]	[redacted]	18.2	24.2
FIGO ≥III, %	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
Ovarian tumour site, %	[redacted]	[redacted]	87.7	80.3	[redacted]	[redacted]	-	-
Serous histology, %	[redacted]	[redacted]	100	100	[redacted]	[redacted]	-	-
BRCA mutation, %	[redacted]	[redacted]	0	0	[redacted]	[redacted]	100	100
Jewish ancestry, %	[redacted]	[redacted]	10.5	4.9	[redacted]	[redacted]	-	-
Platinum-free interval >12 months, %	[redacted]	[redacted]	59.6	60.7	[redacted]	[redacted]	70.9	69.4
CR to most recent platinum chemotherapy, %	[redacted]	[redacted]	35.1	41.0	[redacted]	[redacted]	50.9	54.8
Prior lines of chemotherapy ≥3, %	[redacted]	[redacted]	-	-	[redacted]	[redacted]	-	-
Prior lines of platinum therapy ≥3, %	[redacted]	[redacted]	43.9	42.6	[redacted]	[redacted]	-	-
Prior use of bevacizumab, %	[redacted]	[redacted]	-	-	[redacted]	[redacted]	13.6	54.8

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

A3. Priority Question: Please run the NMA of PFS (INV) for the BRCA 3L+ population but ensuring olaparib capsules and olaparib tablets are considered different treatments; i.e. please use Study 19 for the capsule formulation of olaparib and SOLO2 for the tablet formulation of olaparib.

Response: The results of the NMA of PFS (INV) for the BRCA 3L+ population with olaparib capsules (Study 19) and tablets (SOLO2) considered different treatments, are presented in Table 3.

Table 3: NMA scenario analyses - PFS-INV, BRCA 3L+ group

	HR (95% CrI)
Rucaparib versus olaparib tablets (SOLO 2)	[redacted]
Rucaparib versus olaparib capsules (Study 19)	[redacted]
Key: 3L+, third line plus; BRCA, breast cancer gene; CrI, credible interval; HR, hazard ratio; PFS-INV, progression-free survival as assessed by investigator; NMA, network meta-analysis.	

No statistical advantage (defined as hazard ratios (HRs) less than 0.80 or greater than 1.25 with credible intervals [CrIs] not crossing one) was observed between treatments; trends favoured rucaparib compared with olaparib tablets but not olaparib capsules. While olaparib capsules are currently used in clinical practice, it should be acknowledged that Study 19 from which the data for this treatment is taken, is not considered to be a robust study when looking at the BRCA 3L+ population – see clinical consultation previously provided.[2]

Moreover, please acknowledge the following discussion points when considering the relevance of this request (here and in scenario analyses requested in Section B) to the decision problem:

1. Although olaparib capsules and olaparib tablets cannot be considered bioequivalent on a milligram-to-milligram basis, the 300mg BD tablet dose was considered to be therapeutically comparable to the 400mg BD capsule dose in Study 24, in terms of efficacy and safety.[3]

2. The EMA therefore concluded that while olaparib capsules and olaparib tablets are not to be substituted on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation, extrapolation of efficacy results obtained with capsule formulation to tablet formulation is reasonably supported by pharmacokinetic data.[4]

3. In the olaparib appraisal (ID1296), tablet and capsule formulations of olaparib were considered and the ERG acknowledged that it could be reasonable to assume equivalence between the tablet and capsule formulation.[5]

4. The capsule formulation of olaparib is to be phased out when no longer needed by patients. The appropriateness of modelling over a lifetime horizon based on this formulation alone is therefore questionable.

5. Survival rates observed in Study 19 are high and have not been replicated in more recent trials of PARPi maintenance treatment for ovarian cancer in the relapsed setting. Along with the Phase II nature of its design, and the retrospective nature of the BRCA 3L+ subgroup analyses, this observation fed into the clinical expert conclusion that the SOLO2 trial provides an overall more robust dataset for the BRCA 3L+ group.[2]

A4. Priority Question: Please provide methods and results for each of the tests for proportional hazards (including Schoenfeld plots, log-cumulative hazard plots and global p-value) for PFS (INV) and OS (for Study 19 only) in the following populations of ARIEL3, Study 19 and SOLO2 in Table 9, Appendix D:

a) **Non-BRCA (for ARIEL3 and Study 19 only**

b) **BRCA 2L (for ARIEL3 only)**

c) **BRCA 3L+**

d) **ITT (for ARIEL3 and Study 19 only)**

Response: The assumption of proportional hazards was investigated in several ways:

1. For each trial arm (i.e. rucaparib and placebo), the log-cumulative hazard was plotted against the logarithm of time.

2. Additionally, the proportional-hazards assumption was investigated on the basis of Schoenfeld residuals after fitting a Cox proportional-hazards model with treatment (0: placebo, 1: active treatment) as the only explanatory variable. A scatterplot and smoothed plot of scaled Schoenfeld residuals versus time was produced for treatment. The smoothing was performed using locally weighted regression with bandwidth 0.8. and the natural log of analysis time was used as the x-axis.

3. The global test was used to test the null hypothesis that the slope of the scaled Schoenfeld residuals when plotted against functions of time is equal to zero. The test of zero slope is equivalent to testing that the log hazard-ratio function is constant over time.[6, 7]

The results for each of these tests are provided below. Please note, due to the need to pool BRCA 3L and BRCA 4L+ data for the BRCA 3L+ population of SOLO2, proportional hazards (PH) tests were not originally conducted for any cohort other than the BRCA 2L+ group representing the total trial population of SOLO2. We have conducted PH testing on the pooled virtual patient-level data for the BRCA 3L+ group here (PFS-INV only as OS data not available for these groups) but please interpret these data with the necessary caution.

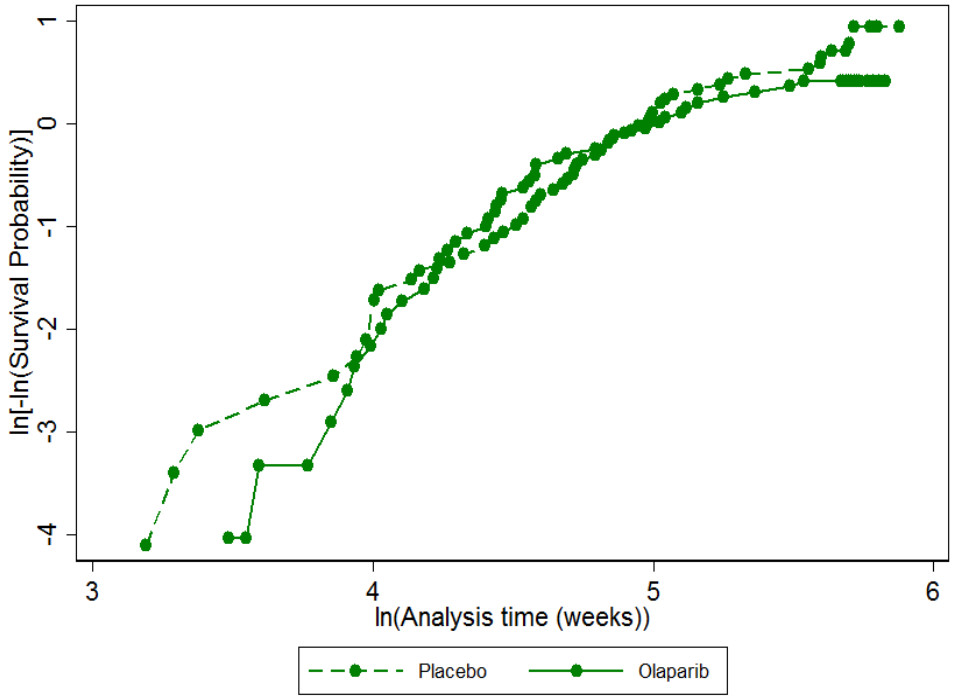
Figure 5: Log-cumulative hazard plot for PFS INV – ARIEL 3 – Non-BRCA

Key: BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 6: Schoenfeld plot for PFS INV – ARIEL 3 – Non-BRCA

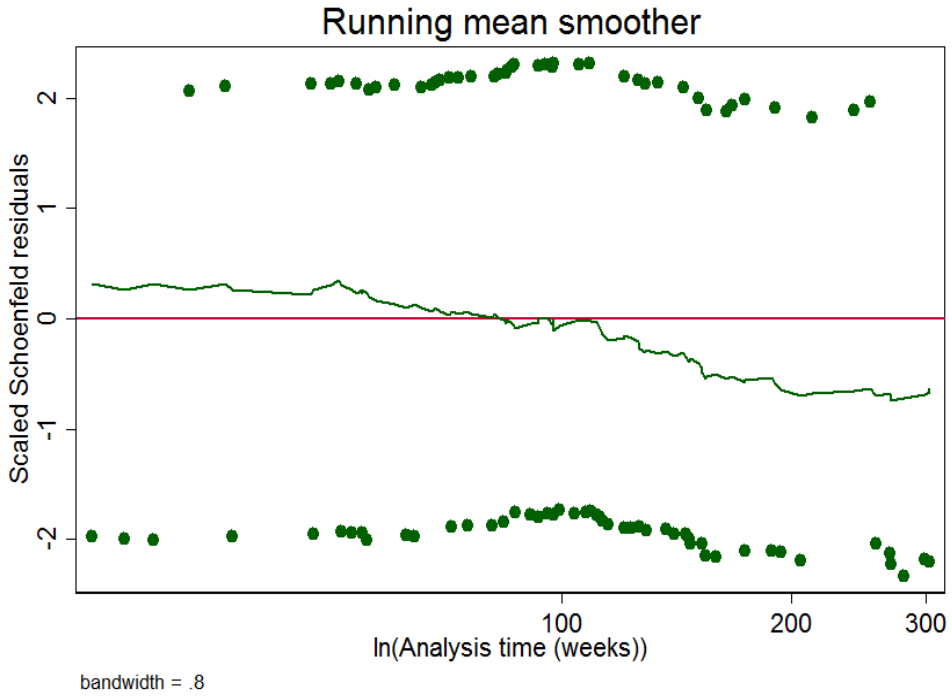
Key: BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 7: Log-cumulative hazard plot for OS – Study 19 – Non-BRCA



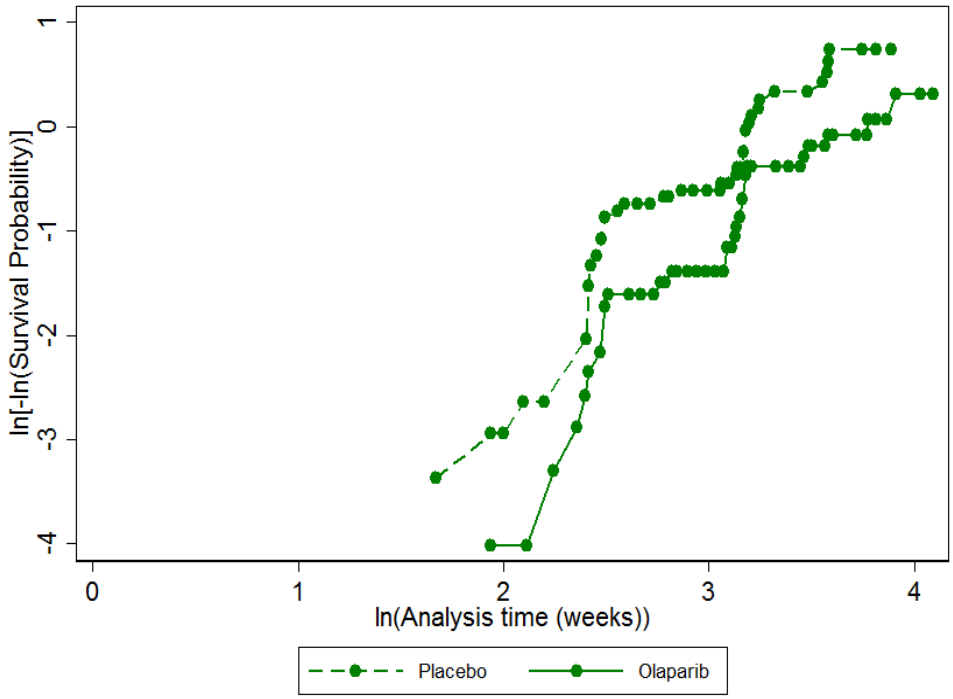
Key: BRCA, breast cancer gene; OS, overall survival.

Figure 8: Schoenfeld plot for OS – Study 19 – Non-BRCA



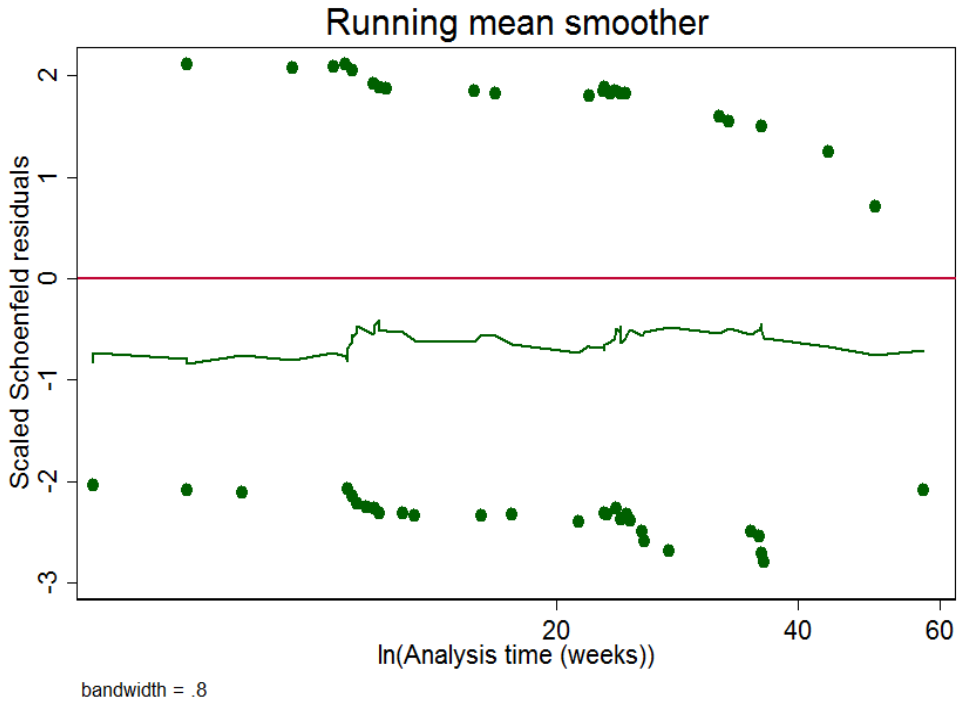
Key: BRCA, breast cancer gene; OS, overall survival.

Figure 9: Log-cumulative hazard plot for PFS INV – Study 19 – Non-BRCA



Key: BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 10: Schoenfeld plot for PFS INV – Study 19 – Non-BRCA



Key: BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 11: Log-cumulative hazard plot for PFS INV – ARIEL 3 – BRCA 2L

Key: 2L, second line; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 12: Schoenfeld plot for PFS INV – ARIEL 3 – BRCA 2L

Key: 2L, second line; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

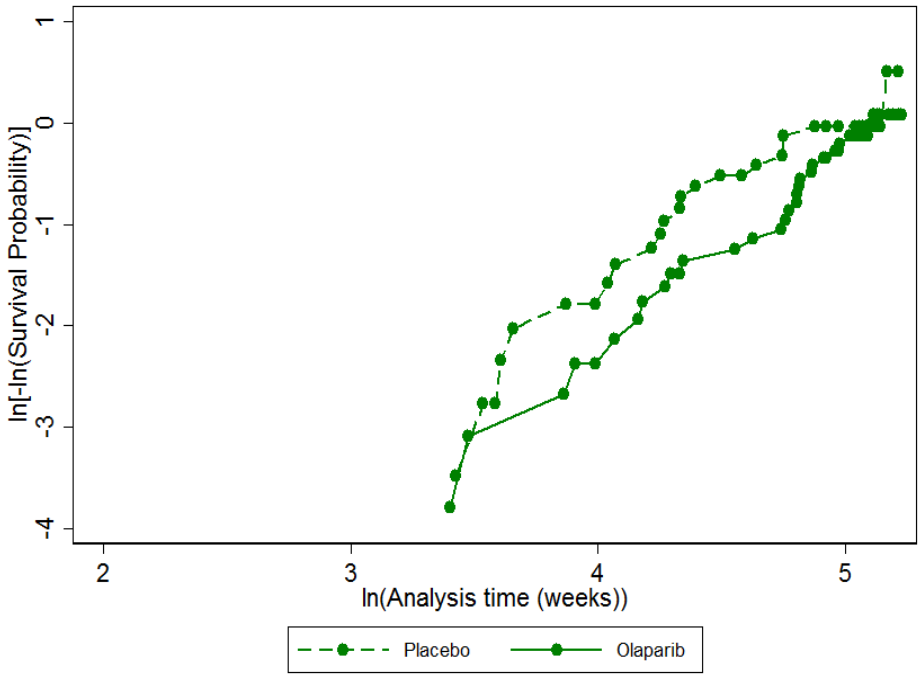
Figure 13: Log-cumulative hazard plot for PFS INV – ARIEL 3 – BRCA 3L+

Key: 3L+, third line plus; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 14: Schoenfeld plot for PFS INV – ARIEL 3 – BRCA 3L+

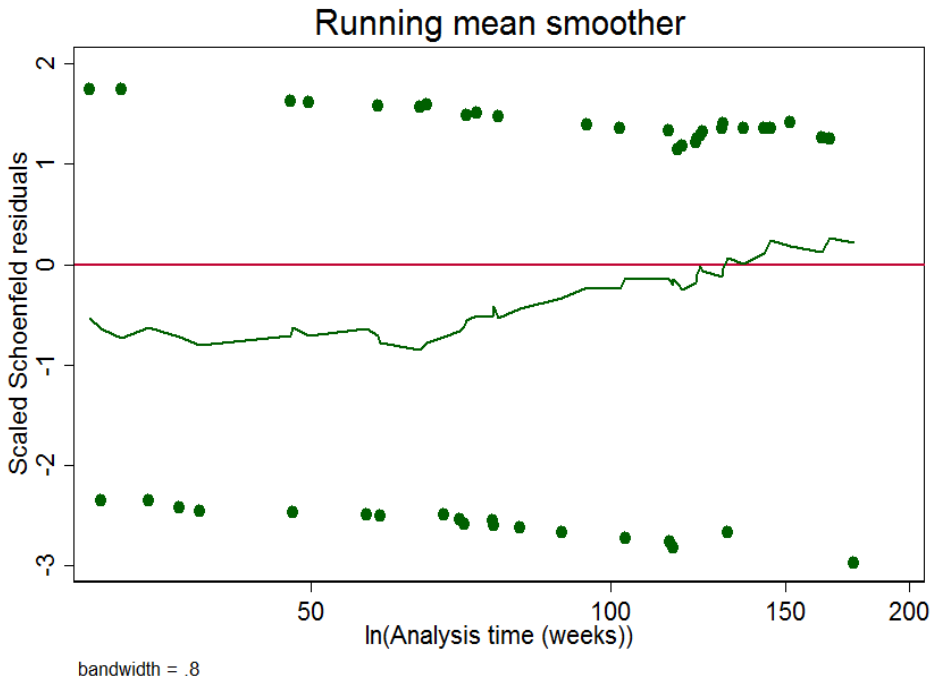
Key: 3L+, third line plus; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 15: Log-cumulative hazard plot for OS –Study 19 – BRCA 3L+



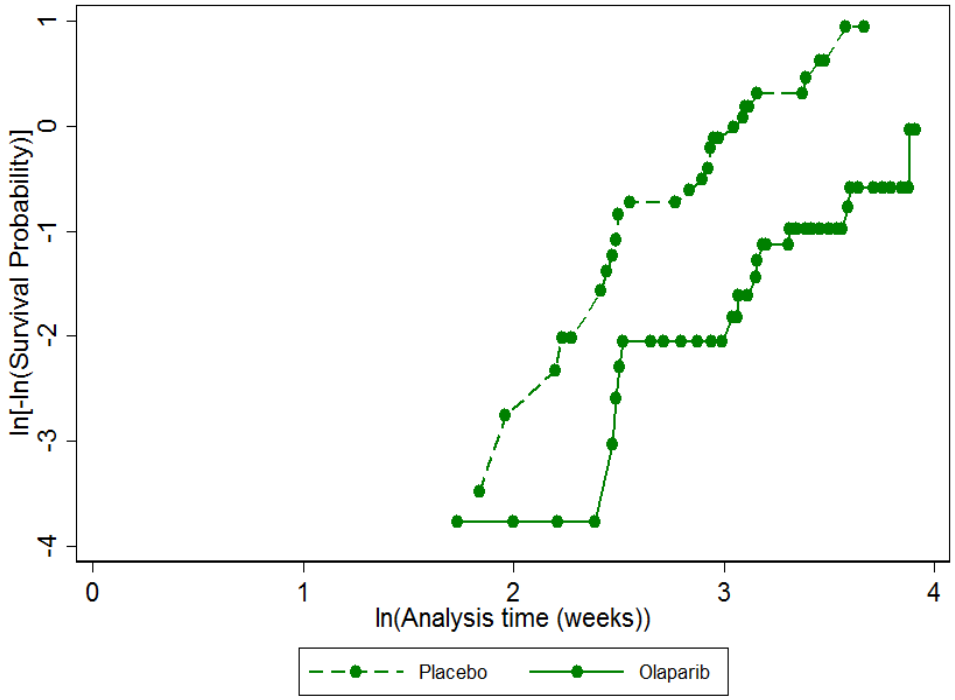
Key: 3L+, third line plus; BRCA, breast cancer gene; OS, overall survival.

Figure 16: Schoenfeld plot for OS – Study 19 – BRCA 3L+



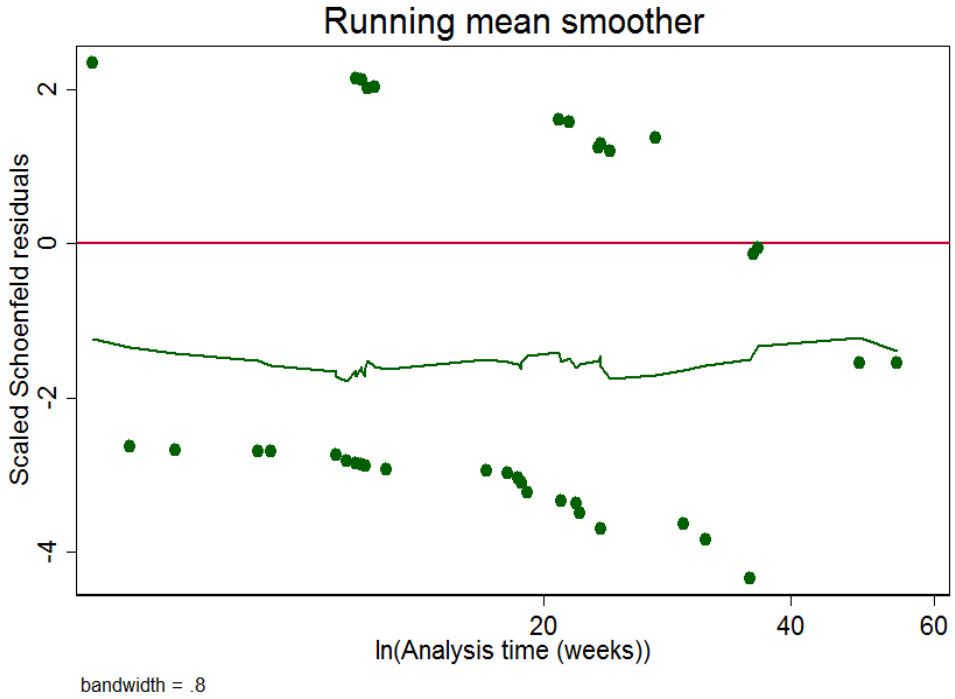
Key: 3L+, third line plus; BRCA, breast cancer gene; OS, overall survival.

Figure 17: Log-cumulative hazard plot for PFS INV – Study 19 – BRCA 3L+



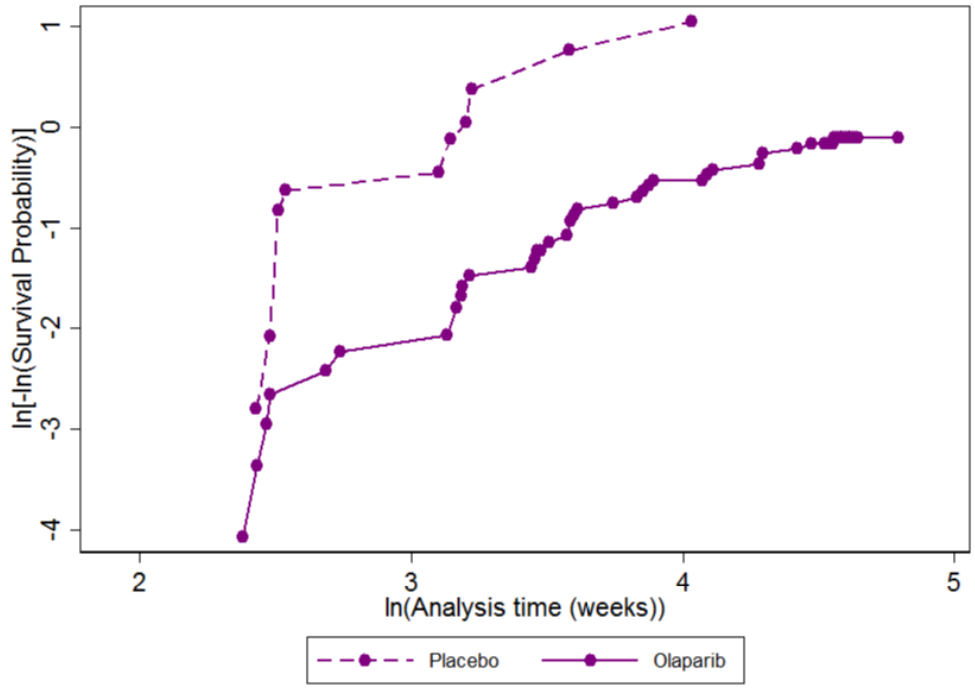
Key: 3L+, third line plus; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 18: Schoenfeld plot for PFS INV – Study 19 – BRCA 3L+



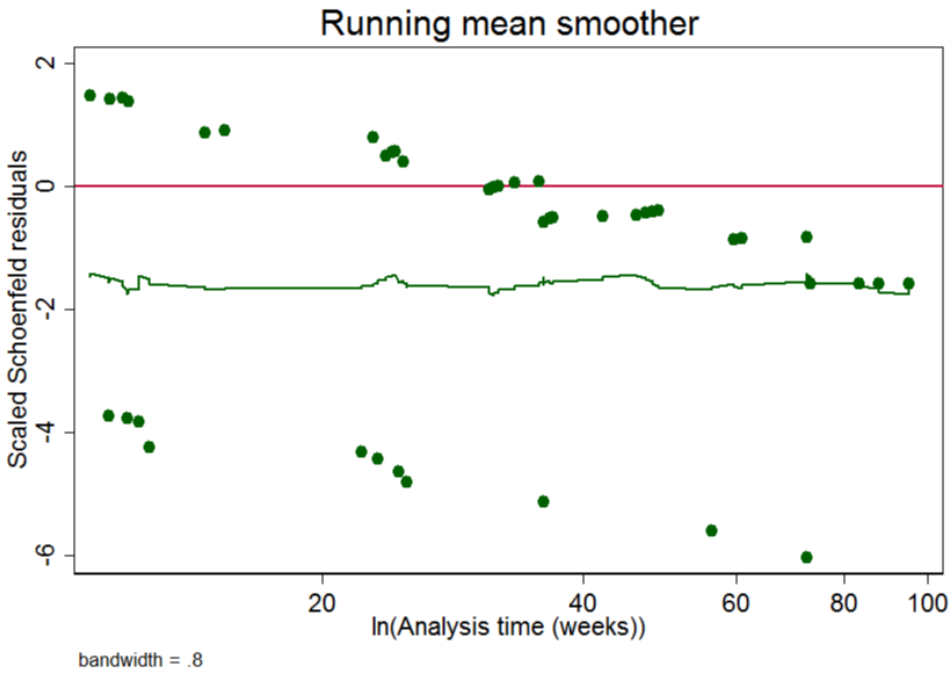
Key: 3L+, third line plus; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 19: Log-cumulative hazard plot for PFS INV – SOLO 2 – BRCA 3L+



Key: 3L+, third line plus; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

Figure 20: Schoenfeld plot for PFS INV – SOLO 2 – BRCA 3L+



Key: 3L+, third line plus; BRCA, breast cancer gene; INV, investigator; PFS, progression-free survival.

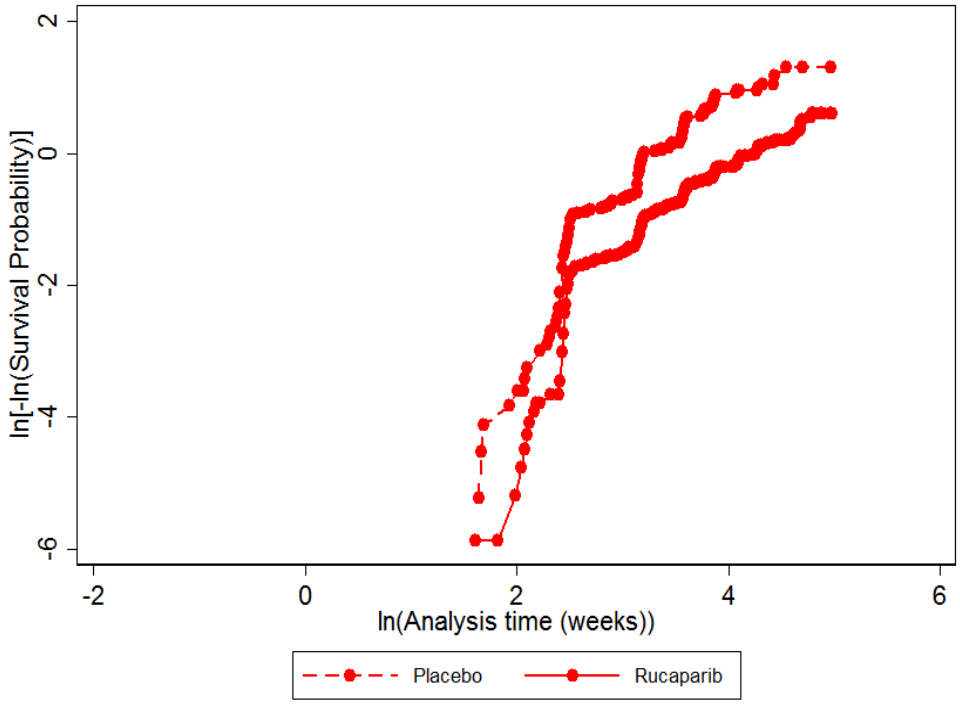
Figure 21: Log-cumulative hazard plot for OS – ARIEL 3 – ITT

Key: BRCA, breast cancer gene; ITT, intention-to-treat; OS, overall survival.

Figure 22: Schoenfeld plot for OS – ARIEL 3 – ITT

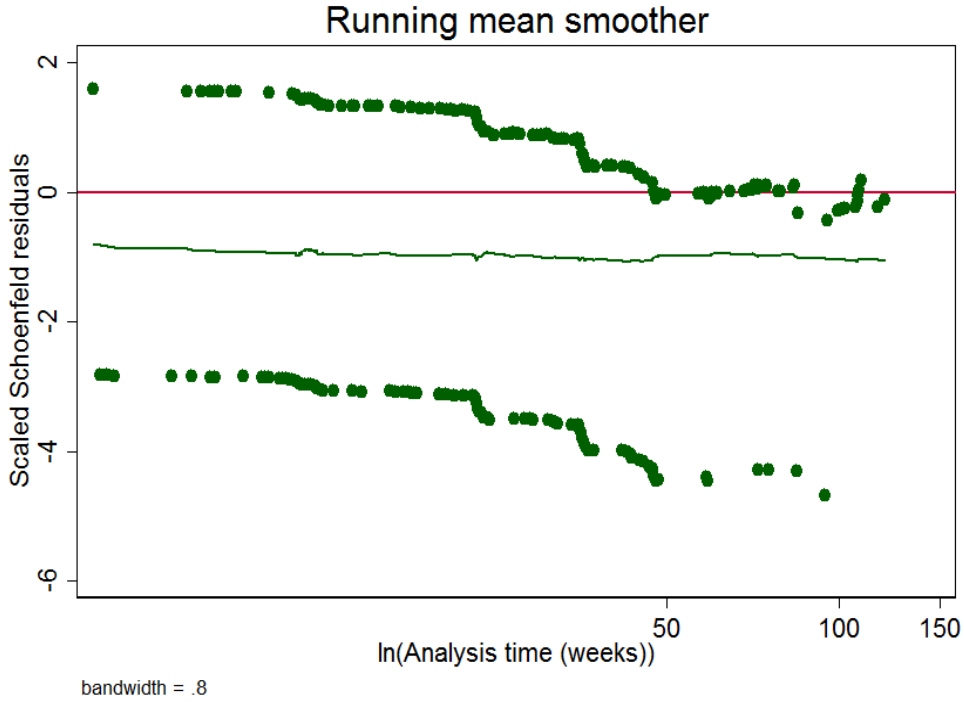
Key: BRCA, breast cancer gene; ITT, intention-to-treat; OS, overall survival.

Figure 23: Log-cumulative hazard plot for PFS INV – ARIEL 3 – ITT



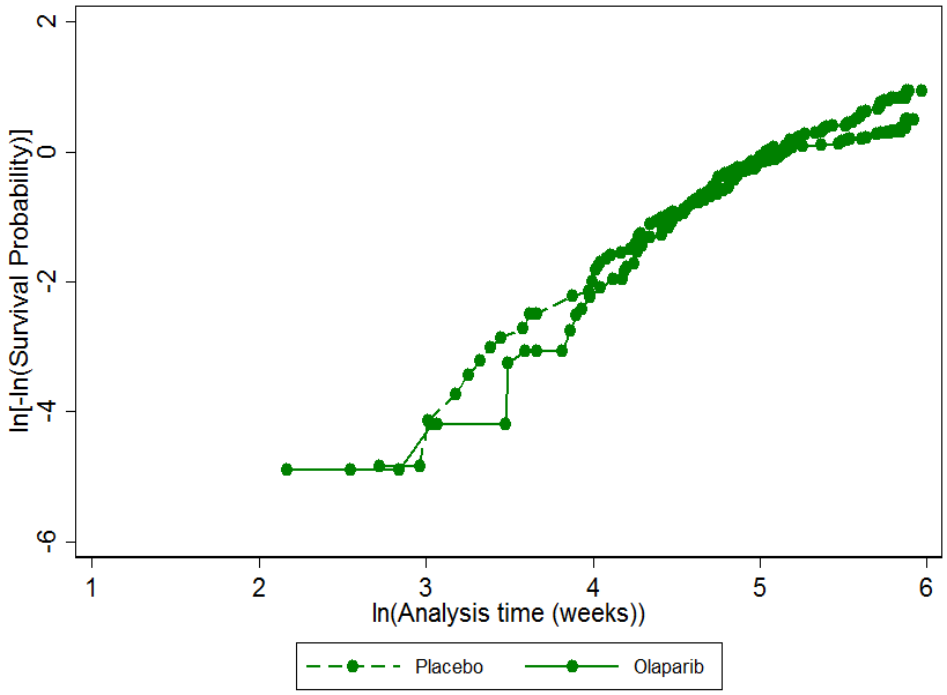
Key: BRCA, breast cancer gene; INV, investigator; ITT, intention-to-treat; PFS, progression-free survival.

Figure 24: Schoenfeld plot for PFS INV – ARIEL 3 – ITT



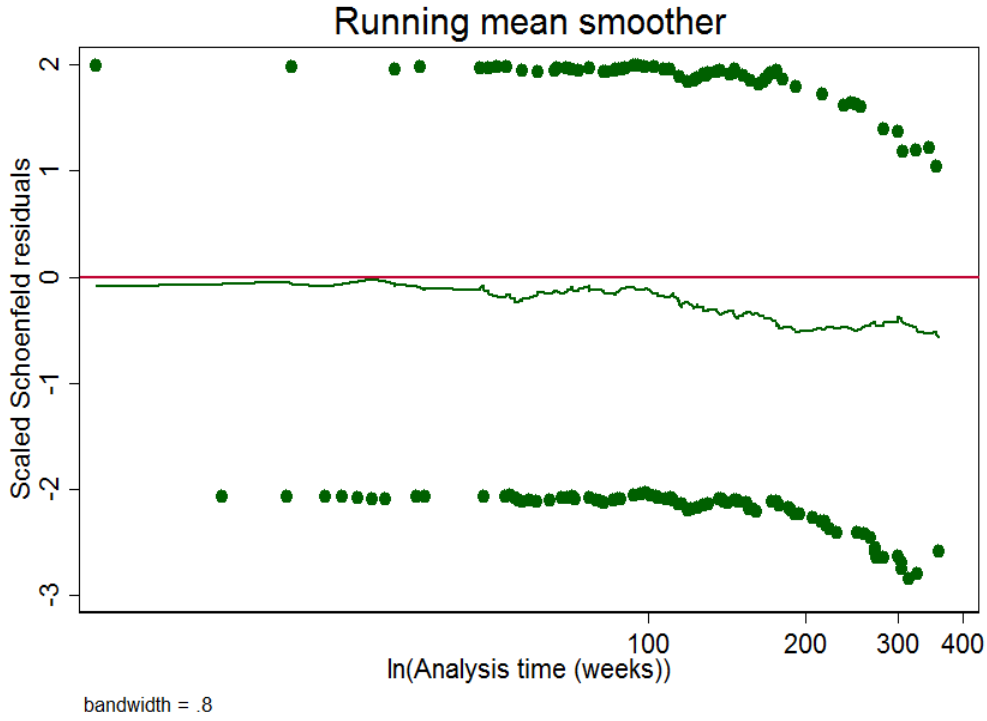
Key: BRCA, breast cancer gene; INV, investigator; ITT, intention-to-treat; PFS, progression-free survival.

Figure 25: Log-cumulative hazard plot for OS – Study 19 – ITT



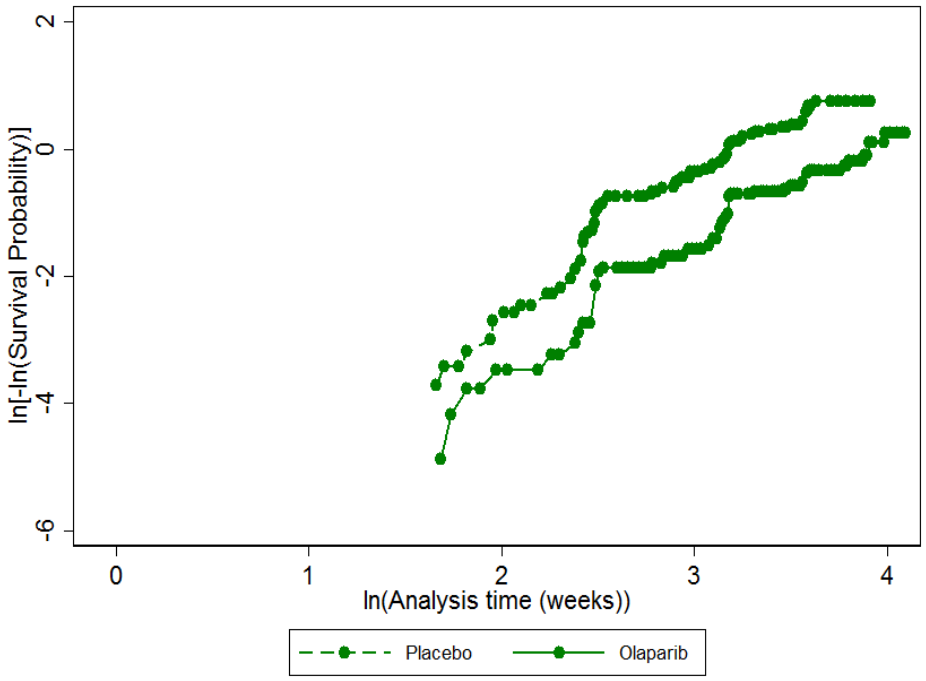
Key: BRCA, breast cancer gene; ITT, intention-to-treat; OS, overall survival.

Figure 26: Schoenfeld plot for OS – Study 19 – ITT



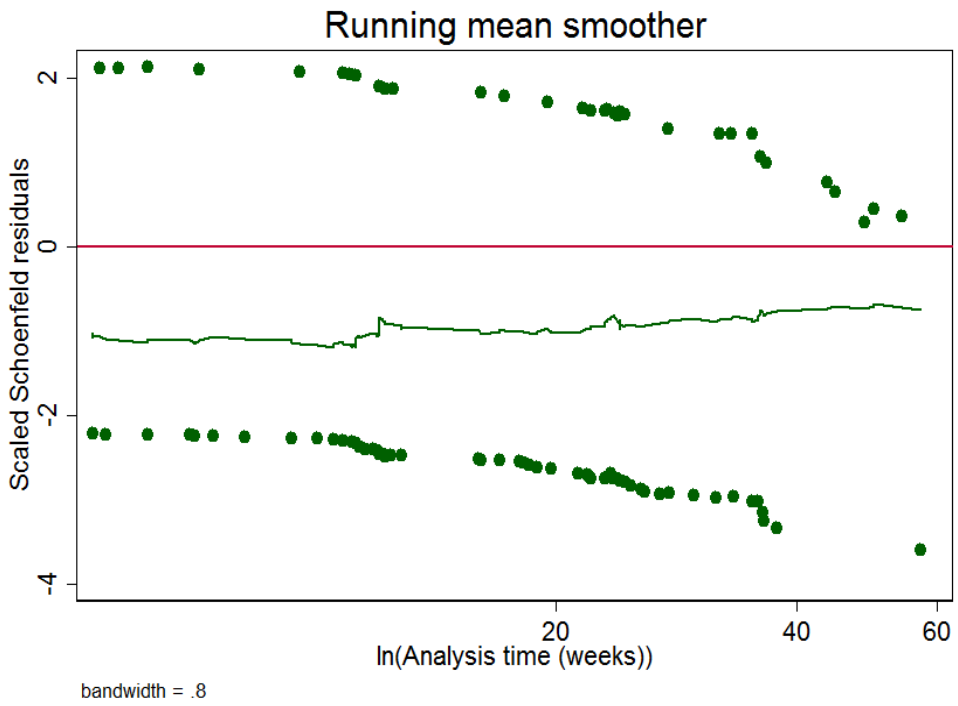
Key: BRCA, breast cancer gene; ITT, intention-to-treat; OS, overall survival.

Figure 27: Log-cumulative hazard plot for PFS INV – Study 19 – ITT



Key: BRCA, breast cancer gene; INV, investigator; ITT, intention-to-treat; PFS, progression-free survival.

Figure 28: Schoenfeld plot for PFS INV – Study 19 – ITT



Key: BRCA, breast cancer gene; INV, investigator; ITT, intention-to-treat; PFS, progression-free survival.

Table 4: Global test of proportional-hazards assumption, p-value

	Non-BRCA	BRCA 2L	BRCA 3L+	ITT
ARIEL 3 – OS	[redacted]	[redacted]	[redacted]	[redacted]
ARIEL 3 – PFS INV	[redacted]	[redacted]	[redacted]	[redacted]
Study 19 - OS	0.134	-	0.190	0.199
Study 19 – PFS INV	0.657	-	0.821	0.521
SOLO 2 – OS	-	-	-	-
SOLO 2 – PFS INV	-	-	0.846	-

Key: 2L, second line; 3L+, third line plus; BRCA, breast cancer gene; INV, investigator; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

We hope the provision of this further information helps the ERG understand the proportional hazards testing and consider this as part of our response to A5.

A5. Priority Question: Please explain the different interpretation of the assessment of proportional hazards between the clinical and economic sections. Table 9, Appendix D concludes that proportional hazards hold for all outcomes in all populations and all trials tested, whereas in Document B, Section B.3.3 separate models are being fitted to the data for PFS (INV) for ARIEL3 ITT and BRCA 3L+ populations, and for PFS and OS for Study 19 ITT and BRCA 3L+ populations, indicating that proportional hazards may not hold.

Response: The assumption of proportional hazards was found to hold for progression-free and overall survival data from ARIEL3 in both the ITT population and the BRCA 3L+ subgroup. In line with NICE TSD 14 guidance[8], as patient-level data were available for ARIEL3, individual models were fitted for each treatment arm, keeping the same functional form across arms. Statistical fit was considered by comparing the sum of individual AICs to the AIC of joint fit models, and found the separate fit models were best. Visual inspection and comparing to reported data at key milestones (1 year, 2 years, median) also indicated separate models fitted best. For the BRCA 3L+ population, only the rucaparib arm of ARIEL3 is incorporated into the model; as such, modelling rucaparib and placebo arms together was deemed to add more noise.

Within the BRCA 3L+ population, PFS and OS outcomes from Study 19 were included in the model. For both outcomes, only the olaparib arm was included in the model. As for ARIEL3 PFS, it was deemed more appropriate to model the olaparib

arm only than to model the olaparib and placebo arms together, acknowledging that placebo would not be required for the model.

Within the ITT population, PFS and OS outcomes from Study 19 were included in the model. PFS outcomes for olaparib and placebo were modelled separately. For modelling OS, it was deemed to be appropriate to choose a distribution consistent with the base case from the ongoing olaparib appraisal (NICE ID 1296), in which Study 19 ITT data are modelled. Within this appraisal, Royston and Parmar spline models were fitted[5], therefore this method was used within the model base case.

A6. Priority Question: In Appendix D, it is mentioned that potential treatment effect modifiers were identified by the systematic literature review (SLR) and that the list of effect modifiers was validated by a clinical expert of ovarian cancer operating in the UK.

a) **Please provide the list of treatment effect modifiers identified through the SLR, with reference details.**

b) **For each treatment effect modifier identified for PARPis (Appendix D, Table 11), please provide the clinical rationale and/or biological plausibility for it to be a treatment effect modifier rather than a prognostic indicator?**

Response: The list of potential effect modifiers was obtained by considering:

- All factors used as stratification factors in the randomisation of the ARIEL3, SOLO2 and Study 19 trials
- All factors identified as potential effect modifiers in previous NICE submissions
- All factors for which baseline characteristics were available in both ARIEL3 and at least one comparator trial (i.e. SOLO2, Study 19)
- All factors for which subgroup analyses were planned in the ARIEL3, SOLO2 and Study 19 trials
- Clinical experts were asked to complement the list of effect modifiers if they believed that any effect modifier was not already included in the list

To clarify, the SLR helped identify publications for comparator trials in which baseline characteristics were available. Treatment effect modifiers and prognostic factors

were discussed during an advisory validation interview with a UK clinical expert on 14 June 2018. The clinical expert confirmed their opinion but did not provide any biological or clinical rationale for these factors being treated as effect modifiers rather than prognostic factors

In Table 5, the effect modifiers confirmed by the clinical expert are listed. Prof. Ledermann was presented with the complete list of potential modifiers without alluding to whether they should be effect modifiers or prognostic factors to come to the list outlined in the table below. A list of potential modifiers was presented to the expert without alluding to whether they should be effect modifiers or prognostic factors. During the interview, the expert considered carefully whether a factor was an effect modifier or a prognostic factor. Main conclusions from this interview were:

- The clinical expert confirmed that in his opinion BRCA mutation, progression-free interval and response to prior platinum therapy are effect modifiers.
- FIGO classification is a prognostic factor rather than an effect modifier. FIGO score is determined at the time of diagnosis and the FIGO classification changed in recent years. Time since diagnosis and tumour size are prognostic factors, not effect modifiers.
- According to Prof. Ledermann, the number of prior lines of therapy, and number of metastatic sites, age, Jewish ancestry and smoking are not treatment effect modifiers. Prior use of bevacizumab is not relevant, and it is not an effect modifier. Asian populations might have a different metabolism dealing with treatment, but race is unlikely to be an effect modifier.
- According to Prof. Ledermann , there is some evidence that BMI affects how well patients tolerate niraparib, with lower BMI associated with worse tolerance. In terms of effect modification, it's a grey area.

Table 5: Effect modifiers and prognostic factors considered

Effect modifiers
BRCA mutation
Number of prior lines of platinum therapy
Length of the progression-free interval (PFI)
Response to prior platinum treatment
Body mass index (BMI)
Other prognostic factors
Number of prior lines of chemo
BRCA type 2
ECOG score
Tumour site
Number of tumour lesion(s) at baseline
Number of metastatic sites
Histological tumour type
FIGO score
Prior use of bevacizumab
Time since diagnosis
Time since last platinum therapy
Age
Race
Jewish ancestry

A7. Please provide number of patients in ARIEL3 who went on to receive subsequent therapy and the number of these patients who received platinum-based therapy as their first subsequent treatment in the following populations:

a) BRCA 3L+

b) BRCA 2L

c) Non-BRCA

Response: The numbers of patients receiving any subsequent therapy and the numbers among those who received a platinum-based therapy as their first subsequent therapy based on the 15 April 2017 data cut are shown in Table 6. Platinum-based therapy was defined as any regimen containing any platinum-based

agent (as combination or monotherapy). Platinum agents received by ARIEL3 patients included carboplatin, cisplatin and oxaliplatin.

Table 6: Subsequent therapy data – ARIEL 3 – post-hoc analyses

	Any subsequent therapy, n/N			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]
Key: 2L, second line; 3L+, third line plus; BRCA, breast cancer gene; ITT, intention-to-treat.						

A8. Please provide the methods and results for the meta-analysis of the 3L and 4L+ data for SOLO2 used in the MAIC (Appendix D, page 50)

Response: Data inputs came from Penson et al. (2017; ESMO poster)[9], which reported that the hazard ratio (95% confidence interval) of olaparib vs placebo in the BRCA3L population in SOLO2 is 0.24 (0.13, 0.42) [based on 80 patients]. The same study reported that the hazard ratio (95% confidence interval) of olaparib vs placebo in the BRCA4L+ population in SOLO2 is 0.26 (0.13, 0.51) [based on 42 patients]. A direct meta-analysis was performed pooling the hazard ratio reported above. The pooled estimate was 0.248 (0.159, 0.387). The pooling results are presented in Figure 29.

Figure 29: Pooling results from the meta-analysis of the 3L and 4L+ data

```
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            Study     |     ES    [95% Conf. Interval]     % Weight
----------------------+-------------------------------------------------
1                     |  0.240       0.130     0.420         57.60
2                     |  0.260       0.130     0.510         42.40
----------------------+-------------------------------------------------
I-V pooled ES         |  0.248       0.159     0.387        100.00
----------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =   0.03 (d.f. = 1) p = 0.862
  I-squared (variation in ES attributable to heterogeneity) =   0.0%

  Test of ES=1 : z=   6.14 p = 0.000
```

A9. Please provide the number of patients in each treatment arm of ARIEL3 recruited in the UK, along with the baseline characteristics of these patients.

Response: In ARIEL 3, a total of [redacted] patients were recruited from the United Kingdom. Of these [redacted] patients, [redacted] patients were randomized to the rucaparib arm and [redacted] patients were randomized to the placebo arm. Baseline characteristics for UK patients are provided in Table 7.

Table 7: Baseline characteristics of UK patients in ARIEL3

	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]

	Rucaparib (n=41)	Placebo (n=26)	Total (n=67)
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]

	Rucaparib (n=41)	Placebo (n=26)	Total (n=67)
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 Gynaecology and Obstetrics; LOH, loss of heterozygosity; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.
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.

A10. Please confirm if the anchored MAIC of the BRCA 3L+ population was adjusted only for platinum-free interval and response to prior platinum-based chemotherapy.

Response: Yes, the anchored MAIC of the BRCA3L+ population (both ARIEL3 vs Study19 and ARIEL3 vs SOLO2) were adjusted for:

- Platinum-free interval >12 months
- Response to prior platinum-based chemotherapy

To avoid confusion, these analyses were conducted on the subset of BRCA patients with 3 or more prior lines of platinum therapy; therefore, the MAIC analyses also "passively" adjusted for these factors.

Section B: Clarification on cost-effectiveness data

Please note that if as a result of the responses to the cost-effectiveness clarification questions the company base case analyses are revised, please indicate for each of the populations (subgroups) what assumptions are considered for the revised base case, ensuring that all parameters are aligned with the population (subgroup) under consideration and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses in the response document.

B1. Priority Question: Please clarify if the patient access scheme (PAS) for olaparib is included in the model (i.e. the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company)? Please see here for further details: (https://www.nice.org.uk/guidance/ta381/chapter/5-implementation

a) **If it has not been included, please provide revised results including the PAS for olaparib for the base case analysis, deterministic sensitivity analysis, probabilistic sensitivity analysis and all scenarios requested in this letter.**

Response: The originally submitted model did not include the PAS for olaparib. This has been added, in addition to other requests to change the base case in questions B20, B21 and B22. As such, in the new company base case, the vial sharing option is switched off, no costs are applied for BRCA testing, and all costs have been inflated to cost year 2018.

A summary of the results of the revised base case for the ITT population is presented in Table 8, and the results for the BRCA 3L+ population are provided in Table 9. Revised probabilistic results are provided in Table 13 and Table 14 for 2,000 PSA iterations and indicate that results are consistent with the base case. Revised tornado diagrams are presented in Figure 30 and Figure 31. A revised list of scenario analyses is provided in Table 12. Two additional scenarios have been

incorporated; calculating PPS as the residual of OS from Study 19 and PFS from ARIEL3 (question B2) and considering RDI from ARIEL3 (question B19).

Table 8: Revised deterministic base-case results for the ITT population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	3.060	[redacted]				
Rucaparib	[redacted]	4.919	[redacted]	[redacted]	1.859	[redacted]	50,681
Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.							

Table 9: Revised deterministic base-case results for the BRCA 3L+ population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Olaparib	[redacted]	3.091	[redacted]				
Rucaparib	[redacted]	3.091	[redacted]	[redacted]	0.000	[redacted]	Rucaparib dominated
Key: 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.							

Table 10: Revised probabilistic base-case results for the ITT population

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	49,504

Table 11: Revised probabilistic base-case results for the BRCA 3L+ population

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated

Figure 30: Revised tornado diagram for the ITT population

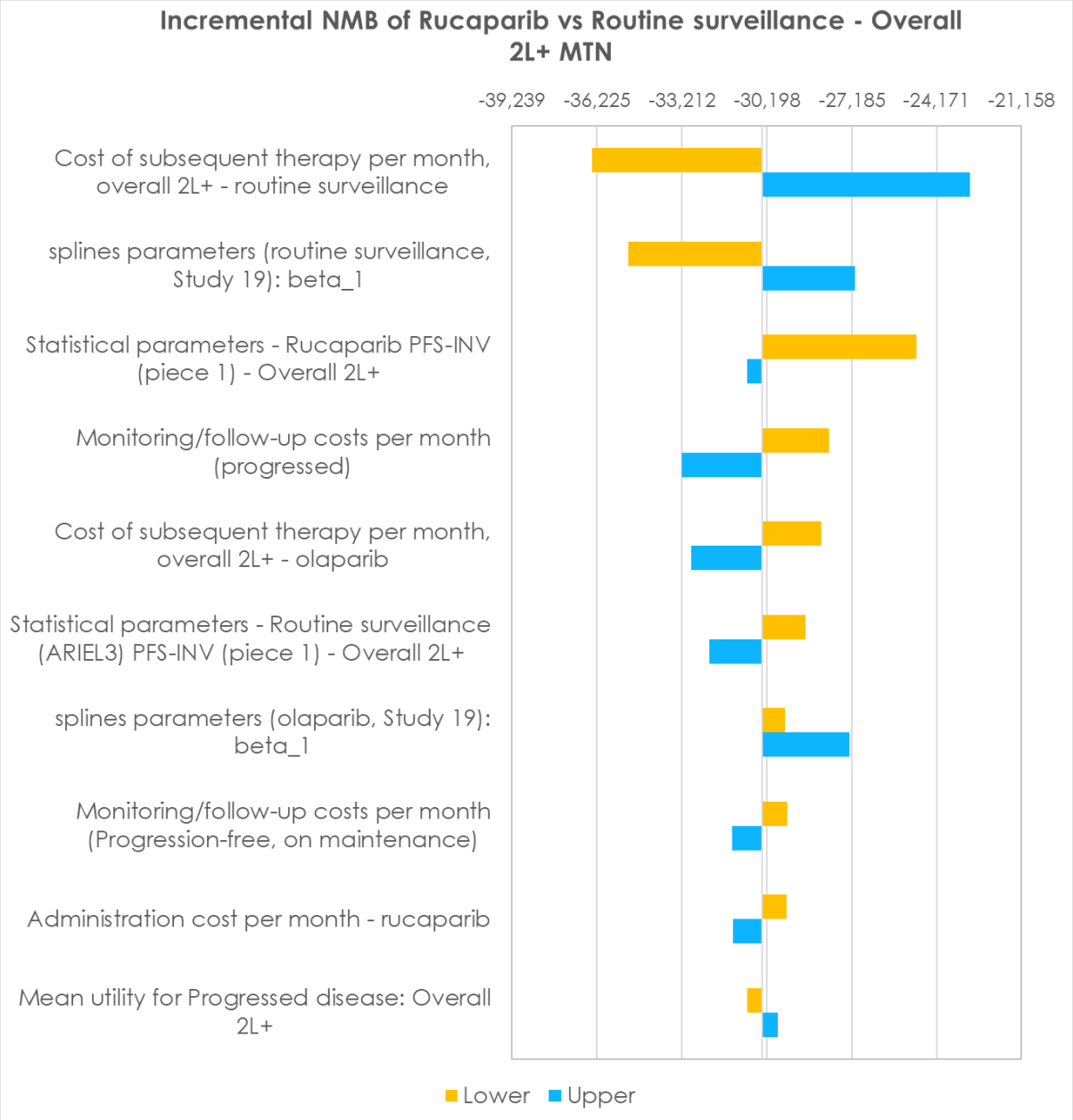

Figure 31: Revised tornado diagram for the BRCA 3L+ population

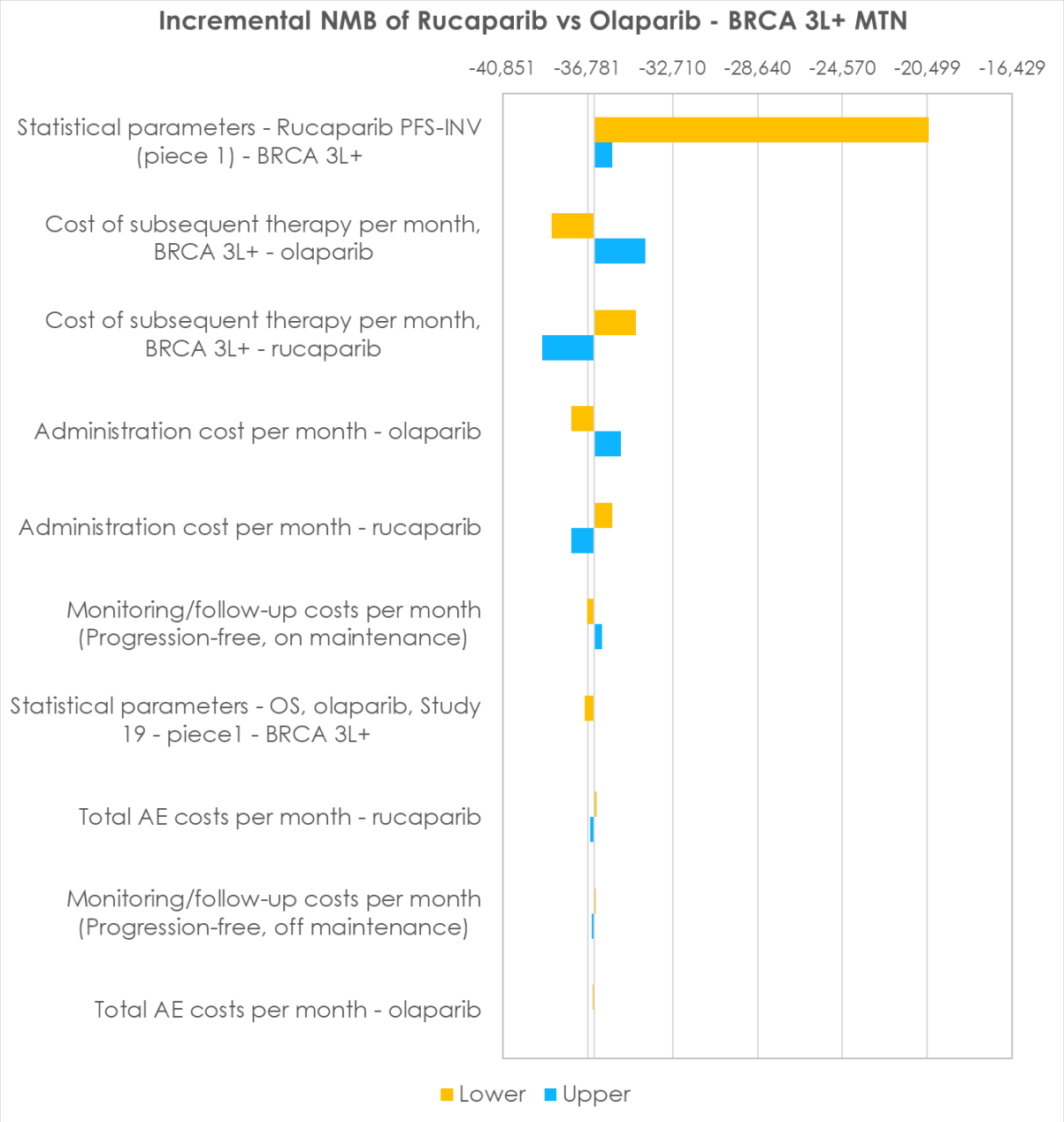

Table 12: Revised list of scenario analyses

	ITT population	BRCA 3L+ population
	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

	ITT population	BRCA 3L+ population
	ICER vs routine surveillance	**ICER vs olaparib**
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

	ITT population	BRCA 3L+ population
	ICER vs routine surveillance	ICER vs olaparib
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		

B2. Priority Question: The NICE final scope states that, "If the evidence allows, consideration will be given to subgroups with or without BRCA mutations". In the economic model, analysis is only provided for the ITT and the 3L+ BRCA populations. Furthermore, the ERG considers that the way OS is calculated for the ITT population overstates the number of patients at the end of each cycles (i.e. the sum of all the health states for each cycle is greater than 1).

a) **In line with the final scope, please provide subgroup analysis for the following populations:**

   i. **Non-BRCA (rucaparib vs routine surveillance)**

   ii. **BRCA 2L only (rucaparib vs routine surveillance)**

The ERG suggests each subgroup is analysed as outlined in Table 13, to ensure that total proportions of patients per cycle sums to 1. Please make sure to include controls in the model so that PFS, TTD and OS curves do not cross.

The ERG acknowledges the following assumptions and limitations with the approach suggested in Table 13, but considers that this methodology best utilises the ARIEL3 data that are available:

- **PFS and OS outcomes are disconnected due to the use of two different sources of data.**
- **OS outcomes for rucaparib are assumed to be at least as good as for olaparib.**
- **Routine surveillance in ARIEL3 and Study 19 are similar.**
- **Study19 OS for the BRCA 2L only subgroup includes all BRCA patients regardless of line of therapy, but this is the best available data for the subgroup.**

Table 13: ERG preferred approach to subgroup analyses

	non-BRCA		BRCA 2L only	
Parameter	Rucaparib	Routine surveillance	Rucaparib	Routine surveillance
PFS	ARIEL3	ARIEL3	ARIEL3	ARIEL3
OS	Study 19 (Ledermann 2016, Figure 2, graph C)	Study 19 (Ledermann 2016, Figure 2, graph C)	Study 19 (Ledermann 2016, Figure 2, graph B)	Study 19 (Ledermann 2016, Figure 2, graph B)
PPS	Study19 OS minus ARIEL3 PFS	Study19 OS minus ARIEL3 PFS	Study19 OS minus ARIEL3 PFS	Study19 OS minus ARIEL3 PFS
TTD	ARIEL3	-	ARIEL3	-

Response:

Health states summing to one in submitted model

The approach in the company base case aims to combine pre-progression outcomes from ARIEL3 and post-progression outcomes from Study 19 to approximate overall lifetime outcomes for patients receiving rucaparib. Individual partitioned survival

models, one for rucaparib in ARIEL3 and one for olaparib in Study 19, are used to calculate cumulative, discounted mean health and cost outcomes. Those outcomes are then combined to provide overall lifetime health and cost outcomes for rucaparib. This method uses mature ARIEL3 PFS trial data and mature OS data from Study 19 and follows past ERG recommendations for assuming equal PPS between PARP inhibitors.

Within each individual partitioned survival model, the patient flow across health states always sum to one. However, it is not appropriate to expect the patient flow across the individual partitioned survival models to sum to one using this method. Between the models, there is no direct link at each cycle since only the cumulative lifetime outcomes are summed. The approach does not involve any combination of states between different partitioned survival models at the cycle level.

Method for predicting post-progression outcomes

A simplified means-based approach has been implemented in previous TAs in maintenance therapy for advanced ovarian cancer.[10] Mean LYs in pre- and post-progression were multiplied with utilities and unit costs to calculate overall outcomes. This approach was criticised in TA528 and described as an 'oversimplified' method of estimating outcomes, as opposed to a partitioned survival approach.[10] The approach used within this appraisal was developed specifically to improve on that main concern, while not restricting the analysis so that PFS gain can still translate into OS benefit. Mean outcomes are calculated from partitioned survival models, in which costing and discounting are applied to fully extrapolated curves. Calculated costs and QALYs accurately reflect the rate at which health state occupancy changes each cycle over time by considering each partitioned survival model, and as such we believe this approach to be preferable compared to the means-based approach in TA528 for predicting post-progression outcomes.

It is acknowledged that this approach still has limitations. One is related to the application of discounting in post-progression outcomes. In Study 19 post-progression outcomes start to be discounted upon progression, therefore the degree of discounting over the time horizon depends on the PFS for the olaparib arm from Study 19. The discounted outcomes are then added to rucaparib's pre-progression

outcomes. However, since rucaparib and olaparib PFS differ, there will be a slight discrepancy in the degree of discounting for post-progression outcomes between rucaparib and olaparib. The impact of this discrepancy on the results is expected to be minimal - approximately 1.4%, proportional to the mean difference between PFS for olaparib and rucaparib.

In addition, with the olaparib PFS the incident number of progressing patients is different and the mortality hazard impacting those who are progressing could be different. Since PFS is longer with ARIEL3, patients would be dying with a hazard rate of that later timepoint. These issues could only be resolved if time from progression to death (i.e. complete post-progression survival curves) were to be available from olaparib based on Study 19. However, these data were not available to us in the public domain. With those data, patient level modelling techniques would be required to overcome limitations faced by the current approach; however, these have been criticized in previous ERG reports, where there was a stated preference for a simple partitioned survival analysis approach. Our approach was determined based on previous TAs in maintenance therapy for advanced ovarian cancer and stated preferences by the ERG. [10]

Concerns with the ERG's suggested approach

It is acknowledged that health states would sum to one using a simple partitioned survival approach suggested by the ERG, where PFS is estimated using ARIEL3 data, OS is based on mature data from Study 19, and PPS is the residual of PFS and OS.

However, this recommended approach has also implications on the mortality hazard. Namely, the modelling approach suggested by the ERG assuming the same OS irrespective of any PFS gain suggests that patients progressing later on a treatment providing PFS benefit will have a much higher mortality hazard, resulting in shorter PPS outcomes. The company is not aware of any clinical rationale supporting the ERG's assumption. Conversely, long-term Study 19 data from Friedlander *et al.* 2018 demonstrate a continued benefit of olaparib versus placebo for TSST and OS, supporting the notion that responders to PARP therapy see benefits beyond PFS.[11] Clinical experts suggested that the assumption of equivalence in PPS across PARPi

maintenance treatments is plausible. Finally, expert clinicians support the earliest possible use of a PARPi exactly because in their experience the PFS gain is not lost but is longer the earlier the patients can receive the therapy.

Therefore, we do not believe the ERG's suggested approach is consistent with the expected clinical course of the disease with PARP inhibitors. Models should be designed to best reflect the clinical progression of the disease.

Based on the above reasons, the company believes that the most appropriate method for estimating post-progression outcomes is to calculate outcomes from Study 19, as in the original submission, which has been developed based on the ERG's criticisms of TA528 methods. If the ERG's main concern of health states not summing to one remains, an alternative approach based on a PFS-OS relationship is available. We believe the PFS-OS approach, while having severe limitations, is still preferable to the ERG's suggested approach as it does not impose the assumption that patients progressing on a therapy providing longer PFS die at an accelerated rate.

Nonetheless, a scenario using the simple partitioned survival approach suggested by the ERG is shown below for the ITT population, in Table 14, using the updated base case (presented in Table 8). We have updated the list of scenarios to include this scenario (see Table 12).

Table 14: Updated deterministic ITT analysis with implied PPS approach

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	59,078

Subgroup analyses (non-BRCA 2L+ and BRCA 2L only)

As described in detail within the response to question A1, the ARIEL 3 study was not designed to measure differences between rucaparib and placebo in these subgroups. As such, Clovis Oncology advises caution when interpreting results based on this post-hoc analysis, given the uncertainty surrounding this.

However, the desire for the analysis to reflect the NHS funding structure in England is acknowledged. Given that according to England NHS funding, patients in these subgroups have access to niraparib available on the CDF, we believe it is of interest and informative to consider cost-effectiveness results versus niraparib in addition to results versus routine surveillance within the analyses for these subgroups to allow for complete overview. Within this appraisal, NICE's own budget impact assessment considers niraparib as a relevant comparator with relatively large market shares. As such, for this response niraparib is included as a comparator although it is not considered a comparator for the appraisal.

To provide clarity on the approach to this response, we have provided a fuller version of Table 13 below, in Table 15. For PFS and TTD, curve fits were selected based on those providing the lowest AIC/BIC. For OS, one-knot spline models were fit to Study 19 data, consistent with previous submissions.[5] OS data for the non-BRCA population were available from Study 19. However, Study 19 OS curves were not available for BRCA 2L subgroup specifically, therefore, OS data from the BRCA 2L+ group were assumed to be sufficiently similar for responding to this question. Similarly, investigator-assessed PFS data for niraparib were not available for BRCA 2L only, therefore BRCA 2L+ niraparib data from NOVA were used to inform the comparison to niraparib in the BRCA 2L subgroup. Due to imbalances in the studies (detailed within Appendix D of the original submission for this appraisal), the PFS comparison to niraparib uses anchored MAIC-adjusted HRs. The non-BRCA HR for rucaparib versus niraparib is [redacted] (CI [redacted]), while the BRCA 2L+ HR for rucaparib versus niraparib is [redacted] (CI [redacted]). TTD curves were available for niraparib from TA528 and are directly used within these analyses. As highlighted earlier in the response to this question, we believe calculating post-progression outcomes based on Study 19 to be the most appropriate approach and as such this is implemented within the response to this question.

Table 15: Company approach to non-BRCA 2L+ and BRCA 2L subgroup analyses

	ERG				Clovis Oncology					
	non-BRCA		BRCA 2L only		non-BRCA 2L+			BRCA 2L only		
Parameter	Rucaparib	Routine surveillance	Rucaparib	Routine surveillance	Rucaparib	Routine surveillance	Niraparib	Rucaparib	Routine surveillance	Niraparib
PFS	ARIEL3	ARIEL3	ARIEL3	ARIEL3	ARIEL3 Gen gamma	ARIEL3 Gen gamma	MAIC NOVA, ARIEL3	ARIEL3 Lognormal	ARIEL3 Lognormal	MAIC BRCA 2L+ NOVA, ARIEL3
OS	Study 19 (Lederman 2016, Figure 2, graph C)	Study 19 (Lederman 2016, Figure 2, graph C)	Study 19 (Lederman 2016, Figure 2, graph C)	Study 19 (Lederman 2016, Figure 2, graph C)	Study 19 Non-BRCA OS 1-knot spline	Study 19 Non-BRCA OS 1-knot spline	Study 19 Non-BRCA OS 1-knot spline	Study 19 BRCA 2L+ OS 1-knot spline	Study 19 BRCA 2L+ OS 1-knot spline	Study 19 BRCA 2L+ OS 1-knot spline
PPS	Study19 OS minus ARIEL3 PFS (Implicit PPS)	Study19 OS minus ARIEL3 PFS (Implicit PPS)	Study19 OS minus ARIEL3 PFS (Implicit PPS)	Study19 OS minus ARIEL3 PFS (Implicit PPS)	Study19 post-progression outcomes (Spline for OS, Gen gamma for PFS)	Study19 post-progression outcomes (Spline for OS, Gen gamma for PFS)	Study19 post-progression outcomes (Spline for OS, Gen gamma for PFS)	Study19 post-progression outcomes (Spline for OS, Lognormal for PFS)	Study19 post-progression outcomes (Spline for OS, Lognormal for PFS)	Study19 post-progression outcomes (Spline for OS, Lognormal for PFS)

	ERG				Clovis Oncology					
	non-BRCA		BRCA 2L only		non-BRCA 2L+			BRCA 2L only		
Parameter	Rucaparib	Routine surveillance	Rucaparib	Routine surveillance	Rucaparib	Routine surveillance	Niraparib	Rucaparib	Routine surveillance	Niraparib
TTD	ARIEL3	-	ARIEL3	-	ARIEL3 Log-logistic	-	NOVA Non-BRCA 2L+ (TA528) Weibull	ARIEL3 Lognormal	-	NOVA BRCA 2L (TA528) Weibull
Utilities					ARIEL3 ITT			ARIEL3 ITT		
AEs					ARIEL3 ITT	ARIEL3 ITT	Equal to rucaparib	ARIEL3 ITT	ARIEL3 ITT	Equal to rucaparib
Sub tx %					ARIEL3 ITT	ARIEL3 ITT	Equal to rucaparib	ARIEL3 ITT	ARIEL3 ITT	Equal to rucaparib
Acquisition cost					List price after PAS	-	List price	List price after PAS	-	List price

The results for the non-BRCA 2L+ and BRCA 2L only populations are presented in Table 16 and Table 17, respectively.

Table 16: Incremental cost-effectiveness results for non-BRCA population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	2.832	[redacted]				
Rucaparib	[redacted]	5.211	[redacted]	[redacted]	2.378	[redacted]	33,340
Niraparib	[redacted]	4.772	[redacted]	[redacted]	-0.438	[redacted]	Niraparib dominated

Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.

Table 17: Incremental cost-effectiveness results for BRCA 2L population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	3.513	[redacted]				
Rucaparib	[redacted]	6.550	[redacted]	[redacted]	3.036	[redacted]	58,054
Niraparib	[redacted]	6.186	[redacted]	[redacted]	-0.364	[redacted]	Niraparib dominated

Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.

The incremental cost-effectiveness results indicate that rucaparib dominates niraparib in both subgroups, providing similar life year and QALY gains in both comparisons for a lower cost. Results of the BRCA 2L analysis produce a slightly higher ICER versus routine surveillance than the ITT comparison, explained by the longer time on treatment for these patients. As described earlier, the BRCA 2L subgroup carries the most assumptions of those presented due to the limited data available, and as such the outcomes should be interpreted with extreme caution. Results of the non-BRCA 2L+ analysis indicate rucaparib has a much lower ICER in this subgroup (£33,340 versus routine surveillance) compared to the ITT comparison.

Given the uncertainty surrounding the data for the analyses in these subgroups, a variety of scenarios are provided in Table 18 for both populations. To explore uncertainty around OS methodology, as in the originally submitted model several scenarios are tested using the PFS-OS ratio method, using ratios of 1 and 2. Assumptions around niraparib PFS and treatment discontinuation are also explored. The list of scenarios presented here is shorter than that for the main analysis (Table 12), as many of those scenarios correspond to specific inputs for those populations. Notably, rucaparib remains dominant versus niraparib for all the scenarios presented in both the non-BRCA 2L+ and BRCA 2L populations, even when assuming PFS equivalence.

Table 18: Scenario analysis for Non-BRCA 2L+ and BRCA 2L populations

	Non-BRCA 2L+		**BRCA 2L**	
Scenario	**Rucaparib vs routine surveillance**	**Rucaparib vs niraparib**	**Rucaparib vs routine surveillance**	**Rucaparib vs niraparib**
Base case	£ 33,340	Rucaparib dominant	£ 58,054	Rucaparib dominant
PFS-OS ratio = 1, routine surveillance PFS: ARIEL3	£ 58,977	Rucaparib dominant	£ 104,939	Rucaparib dominant
PFS-OS ratio = 2, routine surveillance PFS: ARIEL3	£ 35,560	Rucaparib dominant	£ 61,415	Rucaparib dominant
PFS-OS ratio = 1, routine surveillance PFS: based on HR	£ 57,726	Rucaparib dominant	£ 105,704	Rucaparib dominant
PFS-OS ratio = 2, routine surveillance PFS: based on HR	£ 34,916	Rucaparib dominant	£ 61,819	Rucaparib dominant
PFS-OS ratio = 1, routine surveillance PFS: ARIEL3; Ruca and nira constant discontinuation rate	£ 59,543	Rucaparib dominant	£ 72,373	Rucaparib dominant
PFS equivalence (Nira PFS HR = 1)	£ 33,340	Rucaparib dominant	£ 58,054	Rucaparib dominant
Apply relative mean dose intensity from ARIEL3 for rucaparib and NOVA for niraparib	£29,953	Rucaparib dominant	£52,346	Rucaparib dominant
Subpopulation specific subsequent treatments and subsequent	£36,719	Rucaparib dominant	£43,221	Rucaparib dominant

	Non-BRCA 2L+		BRCA 2L	
Scenario	**Rucaparib vs routine surveillance**	**Rucaparib vs niraparib**	**Rucaparib vs routine surveillance**	**Rucaparib vs niraparib**
PARPi therapy duration				
Mean health state utility values for subgroup	N/A	N/A	£58,201	Rucaparib dominant
Calculate PPS as residual of OS and PFS (ERG's preferred approach)	£45,217	Rucaparib dominant	£79,007	Rucaparib dominant

B3. Priority Question: Please provide a scenario for the 3L+ BRCA subgroup that is modelled as outlined in Table 19. Based on the response to question A4, if proportional hazards only hold for one trial (e.g. ARIEL3), please use the other trial (e.g. Study 19) to model the PFS curves independently and then apply the hazard ratio of treatment vs routine surveillance from the trial where proportional hazards hold to the baseline routine surveillance curve.

a) **As an additional scenario, please perform a simple cost comparison scenario which includes the published olaparib PAS.**

Table 19: ERG preferred approach to 3L+ BRCA analysis

Parameters	**3L+ BRCA**	
	Rucaparib	**Olaparib**
PFS	ARIEL3	**Scenario 1** - NMA Study 19, ARIEL3 (CQ A3a) **Scenario 2** - anchored MAIC, Study 19, ARIEL3
OS	Study 19	Study 19
PPS	Study 19 OS minus ARIEL3 PFS	Study19 OS minus olaparib PFS curve
TTD	ARIEL3	Study 19 (olaparib ACD2 committee papers - company response to ACD2, figure 2)

Response: In addition to the two scenarios requested by the ERG, a full range of ITC scenarios are presented to demonstrate the impact of using different sources for indirect comparisons on the results. For clarity on the approach to this response, a fuller version of Table 19 is presented below, in Table 20.

Table 20: Company approach to 3L+ BRCA analysis

	ERG		Response	
	3L+ BRCA		3L+ BRCA	
Parameters	**Rucaparib**	**Olaparib**	**Rucaparib**	**Olaparib**
PFS	ARIEL3	**Scenario 1** - NMA Study 19, ARIEL3 (CQ A3a) **Scenario 2** - anchored MAIC, Study 19, ARIEL3	ARIEL3	**ARIEL3** **Scenarios based on PFS ITC**
OS	Study 19	Study 19	Study 19	Study 19
PPS	Study 19 OS minus ARIEL3 PFS	Study19 OS minus olaparib PFS curve	Study19 OS minus olaparib PFS curve	Study19 OS minus olaparib PFS curve
TTD	ARIEL3	Study 19 (olaparib ACD2 committee papers - company response to ACD2, figure 2)	ARIEL3	Study 19 (olaparib ACD2 committee papers - company response to ACD2, figure 2) Log-logistic*
Utilities			ARIEL3 ITT Scenario: Subgroup analysis	
AEs			ARIEL3 ITT	Study 19 ITT
Subsequent treatments			ARIEL3 ITT	
Acquisition cost	List price with PAS	List price with PAS	List price with PAS	List price with PAS

*Used in ACD2 response document, and lowest AIC/BIC within parametrisations done for this analysis

Of note, the approach to post-progression survival is essentially the same as for the originally submitted base case, except for the changes to base case taken as part of questions B1, B20, B21 and B22.

The PFS scenarios explored are detailed below, reflecting the multitude of ITC options presented in the original submission (Appendix D):

1. OS equivalence, olaparib PFS predicted by base case NMA (Table 21)
2. OS equivalence, olaparib PFS predicted by MAIC (Study 19, Table 22)
3. OS equivalence, olaparib PFS predicted by MAIC (SOLO2, Table 23)
4. OS equivalence, olaparib PFS predicted by MAIC (pooled analysis [Study 19 and SOLO2), Table 24)
5. OS equivalence, olaparib PFS predicted by NMA (Study 19, Table 25)
6. OS equivalence, olaparib PFS predicted by base case NMA (SOLO2, Table 26)
7. ERG Scenario 1: OS equivalence, rucaparib PFS based on ARIEL3 fitted with a lognormal curve, olaparib PFS based on Study 19 HR applied to ARIEL3 routine surveillance (Table 27)
8. OS equivalence, rucaparib PFS based on ARIEL3 HR applied to Study 19 RS, olaparib PFS based on Study 19 fitted with a lognormal curve (Table 28)

The results of each scenario analysis are presented below and provide extremely consistent incremental QALYs despite differences in approach, ranging from [redacted] to [redacted] incremental QALYs for rucaparib versus olaparib, Overall, with the currently available evidence these results indicate the similarity in clinical effectiveness of the two treatments and further supports the base case assumption of PFS equivalence.

Table 21: Scenario B3-1 - OS equivalence, olaparib PFS predicted by base case NMA estimates

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated

Key: 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.

Table 22: Scenario B3-2 - OS equivalence, olaparib PFS predicted by MAIC (Study 19) estimates

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated

Key: 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.

Table 23: Scenario B3-3 - OS equivalence, olaparib PFS predicted by MAIC (SOLO2) estimates

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	1,639,601

Key: 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.

Table 24: Scenario B3-4 - OS equivalence, olaparib PFS predicted by MAIC (pooled analysis) estimates

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated

Key: 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.

Table 25: Scenario B3-5 - OS equivalence, olaparib PFS predicted by NMA (Study 19) estimates

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated

Key: 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.

Table 26: Scenario B3-6 - OS equivalence, olaparib PFS predicted by base case NMA (SOLO2) estimates

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	2,515,011
Key: 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.					

Table 27: Scenario B3-7 - OS equivalence, rucaparib PFS based on ARIEL3 (lognormal), olaparib PFS based on Study 19 HR applied to ARIEL3 RS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated
Key: 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.					

Table 28: Scenario B3-8 - OS equivalence, rucaparib PFS based on ARIEL3 HR applied to Study 19 RS, olaparib PFS based on Study 19 (lognormal)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	1,910,687
Key: 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.					

Additionally, a comparison of cost outcomes with olaparib using the revised base case assumptions is provided below, in Table 29.

Table 29: Cost comparison with olaparib in BRCA 3L+ population, revised base case

	Rucaparib	Olaparib	Incremental (rucaparib vs olaparib)
Total costs in progression-free state	[redacted]	[redacted]	[redacted]
Maintenance - Drug acquisition costs	[redacted]	[redacted]	[redacted]
Maintenance - Drug administration costs	[redacted]	[redacted]	[redacted]
Disease monitoring costs	[redacted]	[redacted]	[redacted]

Management of adverse events	[redacted]	[redacted]	[redacted]
Total costs in progressed state	[redacted]	[redacted]	[redacted]
Disease monitoring costs	[redacted]	[redacted]	[redacted]
Total cost of subsequent therapy	[redacted]	[redacted]	[redacted]
One-off costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

B4. Priority Question: The scenario analysis for the PFS:OS ratio of 1:2 for the ITT population produces a more conservative ICER than the base case results. Please calculate the PFS:OS ratio generated by the base case approach to OS for the ITT population.

Response: The overall survival for the ITT population is modelled by applying a Royston Parmar spline model to the Study 19 OS data, consistent with the approach used in the recent appraisal of olaparib (ID 1296). The progression-free survival estimates are based on the parametric curve fits using a log-normal distribution estimator. The implied ratio of PFS versus OS in the ITT population, per the base case in the submitted model is [redacted] as presented in Table 30.

Table 30: PFS:OS ratio of the ITT population in the submitted model

ITT Population – Rucaparib vs Routine Surveillance	
OS – difference in undiscounted mean life years	[redacted]
PFS – difference in undiscounted mean progression-free life years	[redacted]
Ratio	[redacted]

Although the spline model produces a higher ratio than 2:1, we believe this to be the best data available (making direct use of mature external OS data and a methodology accepted within a previous relevant appraisal), as opposed to indirect use of external OS data via a ratio. As part of this appraisal, extensive efforts were made to avoid being reliant on the ratio method within the base case, and it is therefore disappointing to still be evaluated from this perspective.

B5. Please clarify why the constant probability of discontinuation per model cycle is raised to the power of the cycle in the economic model. In the engines in the economic model (parSA_brca_ruca, parSA_brca_ola, parSA_itt_ruca, parSA_itt_ola,

parSA_itt_rs_Ar3 and parSA_itt_rs_St19) this relates to the calculations in cells O33:O633 (Partitioned Survival, On treatment).

Response: A simple discontinuation model using a constant risk of discontinuation cumulatively over the time horizon, was used – hence the use of a power rule. The calculated, cumulative probability of discontinuation matches the observed percentage of discontinued patients within a certain time interval. This enables the use of published data points available from literature, because this method only requires a single data point from the trial for each comparator, making it possible to construct a time on treatment curve for all treatment arms using a consistent method.

For example, in the case of rucaparib in the BRCA 3L+ population, within 56 weeks (equal to 12.9 months, i.e. by cycle 13), [redacted] of patients discontinued and [redacted] remained on treatment. The formula as implemented in the model reads:

$$Monthly\ discontinuation\ probability = 1 - (1 - p_{discontinuation})^{Cycle}$$

So, the monthly discontinuation probability for rucaparib in the BRCA 3L+ subgroup would be 1 - (1 – [redacted])^(4.34 / 56) = [redacted] 4.34 is the number of weeks in our monthly cycle and this is divided by the measurement period of 56 weeks, so the monthly probability can be extracted.

A limitation of this method is that the curve potentially only exactly matches one data point as a point of validation and does not guarantee an accurate representation of treatment discontinuation outside of that one data point. However, in this case, a plot of the time on treatment curves calculated using the above method compared to the TTDD curve fitted to the Kaplan-Meier data for rucaparib in ARIEL3 demonstrates that the proposed model compares well in both the ITT and the BRCA 3L+ populations. These fits are presented in Figure 32 and Figure 33.

Figure 32: Rucaparib time to treatment discontinuation modelled with a constant rate versus the curve fitted to the Kaplan-Meier data in the ITT population

Figure 33: Rucaparib time to treatment discontinuation modelled with a constant rate versus the curve fitted to the Kaplan-Meier data in the BRCA 3L+ subgroup

Cost and resource use

B6. Priority Question: As OS informing the model is from Study 19, data on subsequent therapy use should come from the same trial. Please provide a scenario using the subsequent therapies received in Study 19, instead of ARIEL3. Subsequent therapy data for Study 19 is available in the committee

papers (1) for TA381 (Table 7.22 in 02 - Submission from the technology manufacturer - AstraZeneca).

Response: Subsequent therapy data for Study 19 has been sourced from the committee papers for TA381[12], and is presented in Table 31. The results of this scenario are presented in Table 32 and Table 33, and indicate that these data give similar results.

Table 31: Subsequent therapy data from Study 19

Subsequent treatment	Previous PARPi treatment		PARPi naive	
	Proportion of patients receiving in the ITT Population	Proportion of patients receiving in the BRCA 3L+ Subgroup	Proportion of patients receiving in the ITT Population	Proportion of patients receiving in the BRCA 3L+ Subgroup
No subsequent therapy	13.8%	13.8%	10.3%	10.3%
Bevacizumab	0.0%	0.0%	0.0%	0.0%
Carboplatin monotherapy	54.8%	54.8%	38.7%	38.7%
Carboplatin + Cyclophosphamide	44.6%	44.6%	4.8%	4.8%
Carboplatin + Docetaxel	14.9%	14.9%	3.2%	3.2%
Carboplatin + Doxorubicin	20.3%	20.3%	24.2%	24.2%
Cisplatin monotherapy	0.0%	0.0%	0.0%	0.0%
Cisplatin + Cyclophosphamide	12.2%	12.2%	3.2%	3.2%
Cisplatin + Cyclophosphamide + Docetaxel	8.1%	8.1%	0.0%	0.0%
Cyclophosphamide	0.0%	0.0%	0.0%	0.0%
Docetaxel	0.0%	0.0%	0.0%	0.0%
Doxorubicin	0.0%	0.0%	27.4%	27.4%
Etoposide	8.1%	8.1%	6.5%	6.5%
Gemcitabine + Carboplatin	27.0%	27.0%	41.9%	41.9%
Gemcitabine + Cisplatin	0.0%	0.0%	0.0%	0.0%
Gemcitabine monotherapy	5.4%	5.4%	0.0%	0.0%
Hormonal therapy	0.0%	0.0%	0.0%	0.0%

Subsequent treatment	Previous PARPi treatment		PARPi naive	
	Proportion of patients receiving in the ITT Population	Proportion of patients receiving in the BRCA 3L+ Subgroup	Proportion of patients receiving in the ITT Population	Proportion of patients receiving in the BRCA 3L+ Subgroup
Olaparib	N/A	N/A	0.0%	0.0%
Paclitaxel + Carboplatin	14.9%	14.9%	0.0%	0.0%
Paclitaxel + Cisplatin	8.1%	8.1%	4.8%	4.8%
Paclitaxel monotherapy	0.0%	0.0%	16.1%	16.1%
PLDH + Carboplatin	0.0%	0.0%	0.0%	0.0%
PLDH + Cisplatin	0.0%	0.0%	0.0%	0.0%
PLDH monotherapy	0.0%	0.0%	0.0%	0.0%
Topotecan	10.8%	10.8%	21.0%	21.0%
Trabectedin	0.0%	0.0%	0.0%	0.0%
Key: PARPi, ; PLDH, ;				

Table 32: Study 19 subsequent therapy data used to model subsequent treatment in the ITT population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	58,651
Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.					

Table 33: Study 19 subsequent therapy data used to model subsequent treatment in the 3L+ BRCA subgroup

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated
Key: 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.					

B7. Priority Question: Please clarify why patients on routine surveillance incur the costs associated with the PFS on maintenance treatment health state rather than the costs for the PFS off maintenance treatment health state. Please provide a scenario where patients on routine surveillance incur the costs associated with the PFS off maintenance treatment health state.

Response: In the company base case, drug acquisition costs and administration costs are set to £0 for routine surveillance. Monitoring costs for patients on routine surveillance however are applied in the same way as the comparators, determined by PFS on maintenance and PFS off maintenance costs. The results of a scenario where the PFS off maintenance cost is applied for the PFS cohort in the routine surveillance arm is presented in Table 34.

Table 34: Results for the ITT population when off-maintenance costs are applied to the progression-free cohort on routine surveillance

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	51,636

Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.

B8. Priority question: In the CSR on page 93 it states, "Rucaparib was self-administered orally by patients in an outpatient setting." Please provide a clinical justification as to why patients receiving olaparib and rucaparib incur treatment administration costs when oral PARPi treatments in previous NICE appraisal such as TA528 and TA381 do not. Please provide a scenario where oral administration costs are not applied to olaparib and rucaparib.

Response: In TA528, TA381, and ID1296, the manufacturers assumed a £0 administration cost for PARPi treatments as they are orally administered, while applying administration costs for oral chemotherapy in subsequent treatment. In both TA528 and ID1296 the ERG's priority questions (B21 and B12, respectively) suggested that the manufacturer either included or excluded oral treatment administration costs consistently in the model. No preference was stated by the ERG in either of these TAs. Following this, the manufacturers within these appraisals

maintained no administration costs for PARPi treatments and excluded oral administration costs for chemotherapy.

The submitted model for rucaparib consistently applies administration costs for all orally administered treatments (including PARPi and chemotherapy) aiming to be conservative and to avoid underestimation of administration costs. The results of a scenario where administration costs are excluded for PARP inhibitors and oral chemotherapy agents is provided in Table 35 and Table 36. This scenario is consistent with TA528 and TA10303 and as suggested in the CSR for rucaparib.

Table 35: Results for the ITT population when administration costs for oral PARPis and chemotherapy agents are excluded

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	49,346
Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.					

Table 36: Results for the 3L+ BRCA subgroup when administration costs for oral PARPis and chemotherapy agents are excluded

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated
Key: 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.					

B9. Priority Question: Drug administration and drug costs in tabs 'parSA_itt_ruca', 'parSA_brca_ruca', 'parSA_itt_ola' and 'parSA_brca_ola' have been applied to column V (all on maintenance). Please clarify why these costs have not been applied to the half cycle corrected proportions (column AI)?

Response: It is assumed that both rucaparib and olaparib are administered to patients at the beginning of the treatment cycle (i.e. at the start of every 28 days).

Under this assumption, drug acquisition and administration costs do not need to be half-cycle corrected as state membership is counted at the beginning of each cycle. Other outcomes including monitoring costs and health outcomes (life years, quality-adjusted life years) are half-cycle corrected. This approach has been used and explored in other NICE submissions in oncology, for example, in the non-small cell lung cancer indication, such as in TA296.[13]

B10. Please clarify if the subsequent therapies reported in Table 57 of Appendix L include all subsequent therapies received by patients. If not, please clarify how they were selected.

Response: We assume that this question refers to Table 50 of Appendix L, and not Table 57 of Appendix M. Some therapies were mistakenly omitted from the summary table (Table 50 of Appendix L).

A full list of subsequent therapies received by patients in ARIEL3 is given in Table 37. Note that all therapies from the full list were taken into consideration when calculating the proportion of patients with a subsequent therapy. This unintentional omission has no impact on the inputs used to produce the results for the economic model.

Table 37: Correction for Table 50 of Appendix L in company submission - Subsequent therapies received by patients in each arm of ARIEL 3

Subsequent treatment, n (%)	Rucaparib (n=375)	Placebo (n=189)
Any subsequent treatment	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Pegylated Liposomal Doxorubicin (PLD)	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]
Topotecan	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Trabectedin	[redacted]	[redacted]
Rucaparib	[redacted]	[redacted]

Subsequent treatment, n (%)	Rucaparib (n=375)	Placebo (n=189)
Tamoxifen	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Carboplatin + gemcitabine	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]
Nab-paclitaxel	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]
AZD2014	[redacted]	[redacted]
Selinexor	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Lurbinectedin	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Cediranib	[redacted]	[redacted]
Clinical trial	[redacted]	[redacted]
Ganetespib	[redacted]	[redacted]
IPH 2201	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]
PD-1 inhibitor	[redacted]	[redacted]
Chemotherapy unknown components	[redacted]	[redacted]
Tisotumab vedotin	[redacted]	[redacted]
Cdk1/2 Compound	[redacted]	[redacted]
MEDI4736	[redacted]	[redacted]
Cisplatin + paclitaxel	[redacted]	[redacted]
Sorafenib	[redacted]	[redacted]
TAS-120	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]
Co 60 Lt+Rt Groins	[redacted]	[redacted]
Tas-120	[redacted]	[redacted]
Melphalan	[redacted]	[redacted]
Co 60 Lt+Rt Groins	[redacted]	[redacted]
4500 Cgy	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
Apr-246	[redacted]	[redacted]
Avelumab	[redacted]	[redacted]
Carboplatin + Pld	[redacted]	[redacted]
Paclitaxel + cisplatin	[redacted]	[redacted]

Subsequent treatment, n (%)	Rucaparib (n=375)	Placebo (n=189)
Bms-986016 Invest	[redacted]	[redacted]
Imgn853	[redacted]	[redacted]
MEDI9197	[redacted]	[redacted]
Investigational Mirvetuximab Soravtansine (Imgn853) (Gog 3011)	[redacted]	[redacted]
Altretamine	[redacted]	[redacted]
FPAA08	[redacted]	[redacted]
Dasatinib	[redacted]	[redacted]
5Fu	[redacted]	[redacted]
Leucovorin	[redacted]	[redacted]
Vp-16	[redacted]	[redacted]
Gl-Onc1	[redacted]	[redacted]
Ec1456	[redacted]	[redacted]
Carboplatin + gemcitabine + bevacizumab	[redacted]	[redacted]
Not reported	[redacted]	[redacted]
Notes: Data are presented from the primary endpoint analysis database lock of 15 April 2017.		

B11. Please provide the number of patients used to calculate the proportion of patients receiving no subsequent therapy in Table 57 of Appendix M. If the number of progression events includes deaths as a progression event, please correct this estimate to exclude deaths.

Response: In ARIEL 3, there were a total of 401 investigator assessed (INV) progression events, of which 396 were progressions and 5 were deaths (Table 38). Of the 230 rucaparib patients who progressed, 31 did not receive subsequent treatment. Expressed as a proportion, this is 13.48% (i.e. 31/230) of rucaparib patients in ARIEL3 who progressed and did not receive subsequent treatment.

Table 38: Summary of progression and death events in ARIEL 3

	Rucaparib	Placebo	Total
Total PFS events	234	167	401
of which deaths	4	1	5
of which progressions	230	166	396

The numbers of patients used to calculate the proportion not receiving any subsequent therapy upon progression is summarised in Table 39, which provides a

split of patient numbers in ARIEL 3 based on both progression status and receipt of subsequent therapies Progression events did not include deaths. The number of patients included in the analysis of subsequent treatment was calculated as (230 / 375) * (375 – [redacted]) = [redacted] in the rucaparib arm and (166 / 189) * (189 – [redacted]) = [redacted] in the placebo arm. The proportion of patients not receiving subsequent treatment were calculated as [redacted] and [redacted] in the rucaparib and placebo arms, respectively.

Table 39: Detailed description of progression and death events, and subsequent therapy, in ARIEL3

	Rucaparib	Placebo	Total
All patients	375	189	564
Patients who progressed	230	166	396
Patients who progressed and received subsequent therapy	[redacted]	[redacted]	[redacted]
Patients who did not progress but received subsequent therapy	[redacted]	[redacted]	[redacted]
Patients who received subsequent therapy	[redacted]	[redacted]	[redacted]
Patients who progressed and did not receive subsequent therapy	[redacted]	[redacted]	[redacted]
Patients who only received therapies not funded by the NHS	[redacted]	[redacted]	[redacted]

B12. The ERG is unable to identify data on subsequent therapies in the CSR. Please provide the number of patients used to inform the subsequent therapy proportions in Table 57 of Appendix M, prior to any adjustments.

Response: The absolute numbers of patients receiving subsequent therapies used in calculating their proportions are reproduced in Table 40. Hormonal therapies and PARP inhibitors are reported separately.

Table 40: Absolute patient numbers of treatment with subsequent therapy in both ARIEL 3 arms

Regimen	Rucaparib	Placebo
No subsequent therapy (patients with progression even only)	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Carboplatin + gemcitabine	[redacted]	[redacted]
Carboplatin + gemcitabine + bevacizumab*	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]
Carboplatin + PLDH	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Cisplatin + gemcitabine	[redacted]	[redacted]
Cisplatin + PLDH	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]
Exemestane	[redacted]	[redacted]
Experimental PARP inhibitor	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Paclitaxel + cisplatin	[redacted]	[redacted]
PLDH	[redacted]	[redacted]
Rucaparib	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]

* Patients receiving carboplatin + gemcitabine + bevacizumab combination therapy were included in the proportion of patients receiving carboplatin + gemcitabine in Table 57 in the submission.

B13. In Appendix M it states that, “the proportion of patients receiving bevacizumab, topotecan and trabectedin were amended to 0%”. Please clarify why the proportions of alternative subsequent therapies were not inflated to reflect the treatments received instead of bevacizumab, topotecan and trabectedin in UK practice.

Response: The proportions of the use of alternative subsequent therapies were inflated to reflect the treatment received instead of bevacizumab, topotecan and trabectedin. The description preceding Table 57 in Appendix M merely emphasised

that proportions of these treatments in the table were not based on ARIEL3 data, but instead were assumed to be 0%.

B14. Please clarify why patients on routine surveillance (patients with no prior use of PARPi) in the BRCA 3L+ subgroup are assumed to receive the same proportion of PARPi therapy (olaparib) as patients on routine surveillance in the ITT population (Table 57 of Appendix M, 29.6%).

a) Please clarify why the proportion of PARPi therapy in Table 22 of the company submission (43.9%) is not employed in the economic analysis for the BRCA 3L+ subgroup.

Response: Routine surveillance is not a comparator in the BRCA 3L+ subgroup. Therefore, it was not necessary to make any assumptions about subsequent therapies after routine surveillance in this subgroup.

B15. Instead of assuming the proportions and types of subsequent therapy from the ITT population in ARIEL3 are equivalent to the BRCA 3L+ subgroup, please provide a scenario using subgroup specific data from ARIEL3.

Response: Subsequent therapy data specific to the BRCA 3L+ subgroup from the ARIEL 3 trial are presented in Table 41. The effect on the results for this subgroup are summarised in Table 42 and indicate little impact on the ICER.

Table 41: Subsequent therapy distribution in the BRCA 3L+ subgroup in the ARIEL3 trial

Subsequent treatment	Previous PARPi treatment		PARPi naive	
	Proportion of patients receiving	Mean duration (months)	Proportion of patients receiving	Mean duration (months)
No subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]

Subsequent treatment	Previous PARPi treatment		PARPi naive	
	Proportion of patients receiving	Mean duration (months)	Proportion of patients receiving	Mean duration (months)
Cisplatin monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin + Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin + Cyclophosphamide + Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Etoposide	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine + Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine + Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Hormonal therapy	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel + Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel + Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
PLDH + Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
PLDH + Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
PLDH monotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Topotecan	[redacted]	[redacted]	[redacted]	[redacted]
Trabectedin	[redacted]	[redacted]	[redacted]	[redacted]
Key: PARPi, ; PLDH, ;				

Table 42: Results when ARIEL 3 subgroup-specific subsequent therapy data are used to model the 3L+ BRCA subgroup

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated

Key: 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.

B16. Given that OS data from ARIEL3 are immature, please explain why subsequent therapy data from ARIEL3 do not underestimate the proportion of patients receiving each type of subsequent therapy.

Response: In a patient population of 230 patients who progressed while being treated with rucaparib, [redacted] subsequent therapies were registered, with [redacted] cases where no subsequent treatment was applied. In the placebo group, [redacted] patients progressed of which [redacted] received no subsequent treatment, and the other patients in this group were prescribed a total of [redacted] subsequent therapies. This means, on average, each patient in the rucaparib group receiving subsequent therapy received [redacted] different treatments. In the placebo group patients receiving subsequent medication received [redacted] different subsequent treatments.

Within the completed olaparib appraisal (TA381) total subsequent therapy costs only included two lines of subsequent therapy.

As such, although OS data were immature, patients spent substantial time on subsequent therapy during the ARIEL3 study, and the model costs these appropriately within the context of previous appraisals. Nevertheless, as data accumulates, there will likely be more subsequent therapies received by patients. Overall, the data used in the model are likely to give at most a minor underestimation, given that most patients already have received 1-2 subsequent therapies.

B17. Please provide a scenario where PLDH monotherapy is given at a dose of 40 mg/m2 and where PLDH in combination with cisplatin or carboplatin is given at a dose of 30 mg/m2.

Response: The results of this scenario analysis are presented below in Table 43 and Table 44 for the ITT and BRCA 3L+ populations, respectively. The scenarios have been run according to the updated base case.

Table 43: ITT population results for the scenario with differential PLDH monotherapy dosing

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	50,483
Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.					

Table 44: 3L+ BRCA subgroup results for the scenario with differential PLDH monotherapy dosing

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated
Key: 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.					

B18. Please clarify why the costs of concomitant medications have not been included in the cost estimates.

Response: Rucaparib is authorised for the use as monotherapy in the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. No other anti-cancer therapies (including chemotherapy, radiation, hormonal treatment, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs)

of any kind were permitted when patients were participating in the study, except for ongoing hormonal treatment for previously treated breast cancer. During the ARIEL3 study, supportive care (for example, antiemetics; analgesics for pain control) was used at the investigator's discretion and in accordance with institutional procedures. Herbal and complementary therapies were not encouraged because of unknown side effects and potential drug interactions, but any taken by the patient were documented appropriately on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life threatening medical problems, were avoided. Any concomitant medication taken as supportive care was therefore assumed to represent a minimal cost, and that it would be included in the ongoing cost of monitoring/follow-up and with the costs associated with relevant adverse events.

B19. Please provide a scenario where rucaparib is costed using the mean dose received in ARIEL3, and olaparib is costed using the mean dose received in Study 19 (mean daily dose 675.9 mg). Please include drug wastage in these scenarios (i.e. tablets/capsules cannot be split).

Response: Relative mean dose intensity was not readily available from the ARIEL3 trial. The originally submitted model provided applies the mean dose intensity from ARIEL2 for rucaparib, assuming that a similar relative dose intensity would be applicable between the treatment and maintenance indication; and from Study 19 for olaparib. RDI data from ARIEL3 have now been included as a scenario in the revised model; the results of these analyses are presented in Table 45 and Table 46 for the ITT and BRCA 3L+ populations, respectively, and indicate little change from the revised base case.

Table 45: Revised model results including ARIEL3 RDI, ITT population

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	46,839

Table 46: Revised model results including ARIEL3 RDI, BRCA 3L+ population

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated

B20. BRCA testing is done routinely in the NHS, therefore the cost does not need to be considered in the model as it is inflating total costs for all comparators. The ERG suggests that this is removed from the base-case analysis.

Response: The model included a cost of £795 for BRCA testing, sourced from the UK genetic testing network.[14] The base case ICER in the ITT population within the submitted model was £50,429; setting BRCA costing to £0 in addition to other base case changes gives a new base case ICER of £50,681. As such, this change has negligible effect on the ICER. A summary of the results of the revised base case is presented earlier within this document, in Table 8 and Table 9.

B21. Vial sharing does not routinely occur in the NHS, therefore the ERG suggests that vial sharing is removed in the base-case analysis

Response: When the settings for vial sharing on the Drug cost sheet are changed to not allow vial sharing, subsequent therapy costs increase very slightly. No other treatment costs are affected; rucaparib and olaparib costs remain the same as they are oral therapies. The base case ICER for the ITT population is not affected and stays at £50,681. In the amended model, the vial sharing option has been removed from the base case analysis. A summary of the results of the revised base case is presented earlier within this document, in Table 8 and Table 9.

B22. Please clarify the cost year. If the same cost year is not used throughout the analysis, please inflate unit costs to the same cost year, or use the most recent version of cost sources. NHS Reference Costs 2017/18 (https://improvement.nhs.uk/resources/reference-costs/) and the Unit Costs of Health

and Social Care 2018 are now available (https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/)

Response: The cost year for unit inputs in the company submission varied from 2016-2018 depending on the specific input source. We have inflated all costs to 2018 using the harmonised index of consumer prices (HICP) in the base case, sensitivity analysis and scenario analysis. A summary of the results of the revised base case is presented earlier within this document, in Table 8 and Table 9 for the ITT and BRCA 3L+ populations, respectively.

Health-related quality of life

B23. Priority Question: Please undertake a subgroup analysis of the EQ-5D data collected in ARIEL3 for patients receiving 2 prior therapies and 3 or more prior therapies. Please implement the results of this analysis into the scenarios requested in B2 and B3.

Response:

Table 49 summarises the EQ-5D subgroup analysis for ARIEL3 patients receiving 2 prior therapies and 3 or more prior therapies. The mean health state utility values for the progression-free and post-progression health states are 0.83 and 0.751 for the 2L only subgroup, and 0.829 and 0.769 for the ARIEL3 3L+ subgroup, respectively. The model has been adapted to test the impact of using this subgroup analysis of the EQ-5D data collected in ARIEL3. The results from the requested scenarios are provided in Table 47 and Table 48.

Table 47: ITT population results when subgroup EQ-5D data are used to model health state utility values

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	50,681

Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.

Table 48: 3L+ BRCA subgroup results when subgroup EQ-5D data are used to model health state utility values

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated

Key: 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.

Table 49. Mixed effect linear regression models: Parameter estimates with confidence intervals and p-values based on EQ-5D utility data up to Cycle 39, at EOT and 28 day follow-up

Covariates	Intercept			Progressed (Reference = Before progression)			Random Effect	
Mixed Effect Models	**Coefficient**	**95% CI**	**P-value**	**Coefficient.**	**95% CI**	**P-value**	**Intercept**	**95% CI**
Model 7 - Stratified: 3L+ platinum regimens, Progression as main effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model 8 - Stratified: 2L platinum regimens, Progression as main effect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B24. Please add the results of patients with progressed disease to Table 53 (Summary of EQ-5D-3L utility scores for both treatment arms of ARIEL3).

Response:

These are shown in Table 49 and outlined in the response to Question B23.

Adverse events

B25. Please clarify whether treatment-related adverse events or treatment-emergent adverse events are used in the model for rucaparib, routine surveillance and olaparib. Please ensure that the same measure is used for all treatments.

Response: The model used grade 3 or higher related treatment emergent adverse events adverse events associated with rucaparib and placebo (routine surveillance) from the safety population of ARIEL3 (Table 14.3.1.1.9.1 of the CSR Appendices). Adverse events reported for olaparib were sourced from the TA381 committee papers. This data matched what was reported in the EMA CHMP assessment report for Lynparza (2014), Table 69; all patients (N=136), safety analysis set. We assumed that the description in NICE TA381 is correct per the clarification response in the committee papers, and that these reflect treatment-related adverse events from Study 19. Therefore, no change is needed in the model.

B26. The ERG is unable to correlate the risk of AEs used in the model ('AEs' C34:F40) with the risks reported in Table 14.3.1.1.8.1 of the CSR (references 38 and 86). Please clarify the source of the data used in the model.

a) If the latest database lock (31 December 2017) was not used, please explain why.

Response: The latest database lock was not used in the modelling of the adverse events. The updated safety data from the December 2017 database lock had only been included in the company submission to demonstrate that the adverse events are consistent and that there were no changes to conclusions from longer follow-up. As there were no meaningful clinical differences between the two data sets it was deemed unnecessary to update adverse event data in the model.

B27. The ERG is unable to identify a risk of 5.9% for neutropenia in the EMA CHMP assessment report for Lynparza 2014, Table 69; all patients (N=136), safety analysis set. Please clarify the source of the data used in the model.

Response: The source of the data is NICE TA381, which matches data in the EMA CHMP assessment report for Lynparza 2014. However, the 5.9% includes neutropenia (3.7%) and leukopenia (2.2%). These conditions are closely related, and it was assumed that they would be indistinguishable in terms of their impact on quality of life and costs. The incidence of adverse events from ARIEL3 are available in the CSR Appendices Table 14.3.1.1.9.1. The risk of neutropenia associated with rucaparib in the model (5.6%) is for the 'combined neutropenia and/or low/decreased neutrophil count' terms. The risk of neutropenia itself is reported as 4.0%; and 1.9% for decreased neutrophil count. The risk of leukopenia from ARIEL3 is 0.5%. Adverse events as whole have a minimal impact on the model results

B28. Please provide a scenario analysis with an alternative AE assumption. That is, apply AE disutilities and accrue AE costs.

Response: The results of a scenario where adverse event disutilities and adverse event costs are applied are presented in Table 50 and Table 51.

Table 50: ITT population results under alternative adverse event assumption

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	50,772
Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.					

Table 51: BRCA 3L+ subgroup results under alternative adverse event assumption

Technologies	Total costs (£)	Total QALYs	Incremental. costs (£)	Incremental QALYs	ICER (£/QALY)
Olaparib	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated
Key: 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.					

Section C: Textual clarification and additional points

C1. Please specify the platform used for each of the electronic database searches in Appendix D.

Response: Please see details of the platforms used for each of the electronic database below:

- EMBASE (via embase.com)
- MEDLINE (via embase.com and PubMed)
- CENTRAL (via the Cochrane Library)
- DARE (via the Cochrane Library)
- CDSR (via the Cochrane Library)

C2. Please confirm if in Appendix D page 30, Table 9, the column marked BRCA should be BRCA 2L as indicated by the table legend? Please also clarify what the different colours mean in Table 9.

Response: The column marked BRCA refers to the BRCA 2L+ population, rather than 2L only. The outcomes presented are for the BRCA group (irrespective of treatment line but as per relapsed OC trial criteria is really representative of the BRCA 2L+ group). The table legend is incorrect - it should not include the 2L abbreviation and should include the following notes regarding colours:

- Green shading indicates no evidence against the proportional hazards assumption
- Blue shading indicates no conclusive evidence against the proportional hazards assumption

C3. Please explain the colour code of Table 14, Appendix D pages 47-48.

Response: The table legend should include the following notes regarding colours:

- Green shading indicates that imbalances for this factor were adjusted for by the MAIC model

- Light blue shading indicates that adjustment for this factor was redundant or not applicable in the MAIC e.g. adjustment for BRCA mutation is redundant in the BRCA population analyses
- Grey/Dark blue shading indicates that this factor was not reported in either the reference or comparator trial
- Red shading indicates that any imbalances for this factor were not adjusted for by the MAIC model

C4. Please clarify why only five studies were appraised in Table 28 of Appendix G when eight studies (across ten publications) were included.

Response: Only five of the identified studies were available as full-text publications and were appraised using the Cochrane Risk of Bias tool. Quality assessment was not conducted for abstract-only publications due to limited information available to assess all the domains in the tool

C5. Please clarify why the following trials were not identified or included in the search for HRQoL evidence: NOVA, OVA-301, Study 19, SOLO2, and Havrilesky LJ, Broadwater G, Davis DM, et al. Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. Gynecol Oncol 2009. 113: 216–220.

Response: OVA-301 and Havrilesky et al. (2009) were excluded during the screening stages of the utility SLR, as they 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. HRQL data for NOVA, Study 19, and SOLO2 were identified in the clinical SLR.

C6. Please clarify why the alternative resource use estimates from a UK expert (applied as a scenario analysis) were not considered appropriate to combine with the estimates from UK experts, which informed the base case estimates.

Response: The original resource use estimates used in the model base case are based on a questionnaire sent to multiple clinicians. In January 2019, in order to validate multiple modelling inputs, another clinical expert was consulted. The resource use estimates were very much in line with the initial estimates, and it was

therefore deemed unnecessary to update the model base case. The ICER for the alternative resource use scenario is £49,700 compared to a base case ICER of £50,429 in the ITT population.

C7. On page 121 of the company submission, Table 45 presents the probability of discontinuation of treatment per model cycle for the ITT population. The text states that this is included to inform the base case OS approach, but no further mention is made about the TTDD risk probability. Please clarify how this has been used for the base case ITT population analysis.

Response: This is a mistake in the description in the text, which should not refer to OS. The probability of discontinuation of treatment per model cycle does not affect OS. When the 'constant discontinuation rate per cycle in PF' option is selected as the discontinuation rule, a constant risk of discontinuation is applied cumulatively over the entire time horizon to produce a time on treatment curve (see company response to question B5 for further information). This is used to calculate drug acquisition costs, drug administration costs, pre-progression monitoring costs on treatment, and pre-progression monitoring costs off treatment. The probability of treatment discontinuation therefore only affects pre-progression cost outcomes.

In the base case ITT population analysis, olaparib is only used in the ITT population to predict post-progression outcomes. Therefore, discontinuation inputs shown for olaparib do not affect the model outputs.

C8. In the company submission it states that "EQ-5D-3L patient responses were converted to utility index scores using the published UK national tariff." Please clarify if this tariff was taken from Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095–108.

Response: This is correct

C9. Please clarify how infusion times were attached to the administration costs reported in NHS Reference Costs (Table 57 of the CS).

Response: The unit cost of administration for treatments administered by IV infusion are available in some detail: "simple parenteral chemotherapy", "more complex parenteral chemotherapy" and "complex chemotherapy, including prolonged infusional treatment". Definitions of when each of these national currencies should

apply are explained in terms of the required nurse time and overall chair time required for delivering chemotherapy.

Therefore, to provide a more accurate costing method according to the data available, the unit cost of administration applied for each IV treatment varied according to the recommended duration of infusion based on the EMC Summary of Product Characteristics (SmPC). This was then adjusted to a monthly cost based on the treatment cycle length.

A unit cost of administration of £173.99 was applied for treatments with a duration of infusion between 0 and 60 minutes (simple parenteral chemotherapy), £264.56 for treatments with a maximum duration of infusion between 60 to 120 minutes (more complex parenteral chemotherapy), and £269.86 for treatments requiring administration time of 120 minutes or greater (complex chemotherapy, including prolonged infusional treatment). For combination regimens, a single unit cost of administration was selected using the maximum infusion time of the individual treatments.

For example, a unit cost of £269.86 per treatment cycle was applied to the subsequent treatment regimen paclitaxel + carboplatin because the recommended duration of administration of paclitaxel is over a period of 180 minutes, and a period of 30 minutes for carboplatin. The monthly cost was £391.13 based on a treatment cycle length of 21 days.

C10. Please clarify why TA381 and TA528 were not included in the search for cost-effectiveness evidence or cost and resource use evidence.

Response: The SLR focused on indexed databases and key conference proceedings, therefore, technology appraisals would not be picked up here as part of the search. TA381 and TA528 were identified and reviewed separately to inform the rucaparib submission i.e. during model development, as detailed throughout the submission.

C11. Please provide the results for one-way sensitivity analyses on ICERs rather than on incremental NMB (Figures 38-39).

Response:

Net monetary benefit was originally used as the outcome in one-way sensitivity analyses as ICERs are not informative for the 3L+ BRCA subgroup, given that equivalence to olaparib is assumed. The effects of individual parameters on the ICER compared to the revised base case analyses are presented in Table 52 for the ITT population and in Table 53 for the BRCA 3L+ subgroup. Results are tabulated, as it is not possible to generate a tornado diagram for the BRCA 3L+ population.

Table 52: One-way sensitivity analysis for the revised base case with ICER as outcome, ITT population

#	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

Table 53: One-way sensitivity analysis for the revised base case with ICER as outcome, 3L+ BRCA subgroup

#	Parameter	Lower bound ICER	Upper bound ICER	Difference ICER
1	Statistical parameters - Rucaparib PFS-INV (piece 1) - BRCA 3L+	Rucaparib dominated	Rucaparib dominated	Not estimable
2	Cost of subsequent therapy per month, BRCA 3L+ - olaparib	Rucaparib dominated	Rucaparib dominated	Not estimable
3	Cost of subsequent therapy per month, BRCA 3L+ - rucaparib	Rucaparib dominated	Rucaparib dominated	Not estimable
4	Administration cost per month - olaparib	Rucaparib dominated	Rucaparib dominated	Not estimable
5	Administration cost per month - rucaparib	Rucaparib dominated	Rucaparib dominated	Not estimable
6	Monitoring/follow-up costs per month (Progression-free, on maintenance)	Rucaparib dominated	Rucaparib dominated	Not estimable
7	Statistical parameters - OS, olaparib, Study 19 - piece1 - BRCA 3L+	Rucaparib dominated	Rucaparib dominated	Not estimable
8	Total AE costs per month - rucaparib	Rucaparib dominated	Rucaparib dominated	Not estimable
9	Monitoring/follow-up costs per month (Progression-free, off maintenance)	Rucaparib dominated	Rucaparib dominated	Not estimable
10	Total AE costs per month - olaparib	Rucaparib dominated	Rucaparib dominated	Not estimable
11	Risk of AEs for Rucaparib: Anaemia	Rucaparib dominated	Rucaparib dominated	Not estimable
12	Risk of AEs for Olaparib: Anaemia	Rucaparib dominated	Rucaparib dominated	Not estimable
13	Risk of AEs for Olaparib: Neutropenia	Rucaparib dominated	Rucaparib dominated	Not estimable
14	Risk of AEs for Olaparib: Nausea/vomiting	Rucaparib dominated	Rucaparib dominated	Not estimable
15	Risk of AEs for Olaparib: Fatigue/asthenia	Rucaparib dominated	Rucaparib dominated	Not estimable
16	Risk of AEs for Rucaparib: Neutropenia	Rucaparib dominated	Rucaparib dominated	Not estimable
17	Risk of AEs for Rucaparib: Nausea/vomiting	Rucaparib dominated	Rucaparib dominated	Not estimable
18	Risk of AEs for Rucaparib: Thrombocytopenia	Rucaparib dominated	Rucaparib dominated	Not estimable
19	Risk of AEs for Rucaparib: Fatigue/asthenia	Rucaparib dominated	Rucaparib dominated	Not estimable
20	Risk of AEs for Rucaparib: Hypertension	Rucaparib dominated	Rucaparib dominated	Not estimable

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

Additional clarification question - updated

April 2019

File name	Version	Contains confidential information	Date
Additional clarification question - updated	**1.0**	**Yes**	**04.04.2019**

1. Further to your responses to clarification, please can you provide AIC/BIC statistics and KM data for the non-BRCA and BRCA2L ARIEL3 survival analyses. In the model, the KM data is only for 2L+ regardless of BRCA status.

Non-BRCA

The AIC/BIC statistics are provided below for the ARIEL3 non-BRCA 2L+ population investigator-assessed progression-free survival (PFS) data for rucaparib and placebo in Table 1. The AIC/BIC statistics are provided for the ARIEL3 time to discontinuation or death data for rucaparib and placebo in Table 2. In all cases, the best-fitting distributions were chosen for use in the base case.

Table 1: ARIEL3 non-BRCA 2L+ statistical fit: Investigator-assessed PFS, rucaparib and placebo

Model	AIC	BIC	Total
Rucaparib			
Exponential	602.47	605.97	1208.45
Weibull	592.05	599.05	1191.10
Gompertz	603.76	610.76	1214.52
Log-logistic	569.39	576.39	1145.77
Log-normal	559.85	566.86	1126.71
Generalised Gamma	548.28	558.79	1107.07
Placebo			
Exponential	293.06	295.87	588.93
Weibull	266.61	272.23	538.84
Gompertz	291.05	296.67	587.72
Log-logistic	236.25	241.87	478.12
Log-normal	233.91	239.53	473.44
Generalised Gamma	229.41	237.84	467.25

Table 2: ARIEL3 non-BRCA 2L+ statistical fit: Time to discontinuation or death, rucaparib and placebo

Model	AIC	BIC	Total
Rucaparib			
Exponential	703.32	706.83	1410.15
Weibull	700.70	707.70	1408.40
Gompertz	705.20	712.21	1417.41
Log-logistic	677.64	684.65	1362.29
Log-normal	684.87	691.87	1376.74
Generalised Gamma	684.48	694.98	1379.46
Placebo			
Exponential	310.32	313.14	623.46

Weibull	286.05	291.67	577.72
Gompertz	308.93	314.55	623.48
Log-logistic	257.49	263.11	520.60
Log-normal	263.95	269.57	533.52
Generalised Gamma	265.60	274.04	539.64

KM curves for investigator-assessed PFS and time to discontinuation (TTD) were provided in the original responses (see response to A1 priority question) – KM data for these curves are provided in the accompanying excel file. Please treat these data as confidential.

The KM curve for OS in the ARIEL3 non-BRCA 2L+ population are provided in Figure 1. Please treat these data confidential as marked, and apply the necessary caution to their interpretation given their post-hoc nature and small patient numbers and event rates.

Figure 1: Kaplan–Meier estimates of OS – non BRCA – post-hoc analyses

Key: BRCA, breast cancer gene; OS, overall survival.

BRCA 2L

The AIC/BIC statistics are provided below for the ARIEL3 BRCA 2L population investigator-assessed PFS data for rucaparib and placebo in Table 3. The AIC/BIC statistics are provided for the ARIEL3 time to discontinuation or death data for rucaparib and placebo in Table 4. In all cases but one, the best-fitting distributions were used in the model base case. In one case (rucaparib TTDD), the best-fitting distribution was exponential, however the second best-fitting distribution (log-normal) was selected for consistency with PFS. Additionally, the log-normal distribution gives a much longer mean (186.6 weeks) than the exponential distribution (101.7 weeks) and is therefore more conservative as it results in longer drug use for rucaparib in the model.

Table 3: ARIEL3 BRCA 2L statistical fit: Investigator-assessed PFS, rucaparib and placebo

Model	AIC	BIC	Total
Rucaparib			
Exponential	162.23	164.57	326.80
Weibull	160.03	164.72	324.75
Gompertz	162.14	166.83	328.98
Log-logistic	159.28	163.97	323.25
Log-normal	157.94	162.63	320.57
Generalised Gamma	159.89	166.92	326.82
Placebo			
Exponential	107.26	108.98	216.24
Weibull	105.03	108.45	213.48
Gompertz	109.00	112.42	221.42
Log-logistic	97.18	100.60	197.78
Log-normal	96.19	99.62	195.81
Generalised Gamma	95.97	101.11	197.08

Table 4: ARIEL3 BRCA 2L statistical fit: Time to discontinuation or death, rucaparib and placebo

Model	AIC	BIC	Total
Rucaparib			
Exponential	213.34	215.68	429.02
Weibull	215.31	220.00	435.31
Gompertz	214.46	219.15	433.61
Log-logistic	213.15	217.84	430.99
Log-normal	212.78	217.47	430.25
Generalised Gamma	214.74	221.77	436.51

Placebo			
Exponential	108.98	110.69	219.66
Weibull	105.63	109.06	214.70
Gompertz	110.65	114.07	224.72
Log-logistic	95.22	98.65	193.87
Log-normal	94.75	98.18	192.93
Generalised Gamma	93.04	98.18	191.21

KM curves for investigator-assessed PFS and TTD were provided in the original responses (see response to A1 priority question) – KM data for these curves are provided in the accompanying excel file. Please treat these data as confidential.

The KM curve for OS in the ARIEL3 BRCA 2L population are provided in Figure 2. Please treat these data confidential as marked, and apply the necessary caution to their interpretation given their post-hoc nature and small patient numbers and event rates.

Figure 2: Kaplan–Meier estimates of OS – BRCA 2L – post-hoc analyses

Key: BRCA, breast cancer gene; OS, overall survival.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Ovacome Ovarian Cancer Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are charity formed in 1996 offering information and support to anyone affected by ovarian cancer. We raise awareness of the disease and work with medical schools through the survivors teaching students programme. We have 5 full time members of staff and 2 part-time; there is also 1 full time temporary post. We are funded through charitable donations, trusts and foundations donations, community fundraising and donations. Our members currently number around 4000.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Knowledge and experience from 23 years providing support to those affected by ovarian cancer. Feedback through My Ovacome online forum.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Ovarian cancer has a significant impact on quality of life. The majority of women are diagnosed at Stage III when it has already spread outside of the pelvis. This means treatment is aimed at minimising the burden of the disease and maximising periods of wellness between treatments. As treatment lines are exhausted, women fear being told there is no more treatment available to manage their ovarian cancer. The surgery undertaken is most usually a total abdominal hysterectomy and bilateral salpingo-oophrectomy. This operation can have long term effects on abdominal organs and particularly the bowel with associated continence issues. Women may have to manage a stoma, either short or long term. Associated issues include fatigue and changes to body image and function affecting sexuality. Women live with the anxiety of possible recurrence. The time after treatment whereby women are under routine surveillance can be psychologically very hard to cope with. Having a choice of maintenance therapy to extend progression free survival and continued input from oncology teams offers significant psychological as well as health benefits. For both the women and their carers, ovarian cancer can be very isolating, due to its comparative rarity they may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	They are concerned that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative care only. The development of biological therapies is offering hope when there had been no new chemotherapy options for many years.
8. Is there an unmet need for patients with this condition?	Currently no PARP inhibitors are routinely available second line (niraparib only through CDF). Rucaparib's efficacy has been established through the ARIEL 3 trial which found Rucaparib significantly improved progression-free survival in patients with platinum-sensitive ovarian cancer who had achieved a response

	to platinum-based chemotherapy. For women without the BRCA mutation Rucaparib has the potential to routinely offer a new patient group the option of a further PARP inhibitor which was previously unavailable to them. For women with the BRCA mutation the availability of a PARP sooner than Olaparib at third line has the potential for longer progression free survival between second and third line treatments. Rucaparib as an oral medication offers patients greater choice and flexibility regarding location of treatment as hospital attendance is not necessary for administration. There is a psychological benefit of having a PARP inhibitor available where none existed before; for women with the BRCA mutation to have PARP treatment earlier at second line and not feel they are waiting for a further recurrence in order to access PARP treatment; for non-BRCA women to feel that the benefits of PARP-inhibitor treatment are no longer restricted for them but will be routinely available. Additionally, for patients on follow-up knowing their cancer is likely to recur, having a choice of maintenance therapy and continued input from oncology teams offers significant psychological as well as health benefits compared to routine surveillance.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is expanding availability of PARP inhibitors to patients previously excluded. It is a treatment that offers longer progression free survival with manageable side effects, enabling a good quality of life. In May 2017, one of our members gave the following feedback: “I have been on the Ariel trial from April 2016. It has been successful for me. My first recurrence was 9 months after diagnosis however after finishing chemo in Feb 2016 I have not had chemo again. I'm 15 months and still going with Rucaparib. I'm delighted with these results as I have a really good quality of life on the drug. It was difficult at the start for the first 2 months but it all settled down. I’m hoping I can remain in it for a long time but either way it's

	giving me a good break from chemo with a great quality of life and most importantly prolonging my life. Would have no hesitation in trying it again afterwards should I need more chemo in the future. I was stage 4 with a very poor prognosis in March 2014. This trial has been a blessing for me."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	While they are aware of a drug's side effects they are often prepared to manage these for increased progression free survival. One of our members who has been taking Rucaparib for two months told us that although she experienced side effects "I am coping well and have no desire to stop taking it."
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding maintenance therapies for this group of patients is vital.
- The ARIEL 3 trial has proven Rucaparib's efficacy in extending progression free survival for women with and without BRCA

mutations.

- For patients on follow-up knowing their cancer is likely to recur, having a choice of maintenance therapy and continued input from oncology teams offers significant psychological as well as health benefits compared to routine surveillance.

- Rucaparib as an oral medication offers patients greater flexibility and convenience regarding location of treatment than chemotherapy or other IV treatments, minimising detrimental impact on quality of life.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	

2. Name of organisation	Target Ovarian Cancer
3. Job title or position	Head of Policy
4a. Brief description of the organisation (including who funds it). How many members does it have?	Target Ovarian Cancer is the authority on ovarian cancer. We work with women, family members and health professionals to ensure we target the areas that matter most for those living and working with ovarian cancer. As the UK's leading ovarian cancer charity we work to improve early diagnosis, we fund lifesaving research and we provide much needed support to women with ovarian cancer. We're the only charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. Target Ovarian Cancer's work is supported by charitable trusts and individual giving. Target Ovarian Cancer receives limited support from pharmaceutical companies and has received no support from the manufacturer of rucaparib.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• Target Ovarian Cancer Pathfinder study 2016 • Anecdotal feedback patients and their families • Patient survey on access to cancer drugs • Calls to the Target Ovarian Cancer support line

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	**Patient:** Ovarian cancer is often diagnosed unexpectedly, following a convoluted and protracted pathway to diagnosis or after an emergency admission. 45 per cent of women are waiting over three months from first visiting their GP to receiving a diagnosis.[i] Nearly two thirds of women are diagnosed once the cancer has spread beyond the ovary, making curative treatment challenging.[ii] Women with advanced disease are more likely to face a future of recurrent ovarian cancer requiring multiple rounds of treatment to manage their disease. The prospect of recurrence casts a shadow over the lives of many; over 50 per cent of women with ovarian cancer said they needed support coping with the fear of recurrence.[iii] Fears around recurrence are compounded by the knowledge that there are few treatment options for ovarian cancer and in particular recurrent disease – current clinical guidelines stop after diagnosis and first line treatment.[iv] An ovarian cancer diagnosis can have a negative impact on many aspects of an individual's life, from their physical and mental wellbeing to their body image and feelings relating to sexuality. While the majority (80 per cent) of women with ovarian cancer said they had experienced mental ill health since being diagnosed with ovarian cancer, just 36 per cent of women with ovarian cancer said anyone involved in their treatment had discussed their mental wellbeing. Over two thirds of women with ovarian cancer said they had experienced a loss of self-esteem, 73 per cent reported difficulties with intimacy and 84 per cent reported a lower sex drive.[v] Mutation in the BRCA1 or BRCA2 gene is a significant risk factor for ovarian cancer, accounting for around 13 per cent of all cases of ovarian cancer. Women are often unaware of their genetic status until after their diagnosis. This newfound knowledge and the awareness that members of their immediate family may have inherited the mutated BRCA gene, increasing their personal risk of developing ovarian

	and other cancers, is an unexpected and unwelcome burden. It is therefore important that as genetic testing is rolled out, women are offered the appropriate support and counselling through genetic services.[vi] **Carers:** Women are at the epicentre of an ovarian cancer diagnosis, but the shockwaves are keenly felt among the wider family members and carers. Devastation, shock, disbelief, fear and anger are commonly experienced emotions. Sadly, the emotional impact is often overlooked, just 28 per cent of immediate family members report that a health professional had spoken to them on their own about how they were feeling.[vii] Family and carers often neglect their emotional wellbeing focusing on the needs of their loved one. The practical implications of an ovarian cancer diagnosis on family and carers are often significant. Keen to support their loved one 40 per cent of immediate family take time off work to attend hospital appointments. Family members are likely to step into new roles and responsibilities within the family unit; 15 per cent report taking on greater care responsibilities for other family members and 26 per cent taking over running the house.[viii] This changing family dynamic can put great stress on the whole family and individuals often feel under great pressure to maintain normalcy.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers are concerned about the limited number of treatments for ovarian cancer, particularly for recurrent disease. Target Ovarian Cancer regularly receives emails and phone calls from women and their carers wishing to discuss treatment options available. They may seek impartial advice regarding current treatment options

	or participating in a clinical trial. Or they may have questions regarding the different channels for accessing the latest treatments. Women are keen to consider options that may extend their life or the interval between recurrences. 73 per cent of women with ovarian cancer said they felt it was important to take part in clinical trials so knowledge and treatment can advance. And 66 per cent of women with ovarian cancer wanting to take part in clinical trials were prepared to travel to another hospital to do so.[ix]
8. Is there an unmet need for patients with this condition?	Platinum-based chemotherapy is the primary treatment for recurrent platinum-sensitive ovarian cancer. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited. Maintenance treatments like rucaparib give patients and clinicians a valuable opportunity to extend the progression free survival period and therefore the interval between chemotherapy treatment. This can prolong the efficacy of standard platinum-based chemotherapy; delaying the onset of platinum drug resistance.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The potential to increase the time between chemotherapy treatments. The drug is given as tablets that the patient can take at home without the need for hospital visits. Reducing visits to the hospital reduces the financial burden on the patient in terms of travel time to the hospital and family and carers potentially taking unpaid leave from work to attend appointments.

	For women with recurrent ovarian cancer extending the progression free survival interval is significant. Living under the shadow of ovarian cancer, and not knowing when the disease will recur can be emotionally draining and debilitating, preventing women from making a full emotional recovery and resuming their day-to-day life. Prolonging the interval between episodes of recurrence gives women greater opportunity to focus on their physical and emotional recovery. It allows women greater freedom to make plans that have a positive impact on their emotional wellbeing, for example they might plan a holiday or be well enough to enjoy a family event such as a child's wedding or the birth of a grandchild. Having greater freedom to make plans and enjoy a greater sense of normality has a significant positive impact on a woman's quality of life.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	A major consideration for patients and carers when choosing to start a new treatment is the impact of the treatment. They want to be clear about the potential side-effects and the possible impact on their quality of life.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so,	Women with recurrent ovarian cancer stand to benefit from the technology. There are currently few treatment options. Some women can access bevacizumab through the Cancer Drugs Fund and likewise some women can access olaparib. However, bevacizumab is only available for women with advanced disease and sub-optimal surgery and olaparib was approved under NICE's end-of-life criteria for women who have received three or more rounds of chemotherapy and is only available to women who have a BRCA1 or BRCA2 mutation (roughly 15 per cent of women with ovarian cancer).

please describe them and explain why.	Women with recurrent platinum-sensitive disease in England can access niraparib through the Cancer Drugs Fund but there are still very limited treatment options in routine commissioning.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Ovarian cancer is more common in women over 50 and cancer is considered a disability under the Equality Act 2010. Therefore, age, gender and disability are all relevant protected characteristics for the purpose of this appraisal.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Olaparib is already available for some women with ovarian cancer and niraparib is currently available on the Cancer Drugs Fund for use by women with recurrent platinum-sensitive disease, regardless of whether they have a BRCA mutation. Both olaparib and niraparib are for women who are platinum-sensitive. The more rounds of chemotherapy a woman receives the more likely it is she becomes platinum-resistant. Therefore the role of PARP inhibitors in the overall treatment pathway should be considered.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- **Quality of life impact:** the threat of recurrent disease looms large over the lives of women with ovarian cancer, the emotional, practical and physical implications for women and their family are significant. This makes it hard for women to plan events and activities that would have a positive impact on their quality of life.
- **Limitations of current treatment:** platinum-based chemotherapy is the primary treatment for recurrent platinum-sensitive ovarian cancer. However, the risk of developing platinum resistance is high. Treatment for platinum-resistant disease is extremely limited.
- **Benefits of new treatment:** rucaparib has the potential to extend the time between chemotherapy treatments and therefore potentially prolong the use of platinum-based chemotherapy. This gives women and their families more opportunity to focus on emotional and physical recovery.
- **Mode of delivery:** rucaparib is given in tablet form allowing women to easily continue treatment in their own home and greatly reducing hospital visits. It also reduces the need for women to live their life around their hospital appointments and treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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[i] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 21 February 2019]
[ii] National Cancer Registration and Analysis Service (2016) Stage breakdown by CCG 2014. Available at: www.ncin.org.uk/view?rid=3006 [Accessed 21 February 2019]
[iii] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 21 February 2019]
[iv] National Institute for Health and Care Excellence (2011) Ovarian cancer: recognition and initial management of ovarian cancer. Clinical guidelines 122. Available at: www.nice.org.uk/guidance/cg122/resources/ovarian-cancer-recognition-and-initial-management-35109446543557 [Accessed 21 February 2019]]
[v] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 21 February 2019]
[vi] NHS England (201) Clinical commissioning policy: genetic testing for BRCA1 and BRCA2 mutation. Available at: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e01pb-brca-ovarian-cancer-oct15.pdf [Accessed 21 February 2019]
[vii] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 21 February 2019]
[viii] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 21 February 2019]
[ix] Target Ovarian Cancer (2016) Pathfinder 2016: transforming futures for women with ovarian cancer. Available at: www.targetovariancancer.org.uk/pathfinder [Accessed 21 February 2019]

NICE National Institute for Health and Care Excellence

Clinical expert statement

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Please aim for your response to be no longer than 16 pages.

About you	
1. Your name	**Agnieszka Michael**
2. Name of organisation	**British Gynaecological Cancer Society**

3. Job title or position	**Consultant Medical Oncologist**
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment in relapsed ovarian cancer is to improve overall survival, progression free survival as well as the quality of life. Ovarian cancer is a chemotherapy –sensitive cancer and 85% of women respond to treatment in the first line setting, when the cancer recurs the response to treatment is usually worse than in the first line and a number of women develop platinum resistance. The survival is poor with over 50% of women dying of ovarian cancer at 5 years from diagnosis. The response to treatment in first line as well as in relapsed setting is much improved in women with BRCA mutation and those who have homologous recombination defect in the tumour DNA repair (this can be caused by either germline BRCA mutation or somatic DNA mutation).
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The clinically significant response to treatment is defined by the clinical benefit such as symptoms improvement and improved quality of life. This is usually caused by reduction in tumour volume, improvement in ascites and pleural effusion. The actual tumour volume varies and it is difficult to quantify as the symptoms depend on the location and the nature of relapsed disease; there may be peritoneal disease that is hardly visible on the CT scan but producing large amount of ascites causing multiple symptoms and there are women with large peritoneal tumours that do not experience symptoms. The decision regarding response has to be based on the clinical symptoms and radiological picture but has to be tailored to individual patient.
9. In your view, is there an unmet need for patients and	The unmet need is the treatment of relapsed cancer and maintaining response to chemotherapy. Currently the most frequent scenario is that the response to chemotherapy and the clinical benefit following second and third line treatment are short lasting. Women relapse early and develop disabling symptoms of relapsed malignancy and commence subsequent line of chemotherapy treatment (if there are active

healthcare professionals in this condition?	options). Most women eventually develop platinum resistance and the response to chemotherapy is then very poor, in the range of 15-20%. New active treatment that have an effect on progression free survival in the relapsed setting ae therefore urgently needed
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Current treatment at diagnosis consists of the combination of cytoreductive surgery and chemotherapy with carboplatin and paclitaxel. In stage IV disease as well as in cases where there is residual disease following cytoreductive surgery additional maintenance treatment with bevacizumab is offered for 18 cycles. The treatment of relapsed disease is depended on the duration of the remission following first line treatment. In platinum sensitive disease (PFS ≥ 12-18 moths) patients are offered surgery (if feasible) and further chemotherapy with platinum based combinations of either paclitaxel or liposomal doxorubicin (in Europe and USA –gemcitabine and platinum). If PFS is shorter (<6months) the disease is platinum resistant and patients are treated with chemotherapy -either weekly paclitaxel or liposomal doxorubicin. For PFS >6months but <12 moths the combination of platinum and liposomal doxorubicin is most frequently used. Patients with platinum sensitive disease upon good response to 2nd or third line chemotherapy are offered Niraparib via CDF. Patients who do have platinum resistant disease have extremely poor prognosis
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The clinical guidelines are based on European Society of Medical Oncology guidelines, as well as American Society of Clinical Oncology guidelines. As not all drugs available in UK the guidelines are adopted to the drug availability. British gynaecological Cancer Society reviews the guidelines and these are published on the website and through annual meetings and publications
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	The pathway is consistent within the NHS, the choice of 2nd and 3rd line chemotherapy may differ slightly as it depends on patients' clinical condition and the time to relapse. There are relatively few options of treatment and they are consistent across the country.

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	The technology would be widely adopted and used in line with the published evidence. We would welcome an alternative PARP inhibitor with a favourable tolerability profile and it would be used in the 2nd or subsequent relapse following response to platinum-based chemotherapy in platinum sensitive relapse
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The current practice in the NHS is to use niraparib in platinum-sensitive ovarian cancer in the 2nd or subsequent relapse, as a maintenance treatment following response to platinum-based chemotherapy. The rucaparib would be used in the same setting as an alternative to niraparib, it has a different tolerability profile and many patients may feel better on rucaparib. It could also be used for treatment in women with BRCA mutation in platinum-sensitive relapse
• How does healthcare resource use differ between the technology and current care?	The difference is mainly tolerability as it appears to have an improved side effects profile. It can also be used as treatment as opposed to maintenance post chemotherapy in women with BRCA mutation in platinum-sensitive relapse.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics
• What investment is needed to introduce the technology? (For	It is an oral treatment and apart from the drug and regular clinical follow up no other investment is needed

example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, rucaparib is well tolerated and will provide a treatment option for women who are unable to tolerate niraparib. Women who are BRCA positive will also be able to use it a treatment option in platinum-sensitive setting
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Possibly
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Rucaparib is most effective in women with BRCA mutation somatic or germline, it is also effective for women with platinum sensitive relapsed cancer , it is less effective in platinum-resistant cancer although the trials are ongoing

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The current care for women who respond to platinum based chemotherapy in relapsed ovarian cancer would be to obtain niraparib via CDF. Niraparib as well as new technology-rucaparib require clinic visits every 4 weeks to monitor blood test to ensure adequate count. The two drugs have a different tolerability profile and some patients may tolerate rucaparib better.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The start of the treatment is set upon the completion of platinum based chemotherapy; rucaparib would be started within 3 months of completing and responding to chemotherapy. Regular tumour assessments (by CT every 8-12 weeks) would aid the decision to continue or stop the treatment and rucaparib would be stopped upon progression.

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Rucaparib gives a substantial benefit in progression-free survival and it is likely to improve QALY
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Rucaparib is a PARP inhibitor that is similar to Olaparib and Niraparib however has a different tolerability profile and many women can potentially benefit from it. In addition it can be used as a treatment option for women with BRCA mutation as opposed to maintenance therapy. The aspect is innovative and it is likely to improve the current practice
• Is the technology a 'step-change' in the management of the condition?	Yes, PARP inhibitors such as rucaparib are a substantial "step change" in the treatment of relapsed platinum sensitive ovarian cancer.

• Does the use of the technology address any particular unmet need of the patient population?	The use of the technology gives a substantial benefit in terms of progression free survival and this is an unmet need as outcome of treatment of relapsed ovarian cancer are very poor
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Adverse effects can be moderated by appropriate dose reduction , patients require monitoring every 4 weeks. As it is a maintenance treatment it is important to maintain the quality of life but this can be done with dose adjustment if the side effects occur
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes the published clinical trials reflect the UK clinical practice
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important clinical outcomes are progression free survival, overall survival and quality of life. Progression free survival and quality of life were measured , the results of overall survival are immature

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not used
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not aware
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA389], [TA528], [TA1296]	Not aware

22. How do data on real-world experience compare with the trial data?	Data on real world is not widely available yet, from practice in compares favourably
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. Given the immaturity of ARIEL3 OS data, is it appropriate to assume the same overall survival as for olaparib using Study 19 data?	It is likely that rucaparib will show similar benefit to olaparib, this is based on the clinical activity seen to date. Both drugs have the same mechanism of action and it is reasonable to extrapolate the results and assume that the overall survival benefit will be similar

25. The BRCA group in the ARIEL3 trial includes germline and somatic mutations while the BRCA group in clinical practice would include germline mutations only. Is the response to rucaparib influenced by the type of BRCA mutation?	The response to rucaparib is not influenced by the type of mutation and the drug should equally efficacious in both germline and somatic mutations carers
26. To what extent is testing for somatic BRCA mutations done in the UK?	Currently it is not a standard practice, it is mainly done in the context of trials or research projects. Astra Zeneca was also offering this service on the temporary bases
27. Is it relevant to separate the population into subgroups or is it more appropriate to focus on the ITT population from the trial?	In my opinion it is more appropriate to focus on ITT population as there is an overall benefit

28.Is the assumption of equivalence in post progression survival (PPS) across PARP inhibitors maintenance treatments plausible?	This would depend on the line of treatment the PARP inhibitor is used (2nd or subsequent line) and on the subgroup, one would not assume the same PPS for a BRCA mutated patient when compared to a woman with no mutation. Equally PPS is likely to be better for women treated with PARP after 2 lines of chemotherapy as opposed to 3 or more.
29.How is the benefit of rucaparib in terms of progression-free survival expected to translate into overall survival benefits? What would be a plausible PFS:OS ratio?	The Overall survival benefit is expected to be comparable to other studies with PARP inhibitors , a plausible PFS:Os ratio is around 0.5
30.Is the assumption of all patients having progressed after 10 years plausible?	Yes
31.Would subsequent therapies differ according to	Correct, for patients with BRCA mutation platinum based drugs would be a good option, for those with BRCA wild type other treatment may be chosen

BRCAm status and number of previous chemotherapy regimens?	
32.Are patients expected to receive more than one PARP inhibitor in their treatment pathway (e.g. patient who received rucaparib as 2L maintenance could receive olaparib as 3L maintenance)?	At present there is no data supporting this approach and until clinical trials show benefit of this approach , it is unlikely to happen

Key messages

33. In up to 5 bullet points, please summarise the key messages of your statement.

- Rucaparib provides progression-free survival benefit for women with relapsed-platinum sensitive ovarian cancer
- Rucaparib has a favourable toxicity profile that may be preferred to other PARP inhibitors
- Rucaparib offers a treatment option for women with BRCA mutation (not only maintenance)
- Rucaprib is likely to provide overall survival benefit
- Rucaparib should be available as an option of treatment for women with platinum-sensitive relapsed ovarian cancer

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Please aim for your response to be no longer than 16 pages.

About you	
1. Your name	**Jonathan A Ledermann**
2. Name of organisation	**UCL Cancer Institute and UCL Hospitals, London**

3. Job title or position	**Professor of Medical Oncology and Hon Consultant in Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Rucaparib is given after platinum-based chemotherapy for recurrent ovarian cancer to maintain the response/remission to chemotherapy or increase the depth of response where residual disease remains, extend progression-free survival and increase overall survival. It is given in a situation where chemotherapy alone is not curative, and patients are expected to have a period of approximately 5-6 months before further disease progression and the need for more chemotherapy
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The key aim is to delay progression and the start of the next line of treatment. The drug does this by a combination of deeper tumour response if residual disease is present at the end of chemotherapy and delaying tumour growth by maintaining prevention of DNA repair through inhibiting the PARP enzyme. The evaluation of benefit was made by comparing the progression-free survival from start of rucaparib after chemotherapy with that of placebo
9. In your view, is there an unmet need for patients and	From more than 20 years of clinical trials and practice it is clear that the best chemotherapy, a combination of platinum and another drug leads to an approximately 5-6 month period before progression/regrowth of tumour occurs, and a patient needs a further line of treatment. Virtually all patients with recurrent ovarian

healthcare professionals in this condition?	cancer will eventually succumb to their disease after chemotherapy. The median life expectancy of patients being treated for their first relapse is currently only about 36 months
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	For any patient with high grade ovarian/peritoneal/fallopian tube cancer chemotherapy followed by observation was the standard treatment until the approval by the CDF of niraparib maintenance. NICE has approved olaparib maintenance in women with a BRCA mutation after their third line platinum-based chemotherapy
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Currently, the main European Guidelines in use are the ESMO guidelines for ovarian cancer with the e-update for olaparib in women with a BRCA mutation and the BGCS Guidelines (2017). ESMO guidelines to include niraparib, rucaparib and the expanded licence for olaparib in recurrent ovarian cancer are currently being updated. The ESMO-ESGO Ovarian Cancer Consensus Guidelines (Colombo et al Ann Oncol 2019) provides up-to-date recommendations on therapy. Up-to-date treatment guidelines (May 2019) describing the indications for these drugs can be found in the NCCN guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, the pathway is clearly defined and has recently been updated through the ESMO-ESGO Ovarian Cancer Consensus Conference, April 2018, published in Colombo et al Ann Oncol (May 2019). Patients with recurrent ovarian cancer should be considered for further platinum-based therapy unless platinum-based treatment is clearly not an option. When this is used and patients have at least a partial tumour response PARP inhibitor maintenance is recommended, irrespective of BRCA status. Maintenance therapy is now an internationally recognised standard of care, noting that bevacizumab at relapse, licenced but not NICE-approved in England, is not an option

• What impact would the technology have on the current pathway of care?	It would provide patients with a opportunity of extending progression-free survival, increasing the depth of response, delay the use of further chemotherapy, and ultimately increase overall survival
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology will be used in a similar way to niraparib, a drug currently approved by the Cancer Drugs Fund. The indications for use of rucaparib are similar although the entry criteria of the trials evaluating niraparib and rucaparib were slightly different. For example, in the NOVA trial (niraparib) patients with residual disease ≥ 2cm were excluded, favouring a group of patients likely to have better outcome. In ARIEL3, the rucaparib trial patients could enter with bulky residual disease and a further tumour response to maintenance rucaparib was noted in some patients in this category.
• How does healthcare resource use differ between the technology and current care?	The standard of care, before the introduction of niraparib was observation. Monitoring with blood test and CT imaging if recurrence was suspected was followed by a further course of chemotherapy in most patients. From the results of both the NOVA and ARIEL 3 trials the median progression-free survival on placebo was around 5-6 months; patients then restarted chemotherapy. In the “all-comer” group in ARIEL 3, the median progression-free survival was 10.8 months compared with 5.4 months (HR 0.30; 95% CI 0.30–0.45); P<0.0001. This includes the tBRCA patients, a mixture of gBRCA and sBRCA. In NOVA (CDF approved niraparib), the results in the non-gBRCA cohort (which included patients with sBRCA, but not gBRCA), were median PFS 9.3 versus 3.9 months (HR = 0.45; (95% CI: 0.34–0.61) p < 0.001. It is difficult because of the design of these trials to make direct a comparison, but it appears that the drugs are of equivalent effectiveness, and benefit patients without a BRCA mutation as well as those with a mutation. In all studies patients with a BRCA mutation- germline of somatic respond longer to either PARP inhibitor than those who are BRCA wild-type. Maintenance therapy with niraparib is currently available through the Cancer Drugs Fund following NICE review. Rucaparib is a similar drug providing a significant benefit in PFS for all patients, irrespective of BRCA or HRD status responding to platinum-based therapy. Secondary/exploratory endpoints such as

	Time to First Subsequent Treatment (TFST) and Progression-Free Survival 2 (PFS2) also support the benefit of this drug
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should be offered to all patients responding to platinum-based therapy for recurrent high-grade ovarian cancer.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This is an oral drug with low grade side effects in the majority of cases. Adjustments of dose enable around 87% patients to continue therapy to progression. Hospitals have become familiar with this technology (Olaparib maintenance NICE approved in after 3rd line therapy; niraparib maintenance CDF-approved after recurrence). Novel structures, such as nurse-led or pharmacist-led clinics are being explored to reduce medical workload. Blood testing for rucaparib is less frequent that niraparib, which is a cost-saving
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	If this technology is compared with fully approved NICE recommendations, then yes, as there is no maintenance option. If however, it is compared with the CDF-approved niraparib following NICE appraisal, then the benefit is unlikely to be different. For rucaparib there a significant improvement in PFS compared to placebo (no maintenance) but in addition there are improvements in PFS2 (a surrogate for OS) as well as significant benefit in control of symptoms (as recurrence delayed). [redacted]
• Do you expect the technology to increase length of life more than current care?	Yes, there is no reason to believe there will not be a 'tail on the survival curve' as there has been with the long-term follow up of olaparib maintenance (Study 19). I would expect about 10% of patients to be long-term survivors, a situation currently almost never seen in any patient with recurrent ovarian cancer following platinum-based therapy
• Do you expect the technology to increase	It depends on how it is measured. Standard Quality of Life measurements (used in this trial) are not applicable to maintenance therapy. See above comment (12) in relation to TWisT analysis. It is the delay in

health-related quality of life more than current care?	progression and its symptoms, and the delay in the need to have further chemotherapy that have the greatest impact on patients' well-being. Both these are very important quality of Life Indicators for patients
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology is effective in all patients with recurrent high-grade ovarian cancer responding to platinum-based chemotherapy. Age has been specifically studied, and no evidence of an aged-related effect of this drug either on benefit or toxicity was seen
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	See response to Q11. This technology is easier to manage and cheaper than using chemotherapy. There will be better streamlining of delivery in hospitals as familiarity with this class of drug increases (nurse- or pharmacist-led clinics). The lack of negative effect on QoL and the ability of 87% patients to continue to take the drug until tumour progression supports the notion that the drug is well-tolerated and thus has less resource implications than, for example, managing chemotherapy

or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will initially need to be seen monthly but once the dose is established 2 monthly visits, and then 3 monthly could be implemented. For those patients in whom toxicity can be managed (87%) treatment will continue to progression. Routine blood testing is needed each visit. This is more frequent than the 2-3 monthly blood tests undertaken in routine practice without maintenance therapy. Follow up CT imaging is no more frequent than in routine clinical practice
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, not only will chemotherapy re-treatment be delayed which has a large benefit to patients' well-being but also it is expect that around 10% will be long-term survivors, not requiring any further chemotherapy (see long-term results study 19). This will have a major impact on patients but I don't think the 'flat tail' on the survival curve affects QALY calculations, as these are based more on median results
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, in so far as all PARP inhibitors used for maintenance are innovative therapies. It is difficult to draw any distinction between the three licensed PARP inhibitors in this indication (olaparib, niraparib and rucaparib).

impact on health-related benefits and how might it improve the way that current need is met?	An improvement in median OS is expected when the OS data are mature, and about 10% are expected to be long-term survivors (not seen with any other type of therapy for recurrent ovarian cancer)
• Is the technology a 'step-change' in the management of the condition?	Yes, in so far as it belongs to the class effect of PARP inhibitors in recurrent ovarian cancer
• Does the use of the technology address any particular unmet need of the patient population?	Yes, the median time to starting another line of treatment is 5.4 months. Rucaparib significantly delays this, (median 10.8 months) and it is expected that long-term disease control will occur in a sub-population of patients
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No decrement in standard Quality of Life measurements were seen with this treatment. Thus, the side effects, generally low grade, are manageable in nearly all patients. Only 13% stopped treatment due to reasons other than progression/death. [redacted] support the value of this treatment in relation to patient well-being
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the UK contributed a significant number of patients to the ARIEL3 clinical trial. Apart from the recent CDF approval of niraparib, there has been no opportunity to use maintenance therapy in recurrent ovarian cancer in the UK, other than 3rd line maintenance olaparib in the BRCA-mutated subgroup
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and the PFS2 that gives measure of the longer-term benefit while OS data are awaited clearly demonstrate the value of rucaparib maintenance therapy
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See PFS2 above as a surrogate for OS
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No, the literature on randomised trials of maintenance therapy with PARP inhibitors is small and well-known to specialists/researchers in the field

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA389], [TA528], [TA1296]	No. Long-term follow up information is not available on niraparib (TA528) or olaparib (TA1296). However, recent published data on olaparib first-line maintenance in patients with a BRCA mutation (current NICE review ID 1124) could affect the use of PARP inhibitors in recurrent disease. Approval of olaparib in first-line would shift the use of PARP inhibitors, such that patients with a BRCA mutation would receive first-line olaparib and patients with recurrent disease would only receive a PARP inhibitor if their tumour was BRCA-wild-type
22. How do data on real-world experience compare with the trial data?	There is no evidence to suggest that this is different. Real-world data is beginning to accumulate as these drugs, now licensed are entering into practice
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
24. Given the immaturity of ARIEL3 OS data, is it appropriate to assume the same overall survival as for olaparib using Study 19 data?	Yes, there is no reason to expect that the OS benefit is going to be less. In fact, it may be greater as a larger proportion of patients in ARIEL3 entered the trial in after second-line treatment compared with Study 19.
25. The BRCA group in the ARIEL3 trial includes germline and somatic mutations while the BRCA group in clinical practice would include germline mutations only. Is the response to rucaparib influenced by the type of BRCA mutation?	I think in reality, testing will change and will include tumour testing, particularly in the first-line setting where currently the indication for olaparib is for patients with a BRCA mutation. Without tumour testing, approximately one third of BRCA mutations will be missed (sBRCA mutations are found in 6-7% of all high-grade serous tumours; gBRCA mutations in 15%). For second-line and beyond use, the indication does not depend on whether the patient has a BRCA mutation. In reality in a few years time, all patients will have been offered testing at diagnosis, so the results will be known at relapse.

	There is no evidence from any of the PARP inhibitor trials that patients with an sBRCA mutation respond differently from those with a gBRCA mutation
26. To what extent is testing for somatic BRCA mutations done in the UK?	See comment above. When the new genomic hubs and funding are in place, there should be opportunity for both germ line and tumour testing. With time, I suspect the tumour testing will be done initially, followed by germline testing if the tumour testing is positive. This sequence is likely to be more firmly established when the false negative tumour testing rates fall further
27. Is it relevant to separate the population into subgroups or is it more appropriate to focus on the ITT population from the trial?	There is clear activity in the ITT population. While the PFS benefit in terms of HR was greater in the tBRCA and LOH high groups (ARIEL3), these tests were not able to exclude patients who benefitted from maintenance rucaparib, ie the BRCA wild-type LOH low group. This group still had a significant benefit from maintenance rucaparib. Thus, the treatment benefits all those responding to platinum-based therapy.
28.Is the assumption of equivalence in post progression survival (PPS) across PARP inhibitors maintenance treatments plausible?	If OS is greater in patients receiving rucaparib, the post progression survival will be longer in that group. Not all patients in the control arm will cross over to a PARP inhibitor on progression; some of these patients, relapsing early may not receive further platinum-based therapy and therefore be unable to have a PARP inhibitor at a later date, or may have more symptomatic disease at further progression making the administration of oral medication more challenging.

29.How is the benefit of rucaparib in terms of progression-free survival expected to translate into overall survival benefits? What would be a plausible PFS:OS ratio?	PFS:OS ratio is a figure calculated from medians. This is a rather arbitrary point estimate comparison. For example, if the survival curve flattens after some years (36 months in the case of study 19) this will occur beyond the median OS, so the ratio will miss this difference. It would be better to look at a mixture of landmark survival points (with mature data) eg 3, 4, 5 years, comparing the percentage alive with control and rucaparib arms, and also look at the tail of the curve running out to 6-7 years. For study 19, 11% patients remained on treatment free of recurrence ≥ 6 years. In study 19, estimating the OS at 6 years, around 12% patients on the placebo arm were alive compared with at least 30% on the olaparib arm [Friedlander et al B J Cancer 2018]
30.Is the assumption of all patients having progressed after 10 years plausible?	No. In study 19, 11% patients on olaparib continued beyond 6 years without progression; some of these patients are now coming up to the their 10th anniversary on the drug, still without progression
31.Would subsequent therapies differ according to BRCAm status and number of previous chemotherapy regimens?	Not necessarily. Most patients would be re-treated with platinum-based therapy and the likely benefit will depend on the platinum-free interval. For patients with a BRCA mutation, this is likely to be longer, so the probability of response to subsequent platinum-based therapy will be greater. Whilst this may be the case for first, or possibly second relapse, patients with a BRCA mutation do develop resistance to platinum drugs so that survival rates for the two groups tend to merge, more so perhaps for BRCA1 than BRCA2 tumours, where the survival at 10 years is superior to BRCA wild type tumours. It is most likely better to use the best

	treatments available early on in the disease pathway, at a time when the tumour has least resistance to platinum-based drugs and also PARP inhibitors
32.Are patients expected to receive more than one PARP inhibitor in their treatment pathway (e.g. patient who received rucaparib as 2L maintenance could receive olaparib as 3L maintenance)?	There are no good data examining retreatment with a PARP inhibitor. The small number of cases presented so far suggest that re-treatment after progression on a PARP inhibitor is unlikely to lead to a durable benefit. This is not surprising as PARP inhibitor maintenance is stopped when the tumour becomes resistant. Currently there is insufficient data to know whether switching to another PARP inhibitor after progression and retreatment with platinum-based therapy is clinically useful. These studies need to be done. The situation may be different in first line therapy. Here treatment is stopped after 2 years and tumours relapsing some while after that may not be as resistant to rechallenge with a PARP inhibitor. There are currently no data available to know what the outcome of retreatment is in this group
Key messages	

33. In up to 5 bullet points, please summarise the key messages of your statement.

- Rucaparib maintenance therapy leads to a clinically meaningful benefit in PFS survival in all patient groups
- Rucaparib is an oral drug generally well-tolerated
- The magnitude of benefit is greatest in BRCA mutated ovarian cancer but those with BRCA wt and LOH low still derive significant benefit
- Rucaparib has similar activity to other PARP inhibitors and is expected to lead to an improvement in OS
- OS data are not mature, but PFS2, a surrogate endpoint for OS demonstrates continuing benefit of the rucaparib arm beyond further treatment to second progression

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Appendix D – patient expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by **Target Ovarian Cancer** and consequently I will not be submitting a personal statement.

Name: RACHEL DOWNING

Signed: .....

Date: 03/05/19

.....

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

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 128204

BMJ Technology Assessment Group

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

Produced by: BMJ Technology Assessment Group (BMJ-TAG)

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Declared competing interests of the authors:
No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

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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.

This report should be referenced as follows: Edwards SJ, Karner C, Jhita T, Marceniuk G, Barton S. Rucaparib for maintenance treatment of recurrent platinum sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum base chemotherapy: A Single Technology Appraisal. BMJ Technology Assessment Group, 2019.

Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Samantha Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

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.

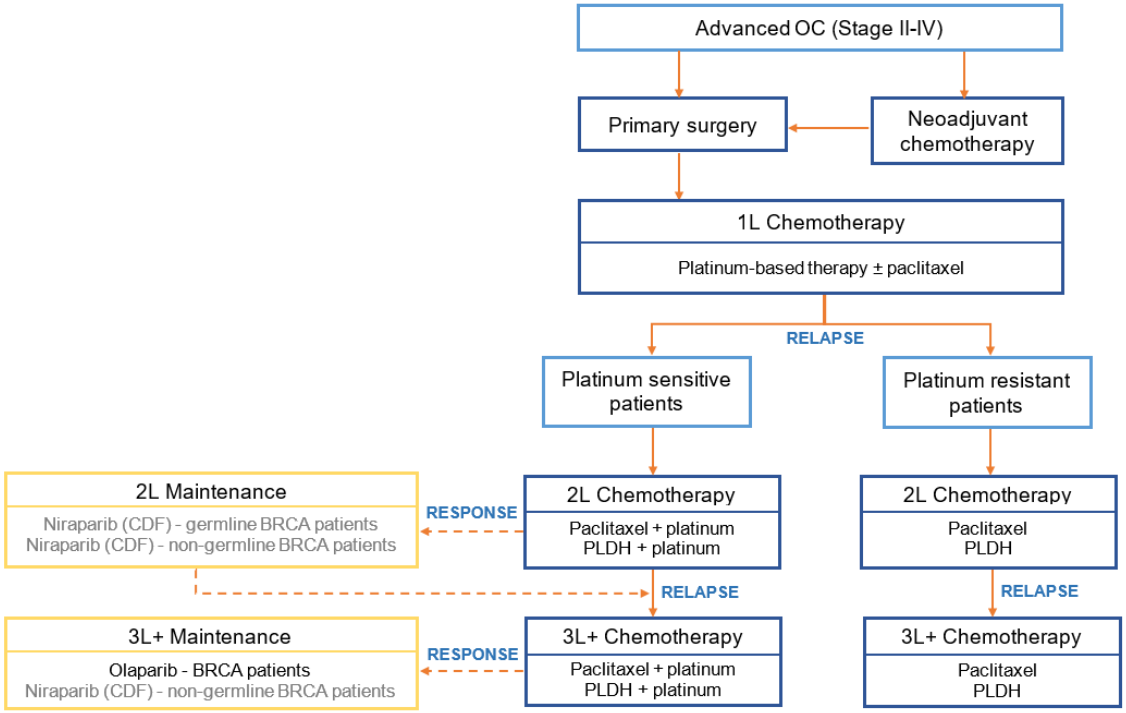
Rucaparib is positioned as an option for maintenance of response to last treatment for people with platinum-sensitive ovarian cancer and who have received two or more prior platinum-based regimens, irrespective of BRCA status. The ERG and its clinical experts consider the proposed position of rucaparib 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 For people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy: •Olaparib (Lynparza®) (subject to ongoing appraisal)	•Routine surveillance For people who have BRCA1 or BRCA2 mutations and who have responded to the third or subsequent course of platinum-based chemotherapy: •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: •Overall survival •Progression-free survival •Progression-free survival 2 (that is, progression-free survival on next line of therapy) •Time to next line of therapy •Adverse effects of treatment •Health-related quality of life	The outcome measures to be considered include: •Overall survival •Progression-free survival •Progression-free survival 2 (that is, progression-free survival on next line of therapy) •Time to next line of therapy •Adverse effects of treatment •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. 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. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. 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 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) Appendix D.3, Table 22 (pages 65–66)	Appropriate People randomised 2:1 to rucaparib:placebo 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. 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 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. 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) 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. Primary outcome PFS as assessed by the investigator. Analysis of PFS by BICR reported as a secondary outcome. HRQoL was assessed by FOSI-18, a symptom questionnaire specific to ovarian cancer. Several outcomes of the specified in the NICE final scope were exploratory outcomes in ARIEL3. 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. 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):

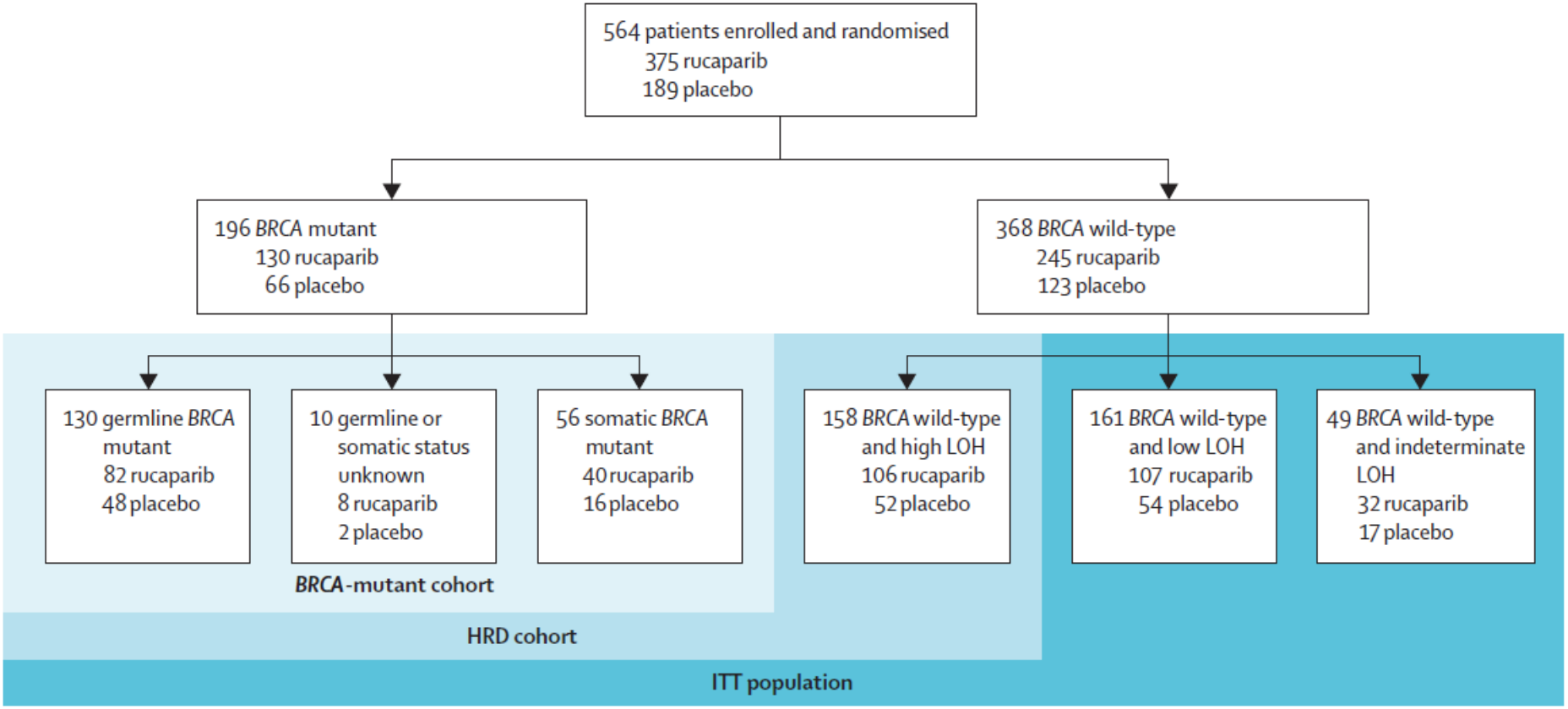
- ITT: all randomised patients;
- HRD cohort: all BRCA mutant patients (germline, somatic, germline/somatic status unknown) and BRCA wild-type with a high loss of heterozygosity (LOH), which is a proposed marker of HRD;
- BRCA mutant cohort: all BRCA mutant patients (germline, somatic, germline/somatic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

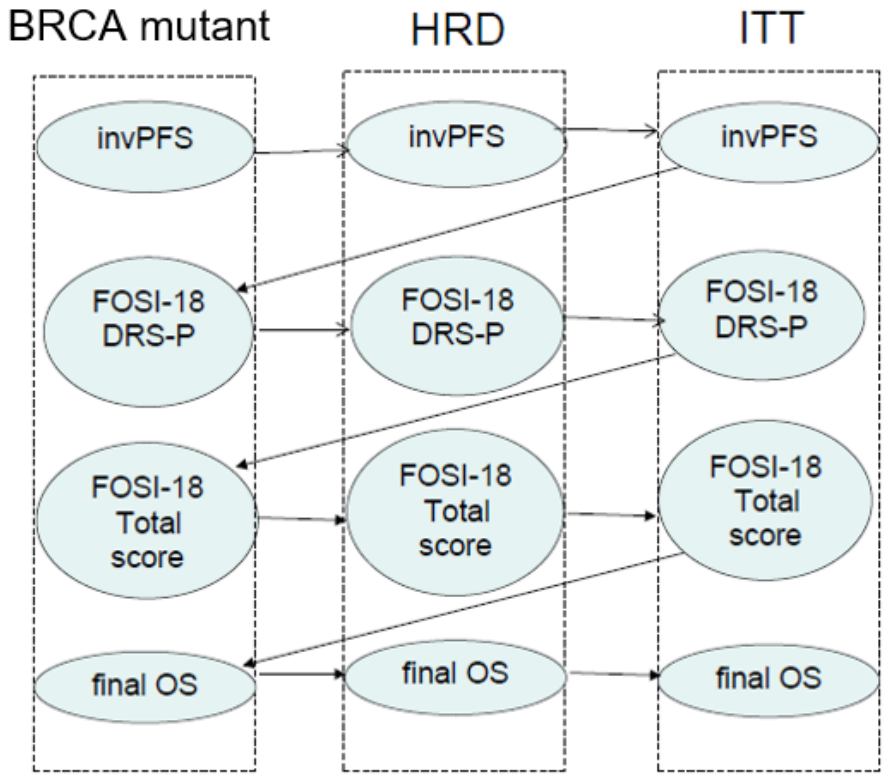
3.2.4 Ordered stepdown multiple comparison

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]

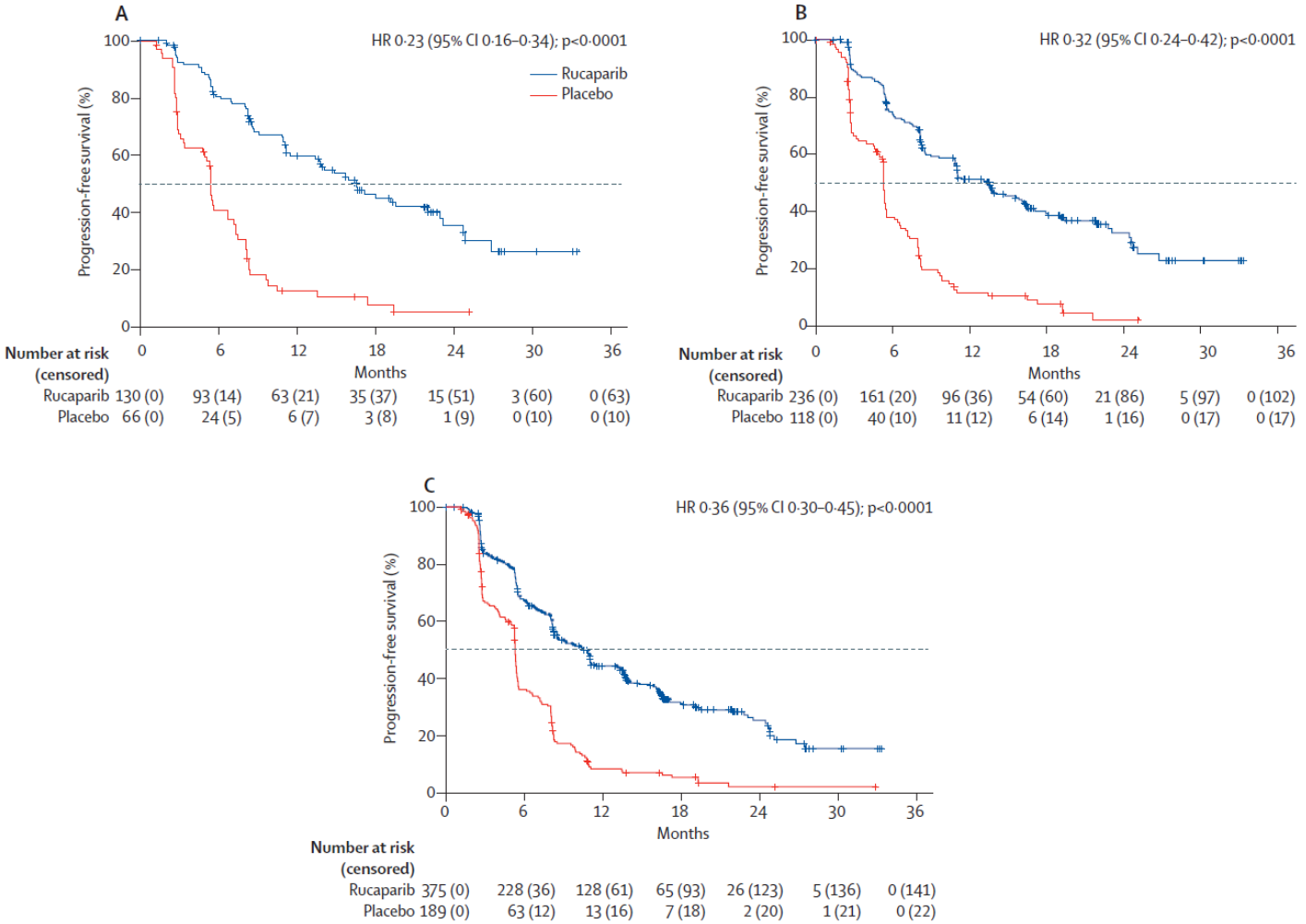
To address the decision problem, as outlined in the NICE final scope, the company also presented data for the BRCA 3L+ subgroup, and, at the clarification stage, also for the BRCA 2L and non-BRCA subgroups. The ERG acknowledges and agrees with the company that some of the groups are *post hoc* subgroups 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)

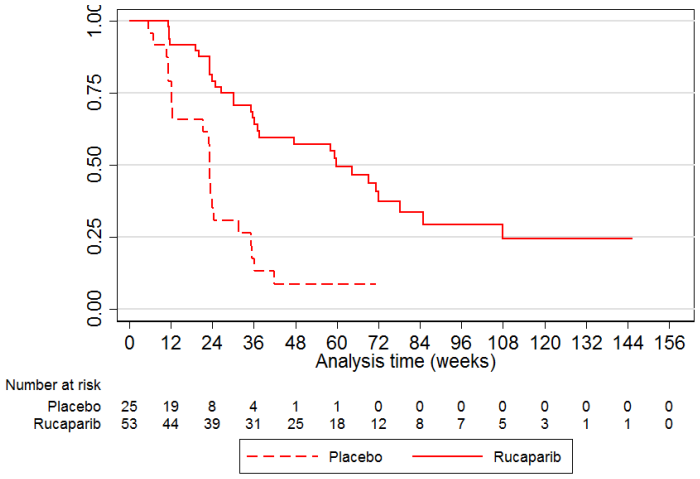
A) non-BRCA

[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) p-value	[redacted]					
Visit cut-off date: 15 April 2017						
TSST, median months (95% CI)	[redacted]					
HR (95% CI) p-value	[redacted]					
Visit cut-off date: 15 April 2017						
PFS2, median months (95% CI)	[redacted]					
HR (95% CI) p-value	[redacted]					
Visit cut-off date: 31 December 2017						
PFS2, median months (95% CI)	[redacted]					
HR 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 (95% CI) 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 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

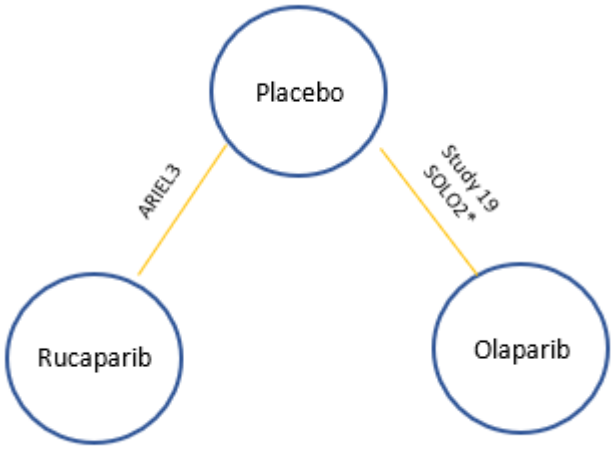
Abbreviations: 2L, two prior lines of therapy; 3L+, three or more prior lines of therapy; BIRC, blinded independent review committee; BRCA, breast cancer gene; INV, investigator-reported; ITT, intention-to-treat; NA, not applicable; OS, overall survival; PFS, progression-free survival.

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 Rucaparib [redacted] Placebo [redacted]	Effective sample size [redacted]	Effective sample size [redacted]
PFS-INV 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. PICOS appropriate for cost-effectiveness evidence and HRQoL evidence. 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. 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.

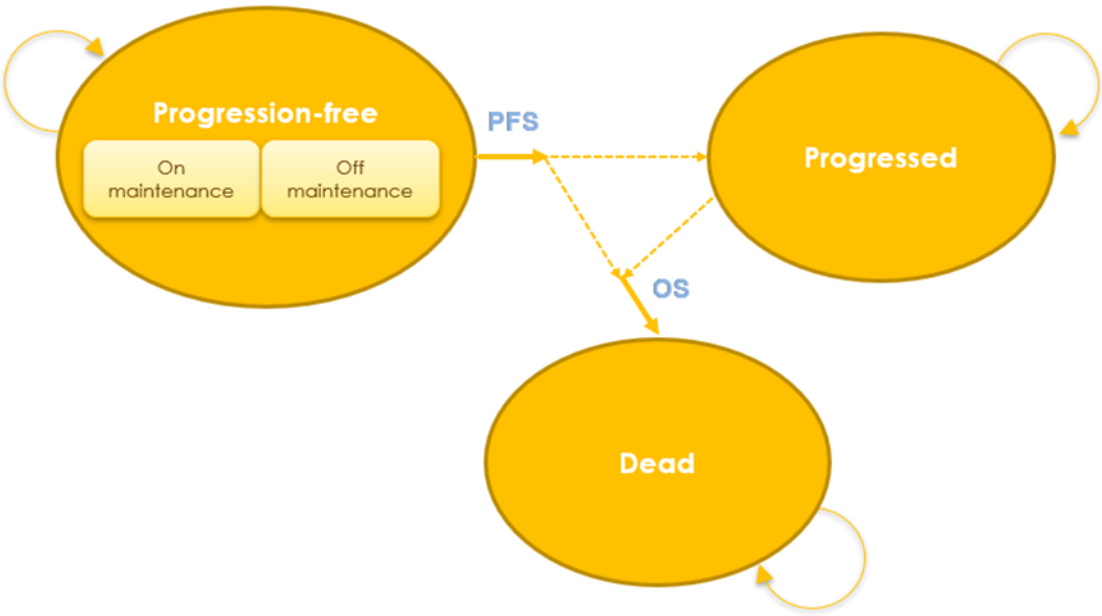
4.2.4 Model structure (incl. perspective, time horizon and discounting)

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 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.

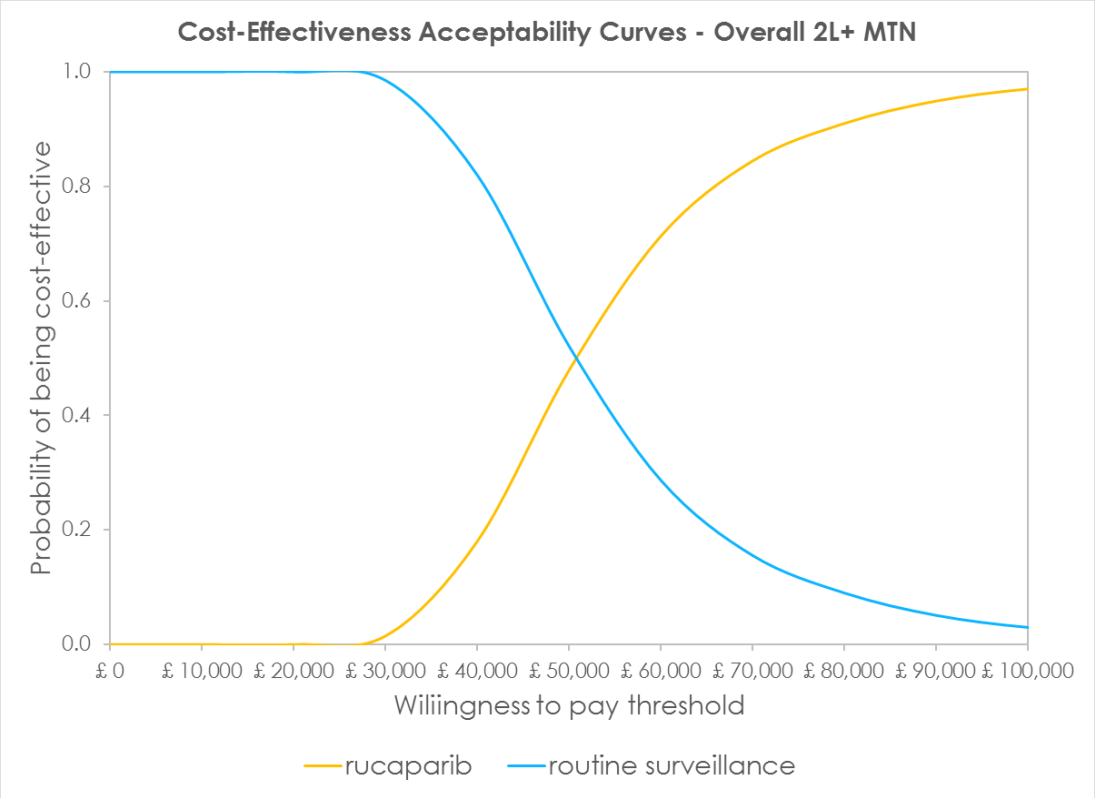
Table 43. Revised probabilistic base-case results for the ITT population (reproduced from Table 10 of the company's clarification responses)

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)

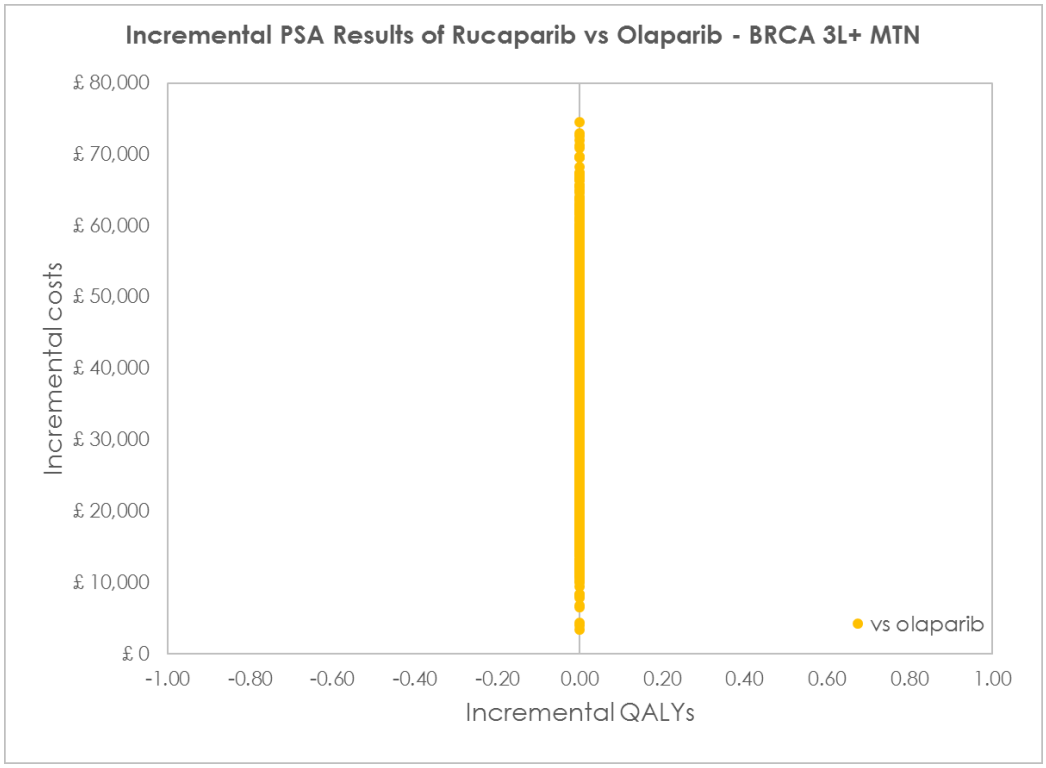


Figure 11. CEAC of 2,000 PSA iterations in the BRCA 3L+ population (taken from the revised economic model)

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)

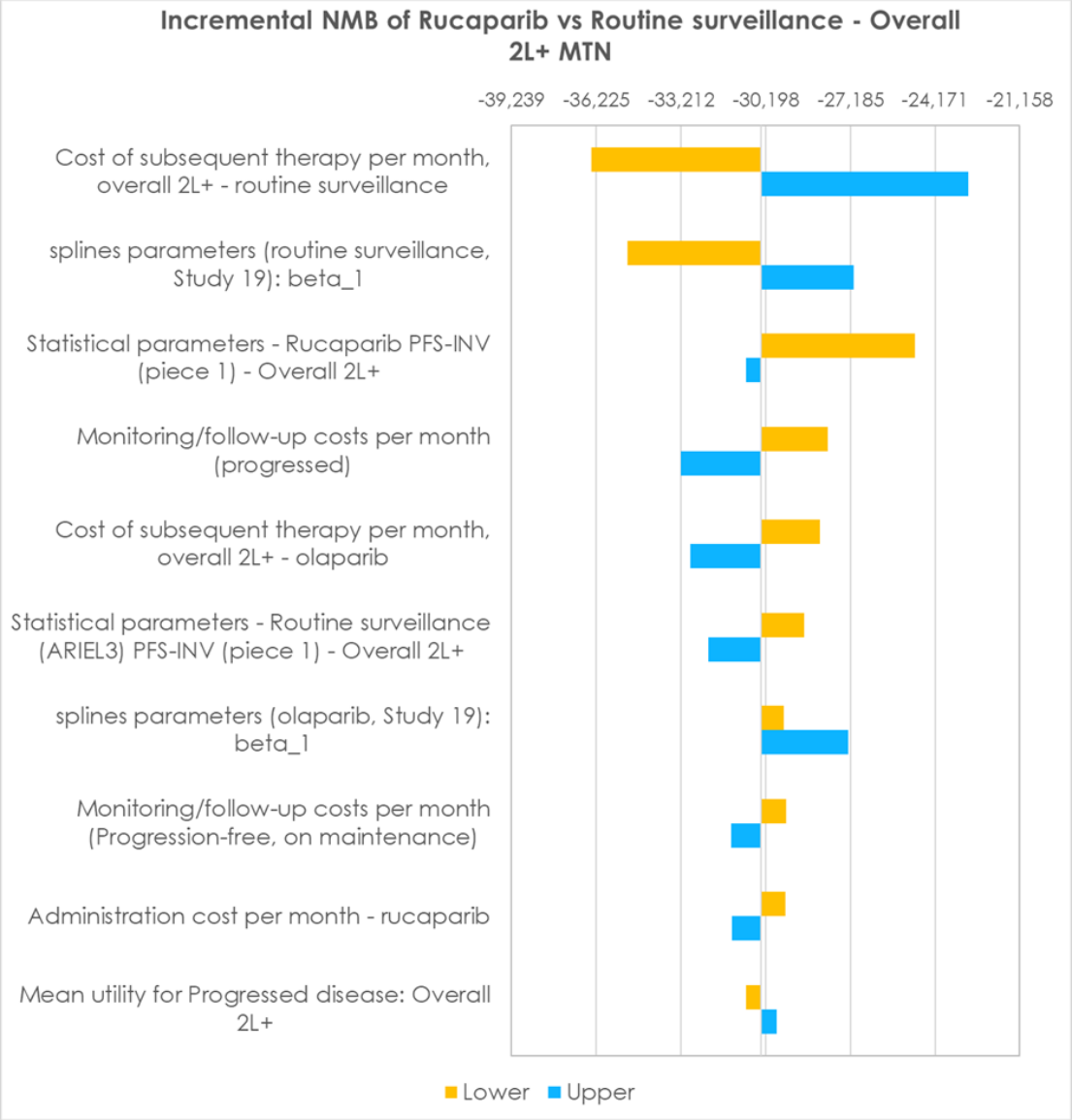


Figure 13. Revised tornado diagram for the BRCA 3L+ population (reproduced from Figure 31 of the company's clarification responses)

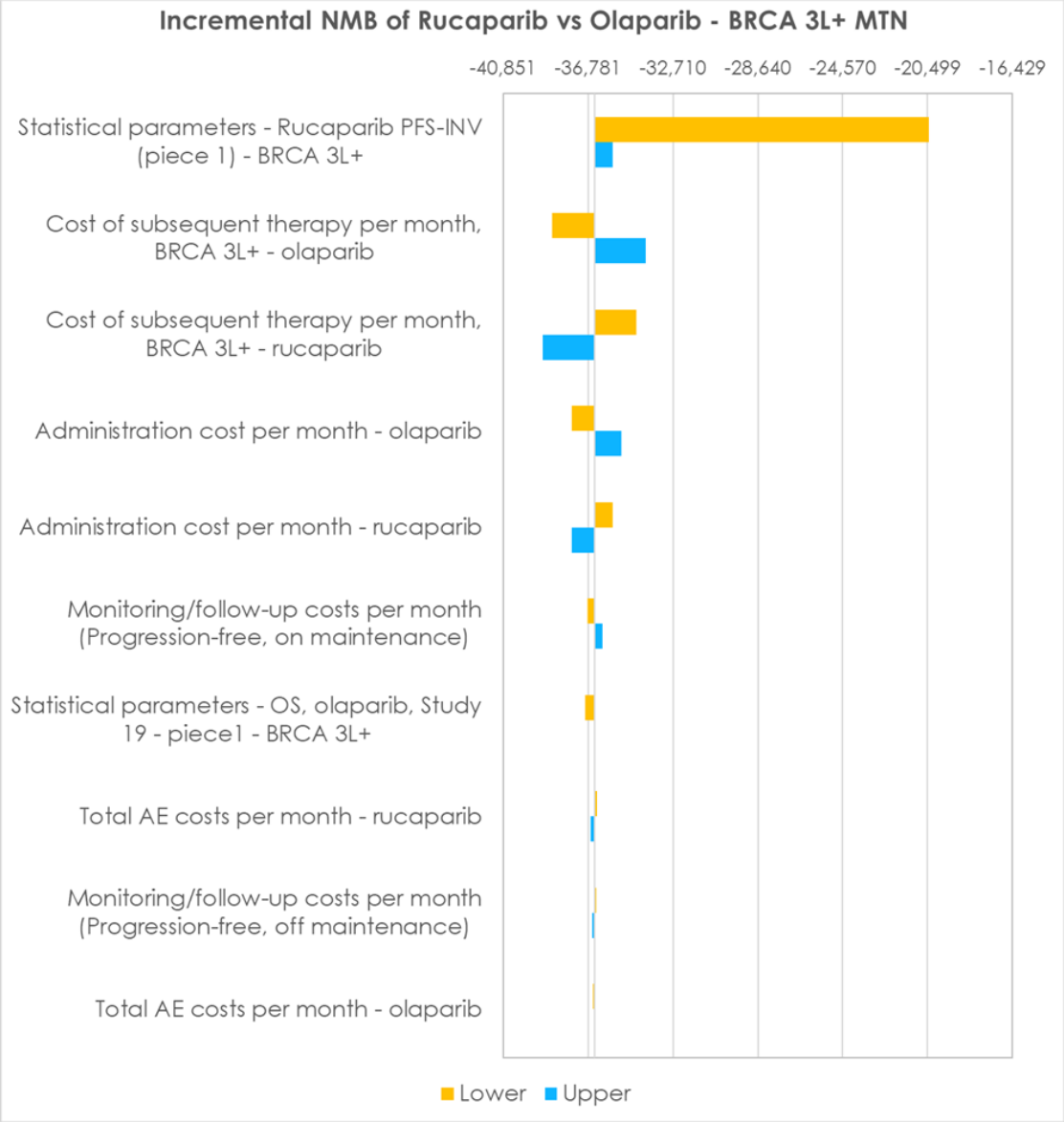


Table 45. OWSA for the revised base-case with ICER as outcome, ITT population (reproduced from Table 52 of the company's clarification responses)

#	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

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.

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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, %: 2: 56.1 3: 30.6 4: 9.2 ≥5: 3.6	Number, %: 2: 62.6 3: 20.2 4: 12.1 ≥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 PR: 66	CR: 34 PR: 66	CR: 46 PR: 54	CR: 47 PR: 53	CR: 42 PR: 58	CR: 49 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.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

You are asked to check the ERG report from BMJ Technology Assessment Group to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 29 April 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Discussion of population versus decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
When discussing the population enrolled in ARIEL3 versus the decision problem on Pages 9, 16 and 20, it has been incorrectly noted that the ARIEL3 population is narrower on the basis that any line of prior treatment is noted in the final scope versus two or more prior platinum-based treatments in ARIEL3. The population specified in the decision problem and addressed in the submission are "people with **recurrent** platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer **that is in response** (complete or partial) to platinum-based chemotherapy". To have recurrence of diseaese and be in response to platinum-based chemotherapy, patients must have received at least two lines of prior chemotherapy; therefore any line of prior treatment in patients who have recurrent platinum-sensitive disease and are responding to platinum-based chemotherapy is equivalent to patients who have had two or more prior platinum-	Please correct discussion of the population enrolled in ARIEL3 versus the decision problem to acknowledge that they are fully aligned.	The current discussion that notes a difference between the population enrolled in ARIEL3 versus the decision problem is incorrect. The company submission fully aligns to the final scope and this should be made clear to the NICE committee.	The ERG thanks the company for highlighting this error which had been corrected on page 9 and 20. The trial population was not discussed in relation to the decision problem on page 16.

based treatments.			

Issue 2 Description of subgroups and appropriate comparator versus decision problem

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
When discussing the subgroups relevant to the decision problem and appropriate comparator on the pages noted below, it has been incorrectly suggested that the comparison to routine surveillance was only considered relevant in subgroups of non-BRCA and BRCA 2L patients. In the final scope issued by NICE, routine surveillance is listed as a relevant comparator without restriction i.e. for the total population of interest (irrespective of BRCA mutation status). The company base case analyses fully aligns to this and importantly to the clinically relevant population of patients who would be considered for rucaparib maintenance in clinical practice as per the population enrolled in ARIEL3 and the marketing authorisation for rucaparib maintenance. It is acknowledged that the final scope states that **if the evidence allows**, consideration will be	Description of subgroups and appropriate comparator versus decision problem should be aligned to the final scope issued by NICE at all mentions. Of particular concern are the bullets summarising the key issues in the clinical effectiveness evidence that state: • estimates of effect in population 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). The first of this is not true and the subsequent bullets need amending accordingly - for example:	The current description of the final scope with regard to subgroups and appropriate comparators is incorrect. The company submission fully aligns to the final scope and this should be made clear to the NICE committee.	This is not a factual error.

given to subgroups with or without BRCA mutations. The ARIEL3 trial was not designed to investigate these subgroups, rather it prospectively evaluated treatment effect in molecularly defined HRD subgroups. Therefore, **the evidence does not allow** a robust analysis for these subgroups. On request from the ERG they have been provided, but it should be clear when discussing subgroups and appropriate comparators what the final scope listed, and what the company provided in line with the final scope and the evidence base of rucaparib maintenance. Page numbers in ERG report: 9, 10, 18, 19, 20, 21, 23, 24, 26, 28, 32, 37, 44, 45, 47, 57, 61, 67, 98	• estimates of effect for the population of interest to the comparison of olaparib in the decision problem (BRCA 3L+) are generated from a subgroup of the full trial population of ARIEL3, with accompanying potential weaknesses • imbalances in baseline characteristics between treatment groups and small patient numbers for this subgroup (Section 3.2.1); • the BRCA 3L+ subgroup was not pre-specified in ARIEL3 and, as such, analyses for this group are post hoc (Section 3.2.3). Table 6 where the ERG comments on the decision problem also needs correcting to acknowledge the final scope issued by NICE versus the ERGs interpretation of the decision problem i.e. rather than state: • 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 And • 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 The following should be noted: • In the CS routine surveillance was presented as the comparator for the full		

	population as listed but not for the subgroups of people who can't receive olaparib, i.e. non-BRCA and BRCA 2L And • The company did not consider the evidence allows consideration of subgroups with or without BRCA mutations but provided post-hoc analyses of non-BRCA and BRCA 2L subgroups in response to a clarification request		
The ERG writes in section 4.2.5.1, page 67, that *"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."* The ERG also acknowledges that "*subgroup analyses for the non-BRCA and BRCA2L populations … have 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*" (section 4.2.2, page 61) The company was asked at the clarification stage to submit data on the BRCA 2L and non-BRCA subgroups. In this instance, the company indicated that such post-hoc analyses are not applicable	The ITT population in ARIEL3 is fully aligned with the population in the final scope. The final scope is the NICE reference case for the Decision Problem. This is the population used for modelling treatment effectiveness and the ERG report should acknowledge this. The ERG should focus on the available data for the ITT population, as formulated in the scope, which already has uncertainty around it and comprises of immature OS data.	As noted above, the final scope defines the population of interest as "*People with recurrent platinum-sensitive epithelial ovarian, fallopian tube or peritoneal cancer that is in response (complete or partial) to platinum-based chemotherapy*". This is the population used for modelling treatment effectiveness. It is also stated that "*If the evidence allows, consideration will be given to subgroups with or without BRCA mutations*". For all the reasons stated above, the company does not believe that the available sub-group evidence is sufficient to inform decision-making. Further investigation into subgroups (even though they might be of clinical relevance) would only include bias and further dilute the conclusions when it comes to interpretation of	This is not a factual error.

from many perspectives, including but not limited to immaturity of the data, as these sub-populations were not pre-specified and do not reflect treatment decision making from a clinical perspective.		the results.	

Issue 3 Description of approach to indirect treatment comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
When describing the appropriateness of the approach taken to ITC on Pages 11, 53 and 54, it is suggested that the MAIC approach to ITC was somehow preferred to the NMA approach.	Please make it clear when describing the approach to ITC that the company basecase takes an assumption of equivalence based on no conclusive evidence of the direction of effect across ITC analyses, and neither the MAIC or NMA are concluded to provide robust analyses, based on the paucity of data in the BRCA 3L+ population for which the ITC is required. Please specifically amend the sub-bullets under appropriateness of NMA and MAIC in the executive summary to reflect the company submission. For example: • a NMA comparing to olaparib in the BRCA 3L+ population and an MAIC adjusting for differences in potential treatment effect modifiers including BRCA status and treatment history were carried out. NMA and anchored MAIC generate similar results. • The ERG does not consider that it has been shown that a MAIC adjusting for	The current description could be misinterpreted as the MAIC approach being preferred to the NMA approach, which is not the case. The ITC approach fully aligned to NICE guidance and attempted to provide the most robust analyses possible given the limitations of the data available for the BRCA 3L+ population for which the ITC is required.	This is not a factual error.

	relevant factors would lead to a less biased estimate than the more standard NMA approach given data are available for the population of relevance to this comparison. The company basecase takes an assumption of equivalence based on no conclusive evidence of the direction of effect across ITC analyses.		
In Section 3.4 of the ERG report that is a critique of the trials identified and included in the indirect comparison, the non-BRCA and BRCA 2L subgroup data requested by the ERG at clarification is discussed alongside the BRCA 3L+ subgroup listed as the relevant population for comparison to olaparib in the final scope issued by NICE. This is not appropriate as the ITC is only required to provide comparison to olaparib in the BRCA 3L+ subgroup. We think the ERG requested subgroups are discussed here as the Study 19 data is used to model overall survival in the requested analyses for these groups but this is a different consideration and it is inaccurate to say this was considered during ITC feasibility and analyses.	Please revise this sub-section to discuss the approach to ITC as titled OR break up the section to discuss trial characteristics followed by the approach to ITC. Please move discussion of appropriateness of using Study 19 data to model overall survival in the economic model to a separate sub-section and make it clear that this was originally considered for the basecase analysis, and applied to non-BRCA and BRCA 2L subgroups at the request of analyses of these subgroups by the ERG.	The current formatting is misleading and suggestive that an ITC was needed to provide comparison to routine surveillance in ERG denoted subgroups.	The ERG agrees that the title of Section 3.4 is a simplification and has changed it to cover the critique of studies both for the purpose of performing ITCs and for modelling.

On Page 54 it is stated that: "The company suggests that the substantial difference in results across the analyses justifies the adjustment for imbalances on treatment effect modifiers between trials"	Please amend this sentence to truly reflect the point made in the company submission and add further information to complete the summary. For example: "The company note that results did differ across adjusted analyses, suggesting that adjustment for imbalances on treatment effect modifiers between trials is appropriate. However, they also note no consistent trends in favour of one treatment or another across ITC analyses and therefore take an approach of assumed equivalence for PFS and OS in the basecase modelling approach."	The current statement is not a complete summary of the company submission conclusion with regard to ITC approach and outcomes, and is not a true reflection of the point made.	This is not a factual error.

Issue 4 ERG's preferred assumptions for the cost-effectiveness analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14 - 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. The ICERs resulting from the ERG's preferred assumptions are presented in Table 2. No reasoning and/or justification for these assumptions are given in the ERG report.	Please provide clear reasons and justification for why the ERG's assumptions are to be preferred over those chosen by the company.	The current discussion around the ERG's preferred approach is incomplete, because it fails to provide the NICE Committee members with a clear explanation or justification for why the ERG's assumptions are in any way more appropriate, robust and/or conservative than the assumptions made by the company.	This is not a factual error.

Issue 5 Discussion of assumption of equivalence for rucaparib and olaparib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG suggests that the assumption of equivalence is based on the non-statistically significant results from ITC on Pages 56, 58. The ERG has further noted on Pages 11, 19, 21 that the company has assumed, based on an interpretation of the ITC analysis, that rucaparib and olaparib can be considered clinically equivalent. This is a misleading and incomplete summary of this topic.	Please correct the discussion of the assumption of equivalence so that it is clear throughout the ERG report that this assumption is based on inconclusive outcomes across the ITC analyses such that no robust conclusions can be made about the relative efficacy of rucaparib compared with olaparib (as acknowledged by the ERG on Page 12). It is implied that the company has made a false or implausible assumption even though the ERG itself 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" (page 47). Please also acknowledge that the assumption of equivalence was validated with two UK clinical experts who noted they would not expect the treatments to differ in terms of efficacy.	The current discussion on this topic is contradictory (and thus inaccurate in some places) and incomplete.	This is not a factual error.
On Page 47 it is stated: "… 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"	Please rephrase the description of the assumption as "uncertain" to reflect that there is limited evidence to show that the assumption is conservative or optimistic. Please also acknowledge that the assumption of equivalence was validated with two UK clinical experts who noted they would not expect the treatments to differ in terms of	The current phrasing is suggestive that the assumption of equivalence is inappropriate.	This is not a factual error.

The description of this assumption as “strong” is slightly misleading when it is stated by the ERG on the same page: “…there is limited evidence to show that the assumption of equivalence between rucaparib and olaparib in terms of OS, is conservative or optimistic.” The validity of this assumption was also supported by clinicians.	efficacy.		

Issue 6 Discussion of olaparib formulations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 44 it is stated that: “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” There is no consideration of other stakeholders’ conclusions around this discussion.	Please add to this discussion the conclusions of: 1. The authors of Study 24 who considered the 400mg BD capsule dose to be therapeutically comparable to the 300mg BD tablet dose, in terms of efficacy and safety. 2. The EMA conclusion that extrapolation of efficacy results obtained with capsule formulation to table formulation is reasonably supported by pharmacokinetic data. 3. The ERG acknowledgement during appraisal ID1296 that it could be reasonable to assume equivalence between the tablet and capsule formulation.	By omitting a full discussion of this topic including conclusions of other stakeholders who have previously considered the comparability of olaparib formulations, the NICE committee do not have a complete overview of the evidence reviews conducted on this topic.	This is not a factual error.

Issue 7 Discussion of olaparib trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
When describing the company conclusions on robustness of olaparib data on Pages 47 and 54, it is stated that the conclusion that SOLO2 provides a more comparable dataset for the BRCA 3L+ group compared with Study 19 is only based on the larger effective sample size in MAIC synthesis using SOLO2 data. This is not a true reflection of the multifactorial considerations given to the robustness of olaparib data from SOLO2 versus Study 19.	Please amend this description to truly reflect the basis of the company conclusions. That is, include reference to: 1. Phase II versus Phase III study design 2. ITT vs BRCA patient population and the associated retrospective (Study 19) vs prospective (ARIEL3) nature of the BRCA analyses 3. Perception of high survival rates 4. Expert opinion of robustness 5. Olaparib capsule and tablet comparability While the larger effective sample size in MAIC synthesis using SOLO2 data is noted to reflect a more comparable dataset for the BRCA 3L+ population, this was not the basis for conclusions on robustness of SOLO2 versus Study 19.	By omitting a full discussion of the basis on which the company conclusions were made, the NICE committee do not have a complete overview of the evidence review that informed this conclusion.	Page 47 has been amended in line with the text in the company's submission.

Issue 8 Approach to calculating PPS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 66 it is stated that: "To calculate the post-progression survival (PPS) for the ITT population analysis, the company extrapolated	The following explanation was provided in the company submission (Page 139 of 180): "This approach has been developed to take on ERG advice from TA528 suggesting an equal	The current summary implies that the approach for the ITT population analysis is not justified. When in fact it is based on an	This is not a factual error.

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." The company's justification for the assumptions are excluded for the ITT population analysis.	risk of death post-progression would be a suitable approach to OS." Please include the company's justification for the approach to the ITT population analysis; for example: • The company's justification for this approach for the ITT population is based on the company's assumption that the post-progression risk of death is equal between rucaparib and olaparib, implying that the gain in PPS outcomes for the two treatments will be equal. This assumption was based on previous advice from TA527 suggesting that an equal risk of death post-progression would be a suitable approach to OS.	important assumption that has been omitted in the ERG report.	
The current ERG report: • Incorrectly interprets and describes the company's assumptions made on PPS in order to model OS for the ITT, non-BRCA and BRCA	The company submission (Page 139 of 180) explains that the approach for the ITT population was developed based on ERG advice from TA528 that assuming an **equal risk of death post-progression** would be a suitable approach to OS." The company's response to CQ B2 and	The statements are incorrect. The company's approach to OS and PPS in the ITT and BRCA 3L+ population analysis are in fact consistent. The justifications for each of the approaches are	This is not a factual error.

2L population analyses • Incorrectly concludes that the company's justification for the approach to OS (and implicitly, PPS) for the ITT, non-BRCA and BRCA 2L population analyses contradicts the assumption of equivalence in efficacy in the BRCA 3L+ population analysis	CQ B3 provide further information. • The same approach is applied for the subsequent non-BRCA and BRCA 2L subgroup analyses • This approach is consistent with the approach taken for the BRCA 3L+ population analysis, where **additional** (not contradictory) assumptions were made that PFS and OS are equal between rucaparib and olaparib. When PFS and OS are equivalent, the assumption of equivalent PPS holds • In the company submission the justification for the approach is based on advice and criticisms published for TA528 and supporting statements from expert clinicians • It is acknowledged that both approaches require assumptions, and that both have limitations. Please revise the current ERG report to accurately describe the approach and justification provided by the company within the company submission and responses to CQ B2 and CQ B3. Please revise statements regarding contradictions in the approaches to OS and PPS between the ITT, non-BRCA and BRCA 2L, and BRCA 3L+ population analyses, as that interpretation is incorrect (Pages 12, 70, 99).	consistent.	
On Page 69 it is stated that:	Please accurately describe the company's	The current report inaccurately	In the company's CQ

"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 a naïve comparison of PFS from ARIEL3, which demonstrates longer PFS than in Study 19.**" The company did not make this statement. This is not a complete nor truthful representation of the company's critique of the ERG's preferred approach described in CQ B2.	clarification response to CQ B2: • Remove the statement that the critique of the ERG's preferred approach to OS is based on any comparison between rucaparib and olaparib data, as this was not claimed, and the company's critique holds regardless of any comparison between PARPi treatments Please provide a balanced argument in the ERG report and acknowledge the company's criticisms of the ERG's suggested approach in CQ B2. The company does not believe that the ERG's suggested approach is consistent with the expected clinical course of the disease with PARP inhibitors: • The ERG's suggested approach assumes the same OS **irrespective of any PFS gain** and suggests that patients progressing later on a treatment providing PFS benefit will have a much higher mortality hazard, resulting in shorter PPS outcomes. The company is not aware of any clinical rationale supporting the ERG's assumption • Long-term Study 19 data from Friedlander et al. 2018 demonstrate a continued benefit of olaparib versus placebo for TSST and OS, supporting the notion that responders to PARP therapy see benefits beyond PFS • Clinical experts suggested that the assumption of equivalence in PPS across PARPi maintenance treatments	reports the company's statements.	response to B2, the company state, "…with olaparib PFS the incident number of progressing patients is different and the mortality hazard impacting those who are progressing could be different. Since PFS is longer with ARIEL3, patients would be dying with a hazard rate of that later timepoint". Based on the company's statement, it implies the company compared PFS between ARIEL3 and Study 19 to determine PFS is longer in ARIEL3 and as no statistical analyses as a basis for the statement, the ERG assumes this is done naively. The ERG has amended the statement to state that it is assumed a naïve comparison was used.

	is plausible • Expert clinicians support the earliest possible use of a PARPi exactly because in their experience the PFS gain is not lost but is longer the earlier the patients can receive the therapy		

Issue 9 **Discussion of adjustment factors in the MAIC**

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 54 it is stated that: "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."	The analyses being referred to here are the MAIC analyses adjusting for effect modifiers - as noted on Page 51 the results of the sensitivity analysis adjusting for both effect modifiers and prognostic factors has not been reported or discussed in the ERG report. As noted in Section B.3.10 of the company submission - the effect modifiers were identified by considering the following, and validated through clinical expert consultation: • All factors used as stratification factors in the randomisation of the ARIEL3, SOLO2 and Study 19 trials • All factors identified as potential effect modifiers in previous NICE submissions • All factors for which baseline characteristics were available in both ARIEL3 and at least one comparator trial (i.e. SOLO2, Study 19) • All factors for which subgroup analyses	The current discussion suggests the factors were not considered effect modifiers in the analyses as per the criteria detailed for effect modifier determination - this is not true. If the ERG do not think the effect modifiers identified and validated through clinical expert consultation are effect modifiers, the rationale and support for this should be detailed.	This is not a factual error.

	were planned in the ARIEL3, SOLO2 and Study 19 trials The company made rigorous efforts to distinguish between the two types of variables to inform the MAIC analyses.		

Issue 10 Description of OS data availability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 47 it is stated that: "However, due to the lack of OS data for rucaparib compared with olaparib or routine surveillance…"	OS data are available for rucaparib compared with routine surveillance but are not mature - please amend the sentence to reflect this.	The current wording suggests there are no OS data for rucaparib compared with routine surveillance from ARIEL3, which is not correct.	The sentence has been changed to reflect that data are immature.

Issue 11 ERG comment on company's review of cost-effectiveness evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 4.1, pages 59 and 60, it is stated that the company did not include relevant TAs in the search for cost-effectiveness evidence. It is correctly mentioned that, at the clarification stage, the company explained that the economic SLR focused on indexed databases and that HRQoL data was identified in the clinical SLR. However, TA381 and TA528 were thoroughly studied and have	Please add a comment that the company extensively cross-referred to TA381 and TA528 and used both to inform modelling decisions and approaches, including base case input values and scenario settings.	The current summary of the cost-effectiveness evidence makes it seem like previous TAs were disregarded, while in fact they have been very informative and were used extensively by the company.	This it not a factual error.

informed both the model and submission. This has been detailed throughout the submission, e.g. in sections B3.2, B3.5, and B3.10.			

Issue 12 Missing parameters

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
When describing the scenario analyses for the ITT population in section 5.2.3, it is mentioned that the most influential parameters are the PFS:OS ratio and the choice of OS curve. If the top influential parameters are selected in the submitted model, this is the result: 1. PFS:OS ratio = 1 (60%) 2. Parametric fit for OS (41%) 3. Subsequent therapy source based on Study 19 (39%) 4. Treatment discontinuation rules (36%)	Please add a scenario to the revised model analysing the original base case (ARIEL 3) subsequent therapy estimates. Please update the text to include the parameters 'Subsequent therapy estimates based on Study 19' and 'Treatment discontinuation rules' in the overview of influential parameters.	Presenting a more balanced view of influential modelling decisions.	This is not a factual error.

Issue 13 Data and confidential marking up errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27 - subsequent PARPi treatment data and confidential marking incorrect	Please correct the placebo data to [redacted] (currently noted as [redacted]) and change CIC marking to AIC	Data and confidential marking error	This has been amended in the ERG report.
Page 32, Table 10 - confidential marking incorrect	Please mark HR data for the BRCA 3L+ group as AIC	Confidential marking error	This has been amended in the ERG report.
Page 38 - confidential marking incorrect	Please mark median duration of treatment data in text as AIC	Confidential marking error	This has been amended in the ERG report.
Page 39 and Page 42 - confidential marking incorrect	Please remove marking from AE Grade ≥3 data in text (and align to Table 16 where data are not marked up)	Confidential marking error	This has been amended in the ERG report.
Page 50 - confidential marking incorrect	Please mark OR data for TEAE NMA as AIC	Confidential marking error	This has been amended in the ERG report.
Page 71 - the 'Rucaparib' and 'Routine Surveillance' columns in Table 31 should be marked AIC	Please mark the 'Rucaparib' and 'Routine Surveillance' columns in Table 31 as AIC	Confidential marking error	This has been amended in the ERG report.
Page 71 - the 'Rucaparib' and 'Routine Surveillance' columns in Table 32 should be marked AIC	Please mark the 'Rucaparib' and 'Routine Surveillance' columns in Table 32 as AIC	Confidential marking error	This has been amended in the ERG report.
Page 72 - The utility decrement for progressed disease should be	Please mark the utility decrement for progressed disease as CIC	Confidential marking error	The company have indicated that this should be CIC, but given the nature of the

marked CIC			information and consistent with the marking of utility data this has been amended in the ERG report as AIC.
Page 73 - In table 34 (section 4.2.7.1) the coefficients for progression have been mixed up between the two subpopulations.	Please correct the table so the data is displayed correctly. The progression coefficient for the subgroup of patients who have received two prior lines of platinum-based chemotherapy should be - [redacted], and the progression coefficient for the subgroup of patients who received three or more prior lines of platinum-based chemotherapy should be [redacted]	These have been copied erroneously from the company's clarification response.	Thank you for spotting the error. This has been corrected in the ERG report.
Page 76/77 - Table 37, The 'Mean months received', '% patients who received maintenance PARPi', and '% patients with no prior use of PARPi' columns should be marked AIC.	Please mark the 'Mean months received', '% patients who received maintenance PARPi', and '% patients with no prior use of PARPi' columns in Table 37 as AIC.	Confidential marking error	This has been amended in the ERG report.
On Page 79 it is stated that: "However, in doing so, the company omitted several combination therapies received in Study 19..." In fact, only <u>one</u> combination was inadvertently omitted: Carboplatin and gemcitabine hydrochloride.	Please correct the sentence to state that: • **One** combination therapy received in Study 19 was mistakenly omitted.	The current statement is incorrect as in fact only one combination therapy received in Study 19 was mistakenly omitted – not several therapies.	Thank you for spotting the error. This has been corrected in the ERG report.
On Page 80/81, Table 40: There are several combination therapies that were erroneously inserted as [redacted] when there are	Please amend the values in "Company's response to CQ B6 (Study 19*)" column to match Table 31 in the company response. For patients treated with a previous PARPi and with no prior	These have been copied erroneously from the company's clarification response.	Thank you for spotting the error. This has been corrected in the ERG report.

[redacted] for these in the company response to CQ B6.	use of PARPi, respectively: • Carboplatin + cyclophosphamide: [redacted] • Carboplatin + doxorubicin: [redacted] • Carboplatin + docetaxel: [redacted] • Cisplatin + cyclophosphamide: [redacted] • Cisplatin + cyclophosphamide + docetaxel: [redacted]		
Page 80/81 - Table 40, the 'Company's response to CQ B6 (Study 19*)' columns should be marked AIC, just like the 'Company's base case (ARIEL3)' column	Please mark the 'Company's response to CQ B6 (Study 19*)' columns in Table 40 as AIC	Confidential marking error	This has been amended in the ERG report.
Page 84 - Figure 8, Incremental PSA results are informative of incremental costs and QALYs and should therefore be marked confidential.	Please mark Figure 8 as AIC.	Confidential marking error	The company have indicated that this should be AIC, but given the nature of the information and consistent with the marking of base-case results this has been amended in the ERG report as CIC.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Friday 14 June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Clovis Oncology UK Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Immature clinical trial evidence - overall survival	
1. Is rucaparib expected to increase overall survival? If so, is it appropriate to assume the same overall survival as for olaparib?	At this point in time, the overall survival (OS) data for rucaparib is immature and the final OS analysis will occur when 70% of deaths have been collected. To clarify, Clovis Oncology used OS data from Study 19 to estimate the potential OS benefit of rucaparib, as Study 19 can be considered to have the most mature OS dataset available at the present time. Clovis Oncology did not assume that rucaparib and olaparib had similar or equal efficacy, except in those limited circumstances, such as the BRCA 3L+ sub-population, where analyses based on the published data were not conclusive. We expand on this point in Issues 4 and 5 below.
2. Is OS expected to vary according to subgroups (BRCA 2L, BRCA 3L+, non-BRCA)?	
3. When is the company expecting a new data cut-off for efficacy?	As specified in the protocol and statistical analysis plan (SAP) for ARIEL 3, the final OS analysis will occur when 70% of death events have been collected. Based on the current rate of OS events, it is estimated that it may take to at least [redacted] before the required 70% of death events occur for the final analysis of OS to be performed.

Issue 2: Generalisability of the clinical evidence to UK clinical practice	
1. Is the population of ARIEL3 broadly representative of UK clinical practice?	Clovis Oncology believes that the population in ARIEL3 is broadly representative of UK clinical practice for this patient population in terms of median age, prior medical history, performance status and prior lines of chemotherapy. Importantly, the ARIEL3 trial did not restrict the extent of residual disease at study entry. In the NOVA study, which supported the approval of niraparib in the second-line platinum sensitive maintenance setting, patients with bulky disease (defined as those with any lesion >2 cm at the time of study entry) were excluded. A subgroup analysis of ARIEL3 was performed to identify the benefit of rucaparib in patients with any lesion ≥2 cm (i.e., bulky disease), as this group represented a patient population with an unmet need not addressed by any of the existing agents. Based on expert clinical advice received by Clovis Oncology, the mix of patients in ARIEL3 better represents the patient population in UK clinical practice.
2. Is the proportion of patients in partial and complete response in ARIEL3 representative of UK clinical practice?	Clovis Oncology believes that the proportion of partial and complete response in ARIEL3 is representative of UK clinical practice as the trial did not exclude patients who had bulky disease at study entry. In addition, R0 surgery (no visible tumour) or R1 surgery (residual disease <1 cm) as a component of the most recent treatment regimen was not permitted in ARIEL3. Clovis Oncology believes this latter point is specifically important for the UK where surgery for recurrent ovarian cancer is not routinely used to treat recurrence as there is not yet level I evidence of secondary surgical cytoreduction improving OS and any possible surgery for recurrent ovarian cancer has to be carried out by a surgeon with expertise in this area and access to specialist ovarian cancer surgery varies considerably around the UK.
3. Is the population of Study 19 comparable to ARIEL3 and representative of UK clinical practice?	
4. Is the response to rucaparib influenced by the type of BRCA mutation?	Clovis Oncology is not aware of any evidence that somatic or germline deleterious BRCA mutations or BRCA1 or BRCA2 deleterious mutations influence response to rucaparib.

5. To what extent is testing for somatic BRCA mutations done in the UK?	Whilst germline BRCA testing for women with ovarian cancer is now commissioned by NHS England, funding for tumour BRCA testing remains limited. AstraZeneca offers a tumor BRCA testing service at specified UK collaboration laboratories but restricted to patients that have ovarian cancer and either a known negative germline BRCA mutation status or an unknown germline BRCA mutation status and have received at least two prior lines of treatment (i.e. patient is third line or beyond).
Issue 3: Most relevant populations	
Is it relevant to separate the population into subgroups or is it more appropriate to focus on the ITT population from the trial?	The ITT population provides the most complete, reliable and robust evidence base to support decision-making. ARIEL3 was not prospectively designed or powered to detect differences in efficacy or safety between BRCA and non-BRCA cohort at different lines of therapy. The sub-group analyses that have been undertaken as requested by the ERG are post-hoc analyses only, often comprising small sample sizes, and cannot be considered sufficiently robust for decision-making purposes. By separating the population from ARIEL3 into non BRCA or BRCA there are two other clinically relevant issues: 1. As somatic testing is not routinely available in the UK, this group would then essentially become a further sub-group of germline BRCA only, as the somatic BRCA patients would not be identified. This means that somatic BRCA patients may not have the opportunity to clinically benefit from rucaparib; and 2. Long-term data from Study 19 with olaparib indicate that long-term responders include patients who have neither germline nor somatic BRCA mutations. This reinforces that the ITT is the appropriate population clinically.

Issue 4: Uncertainty around the relative treatment effect of rucaparib compared to olaparib in BRCA 3L+	
1. Is the company's assumption of clinical equivalence in PFS for rucaparib and olaparib for the BRCA 3L+ population appropriate in light of the level of data available?	Clovis Oncology has undertaken extensive work to explore the relative efficacy on PFS between olaparib and rucaparib in both a network meta-analysis (NMA) and matching-adjusted indirect comparison (MAIC), using data from ARIEL3, Study 19 and SOLO2. The MAIC results conducted vs Study 19 and vs SOLO2 provided numerical estimates in different directions, both of which were not statistically significant. Pooling the MAIC results from both studies gave very similar results to those obtained from the NMA, both of which did not provide any evidence against equivalence of PFS in the BRCA 3L+ population. However, it is acknowledged that the available data to investigate relative efficacy on PFS between rucaparib and olaparib in the BRCA 3L+ population were limited to provide clear conclusions.
2. What conclusion can be made of the relative treatment effect of olaparib vs rucaparib given the ITC results?	There is no direct head-to-head clinical trial evidence comparing rucaparib and olaparib in any population. Although Clovis Oncology has conducted indirect treatment comparisons from a number of different perspectives and using multiple data sources, none of these is without its limitations and nor can further ITC work currently address the lack of direct evidence comparing rucaparib with olaparib in the BRCA 3L+ population, the immaturity of the OS data in ARIEL3 or the Study 19 results for the BRCA 3L+ population, which have not been replicated in any other PARPi trial.
a. Which study (Study 19 or SOLO2) is the most appropriate for informing outcomes for olaparib in the NMA?	
3. Would additional data from ARIEL3 reduce uncertainty in the current NMA?	
4. Is it appropriate to conduct a cost-minimisation for the BRCA 3L+ population?	
Issue 5: Post progression and overall survival calculation	

1. Which approach to modelling post-progression survival is most appropriate?	Clovis Oncology explored the most appropriate way to model post-progression survival (PPS). PPS data for rucaparib in ARIEL3 is extremely immature (more so than even for OS). PPS data for Study 19 has not been published and so was not available for Clovis Oncology to use. In two previous Technology Appraisals of PARP inhibitors (PARPis), the respective ERG reports for those appraisals had both stated that assuming similar PPS across PARPis would have been the preferred approach. Based on these previous ERG recommendations and clinical opinion that PFS gain, once accrued, will not be lost, Clovis Oncology concluded that it was reasonable and appropriate to assume that PPS will not be less for rucaparib patients than what was observed for a given population in Study 19. In light of this, the ERG's assumption in the current appraisal that there is greater post-progression mortality hazard associated with one PARPi over another is not justified. The available data on efficacy in the BRCA 3L+ population is limited and not conclusive. In this sub-group, Clovis' approach was to rely on known PFS data for olaparib from Study 19 and to then assume that patients treated with rucaparib would have the same PPS. The reasons why Clovis Oncology concluded that it was more relevant and appropriate to adopt an approach based on an assumption of equal PPS are explained below.
a. Do the results of the company's comparison of PFS in ARIEL3 and Study 19, which appears to be a naïve comparison, justify its methods?	Far from relying upon a naïve comparison, as the ERG suggests, Clovis has undertaken extensive work to explore the relative effect between olaparib and rucaparib, conducing both a network meta-analysis (NMA) and matching-adjusted indirect comparison (MAIC), and using data from ARIEL3, Study 19 and SOLO2, in order to provide the Appraisal Committee with the most accurate and appropriate data. The results of the NMA have been largely consistent across all populations. Results of the MAIC resulted in divergent results for the BRCA 3L+ population when using Study 19 vs SOLO2. However, please note that for some reason, Study 19 presented results for the use of olaparib capsules in the BRCA 3L+ population that have not been matched in any other PARPi clinical trial, including SOLO2 (olaparib tablets). Clovis Oncology appreciates that olaparib capsules is the only relevant

	comparator for the present appraisal, and so Study 19 is the appropriate source of comparative data but, in the light of the published evidence and the fact that these results were not replicated in any other trial, this begs the question as to what should be the most appropriate methodological approach. Contrary to the ERG's suggestion, our approach for BRCA3L+ does not contradict the approach we took for the ITT analysis. We have chosen to assume PFS equivalence for this sub-population because the point estimate of the indirect comparison based on Study19 favours olaparib, whereas based on other data, the point estimates favour rucaparib. In this respect, and in light of limited evidence to the contrary, we felt that assuming PFS equivalence for this particular population was a fair and conservative assumption.

b. Is the assumption of equivalence in PPS across PARP inhibitors maintenance treatments plausible?	As noted above, two previous ERG reports prepared for previous Technology Appraisals of PARPis stated that assuming similar post-progression survival (PPS) across PARPi's would have been a preferred approach, instead of a PFS:OS ratio based approach. PPS data is even more immature for rucaparib than OS data. PPS data from Study 19 has not been published by the manufacturer of olaparib and was not available to Clovis Oncology. Based on previous ERG recommendations, therefore, and clinical opinion that PFS gain, once accrued, will not be lost, Clovis Oncology concluded that it was reasonable and appropriate to assume equivalence of PPS across PARPis.
2. What would be considered a plausible PFS:OS ratio?	Clovis Oncology do not think it is helpful to discuss whether or not there is a plausible OS:PFS ratio. The concept of a ratio was firmly rejected by the Appraisal Committee in previous relevant appraisals and we therefore spent considerable efforts to try and avoid such an approach. It is primarily for this reason that Clovis Oncology decided that it was more appropriate to assume equal PPS. Clovis considered that the best way to calculate PPS and still keep the benefit of PFS from ARIEL3 would be to utilise Study19 data. It should be noted that the PPS curve using patient-level data from Study 19 has not been published. Therefore, Clovis Oncology calculated the PPS in the following way: We fitted the final published curves from Study 19, and used the ERG-approved PFS and OS distributions to calculate the difference between the mean OS and mean PFS. Clovis Oncology realises that this is not an optimal approach; however, it was the only approach that we were able to incorporate given the available data. We also realise that the "implied" PFS:OS ratio is large. However, note that that is the consequence of the long tail of the OS splines distribution that was validated and agreed by clinicians, as well as by the ERG.
Issue 6: Survival extrapolation for the non-BRCA and BRCA 2L subgroups	

1. For the non-BRCA population, are the company's estimates of PFS and TTD ([redacted]) difference between mean PFS and mean TTD) or the ERG's (0.3 months difference between mean PFS and mean TTD) the most plausible?	The 12 months difference arises from the best-fitting survival function fitted to the patient level data from ARIEL3. The survival function fitted to the patient level TTD data from ARIEL3, which resulted in a mean TTD 12 months shorter than the PFS, was a significantly better fit to the data both statistically and visually than the ERG's preferred approach. The difference may be related to patients discontinuing treatment due to AEs, but still remaining progression-free. It should also be noted that the 12 months difference occurs over a 30-year time horizon, which we do not believe to be clinically implausible.
2. For the BRCA 2L population, is the company's estimate of PFS [redacted] of patients in PFS at 10 years) or the ERG's (all patients have progressed after 10 years) most plausible?	
Issue 7: Subsequent therapy cost calculation	

1. Is the company's estimation of subsequent therapy costs based on selected treatments given in ARIEL3 appropriate and representative of clinical practice (see appendix 1 of the technical report)?	Deriving subsequent therapies that are reflective of clinical practice while considering the available evidence is challenging and there are no clear guidelines to follow. The company attempted to combine both the current UK clinical practice and the full available evidence from ARIEL3. We costed all therapies given as subsequent therapy in ARIEL3, if they are available to patients in the UK. Since many patients got multiple therapies, only a few patients, who received exclusively non-NHS treatments were "excluded" (patients who received both non-NHS and NHS treatments were not excluded). To ensure that we do not distort the calculation, the subsequent therapy distribution was reweighted to ensure that the % of patients receiving subsequent therapy is still the same as it was observed in ARIEL3. Appendix 1 of the technical report lists three approaches to derive the composition of subsequent therapies. The first refers to the company's approach described above, the second refers to the company's approach to use the composition of subsequent therapy from Study 19. The third approach refers to the ERG recommendations for the composition of subsequent therapy from Study 19. In the non-BRCA population, the original ICERs versus routine surveillance with each approach were £50,681, £58,651 and £58,284 per QALY respectively. In the BRCA 2L+ population, the ICER versus olaparib remained unchanged. Therefore, using the composition in Study 19 instead of ARIEL3 increases the ICER in the non-BRCA population from £50,681 to £58,224 per QALY. Therefore, the cost-effectiveness conclusion does not change. Nonetheless, the use of ARIEL3 composition might be more appropriate given that it is a more recent trial than Study 19 and therefore it follows more closely shifts in the treatment landscape (e.g. introduction of PARPis).
2. The ERG re-estimated subsequent therapy costs based on all subsequent therapies given in Study 19. Is this more appropriate and representative of clinical practice (see appendix 1 of the technical report)?	
3. Would subsequent therapies differ according to BRCAm status and number of previous chemotherapy regimens?	
4. Are patients expected to receive more than one PARP inhibitor in their treatment pathway (e.g. patient who received rucaparib as 2L maintenance could receive olaparib as 3L	Prior use of any PARP inhibitors was an exclusion criterion in ARIEL3, Study 19 and NOVA trials. Sequencing PARP inhibitors is an area of active research. It is unclear at the moment if PARP after

maintenance)?	PARP will be recommended in the future.
Issue 8: Cancer Drugs Fund	
1. Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?	The OS analysis is event-driven and final OS data is not expected from the ARIEL3 study until [redacted] at the earliest. Clovis Oncology is open to discussions about whether additional data collection in the Cancer Drugs Fund (CDF) would be of value to help further reduce the current uncertainty around the potential for rucaparib to provide long-term survival benefit.
2. Is rucaparib a good candidate for use in the Cancer Drugs Fund?	Clovis Oncology believes that rucaparib is a suitable candidate for use in the CDF. Updated economic results are included in the Appendix.

Appendix 1: Cost-effectiveness results inclusive of updated PAS

A summary of the results of the revised base case inclusive of a [redacted] PAS discount are presented in Table 1 for the ITT population, and results for the BRCA 3L+ population are provided in Table 2. Revised probabilistic results are provided for the ITT and BRCA 3L+ populations in Table 3 and Table 4, respectively. PSA was run for 2,000 iterations and results are consistent with the deterministic base case. Revised tornado diagrams are presented in

Figure 1 and

Figure 2 for the ITT and BRCA 3L+ populations, respectively. A revised list of scenario analyses is provided in

Table 5.

Table 1: Revised deterministic base-case results for the ITT population (Updated from ERG clarification questions responses, Table 8)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	3.060	[redacted]				
Rucaparib	[redacted]	4.919	[redacted]	[redacted]	1.859	[redacted]	36,319

Key: 2L+, post second line; BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALY, quality-adjusted life year.

Table 2: Revised deterministic base-case results for the BRCA 3L+ population (Updated from ERG clarification questions responses, Table 9)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Olaparib	[redacted]	3.091	[redacted]				
Rucaparib	[redacted]	3.091	[redacted]	[redacted]	0.000	[redacted]	Rucaparib dominated

Key: 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.

Table 3: Revised probabilistic base-case results for the ITT population (Updated from ERG clarification questions responses, Table 10)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]			
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	£ 35,518

Table 4: Revised probabilistic base-case results for the BRCA 3L+ population (Updated from ERG clarification questions responses, Table 11)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Olaparib	[redacted]	[redacted]			

Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	Rucaparib dominated

Figure 1: Revised tornado diagram for the ITT population (Updated from ERG clarification questions responses, Figure 30)

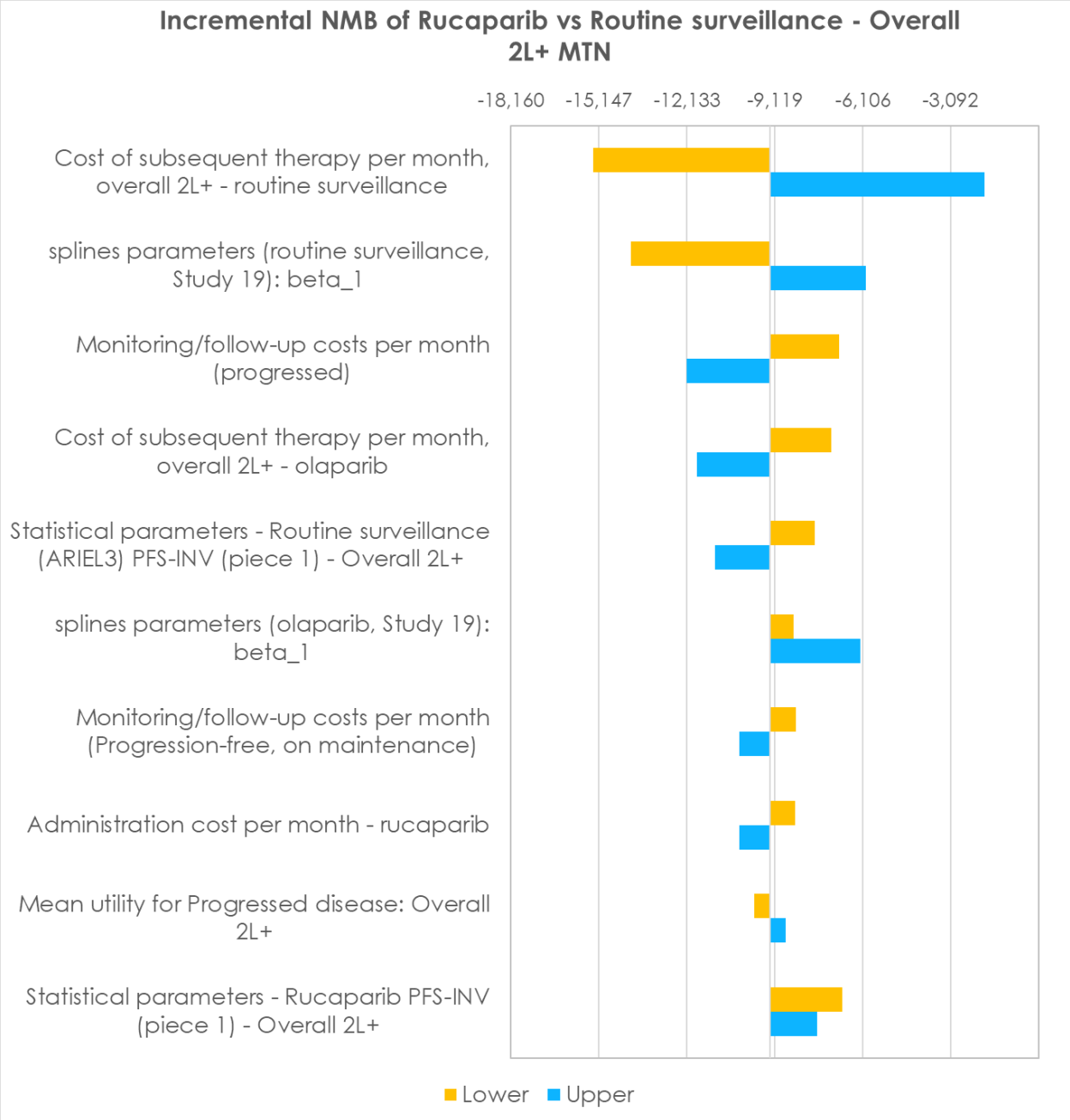

Figure 2: Revised tornado diagram for the BRCA 3L+ population (Updated from ERG clarification questions responses, Figure 31)

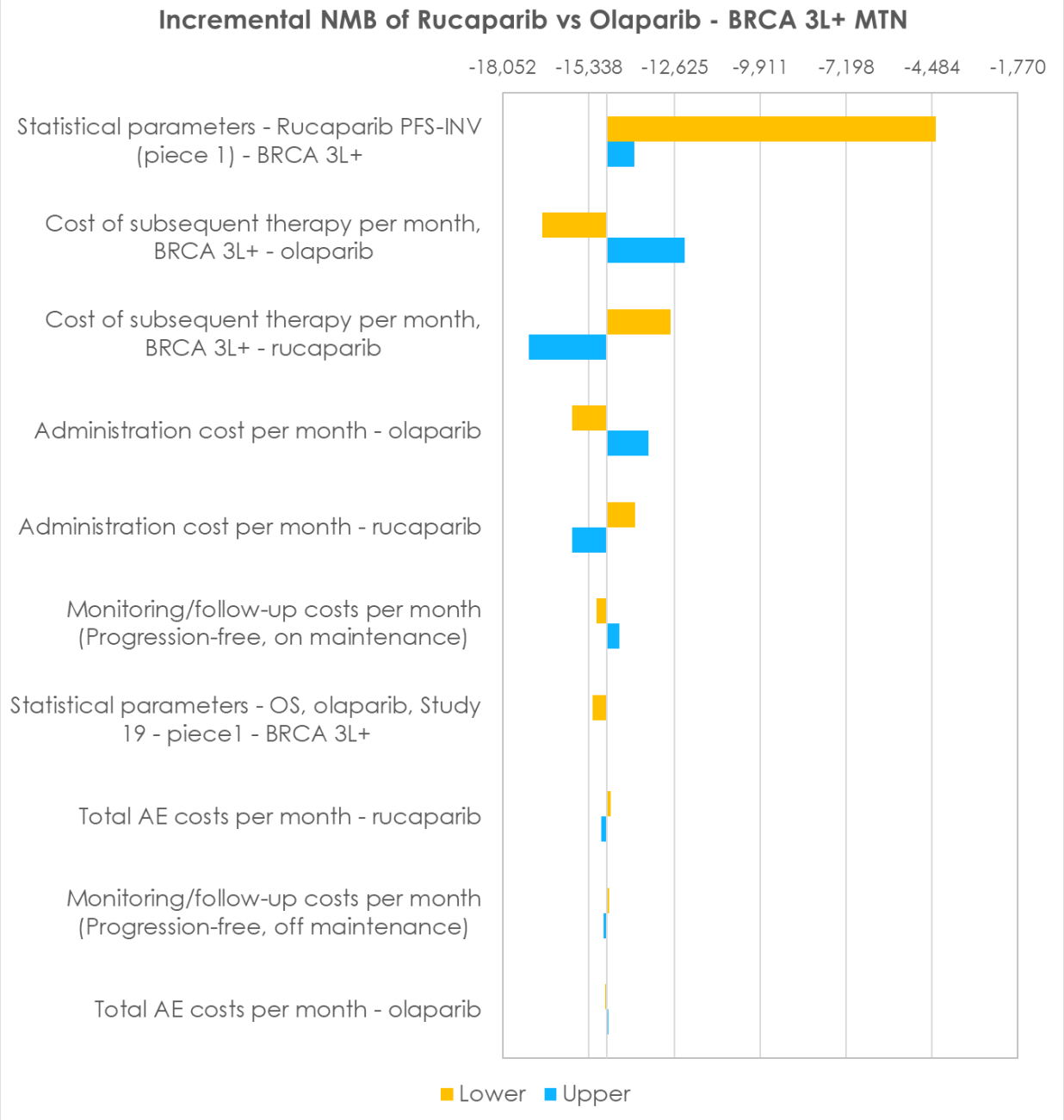

Table 5: Revised list of scenario analyses (Updated from ERG clarification questions responses, Table 12)

	ITT population	BRCA 3L+ population
	ICER vs routine surveillance	ICER vs olaparib
Base case	£ 36,319	Rucaparib dominated
Second-best parametric fits for OS: Log-logistic (BRCA 3L+), Lognormal (Overall 2L+)	£ 49,676	Rucaparib dominated
Third-best parametric fits for OS: Weibull (BRCA 3L+), Loglogistic (Overall 2L+)	£ 54,549	Rucaparib dominated
Second-best parametric fits for PFS: Generalised gamma	£ 29,825	Rucaparib dominated
Third-best parametric fits for PFS: Log-logistic	£ 38,227	Rucaparib dominated
Overall 2L+ MTN: Second-best parametric fits for rucaparib TTDD: Generalised Gamma	£ 35,134	N/A
Discontinuation rule - Constant discontinuation rate for all interventions	£ 30,816	N/A
BRCA 3L+ MTN discontinuation rule: TTDD curves for rucaparib: Exponential	N/A	Rucaparib dominated
Discontinuation rule - Treat until progression for all interventions	£ 40,517	Rucaparib dominated
Overall 2L+ MTN: PFS-OS ratio = 1, routine surveillance PFS: Lognormal	£ 74,716	N/A
Overall 2L+ MTN: PFS-OS ratio = 2, routine surveillance PFS: Lognormal	£ 44,271	N/A
PFS-OS ratio = 1, routine surveillance PFS: based on HR	£ 74,490	Rucaparib dominated
PFS-OS ratio = 2, routine surveillance PFS: based on HR	£ 44,152	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	£ 662,003
(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	£ 36,142	Rucaparib dominated
Alternative AE assumption: Do not apply AE disutilities and do not accrue AE costs	£ 36,077	Rucaparib dominated

	ITT population	BRCA 3L+ population
	ICER vs routine surveillance	**ICER vs olaparib**
Alternative AE costs based on feedback from UK clinical expert	£ 36,094	Rucaparib dominated
Alternative frequency of RU based on feedback from UK clinical expert	£ 35,571	Rucaparib dominated
Extend time horizon to 50 years	£ 34,901	Rucaparib dominated
No discounting for costs and health outcomes	£ 29,342	Rucaparib dominated
Do not allow vial sharing (assume wastage) - IV/SC drugs*	£ 36,319	Rucaparib dominated
Exclude one-off cost of BRCA mutation test at the beginning of the time horizon*	£ 36,319	Rucaparib dominated
Do not apply administration cost of maintenance and subsequent therapies	£ 34,822	Rucaparib dominated
PF and PD mean utility values reported in the niraparib NICE submission [TA528]; PF: 0.831, PD: 0.799	£ 35,256	Rucaparib dominated
Shares for subsequent therapy costs unadjusted for non-UK treatments (all patients, ARIEL3)	£ 37,433	Rucaparib dominated
Question B2: Overall 2L+ MTN: Calculate PPS as residual of OS and PFS	£ 41,828	N/A
*Note, these scenarios are now included in the revised base case, hence no difference from revised base case ICERs is shown		

NICE National Institute for Health and Care Excellence

Technical engagement response form

Rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy [ID1485]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Friday 14 June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted]. If confidential information is submitted, please also send a second version of your

comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Prof Jonathan A Ledermann**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Immature clinical trial evidence - overall survival

1. Is rucaparib expected to increase overall survival? If so, is it appropriate to assume the same overall survival as for olaparib?	**Yes, there is likely to be a small increase in overall survival. However, the likelihood of cross over in the pivotal trial, ARIEL 3 will reduce the magnitude of difference. The degree of crossover for ARIEL 3 will be greater than previous trials with olaparib or niraparib as the availability of PARP inhibitors (worldwide) is greater. There is no reason to believe the potency/effectiveness of rucaparib is different from olaparib or niraparib**
2. Is OS expected to vary according to subgroups (BRCA 2L, BRCA 3L+, non-BRCA)?	**Yes. The greatest benefit seen to date with all PARP inhibitors is in patients with a BRCA mutation (germline or somatic). For OS, differences in 2L or 3L may be less clear cut. It is more the magnitude of HRD that will be responsible for the biggest OS difference and this is more likely to be tumour-dependent rather than time-dependent**
3. When is the company expecting a new data cut-off for efficacy?	**Not sure ? 2021**
Issue 2: Generalisability of the clinical evidence to UK clinical practice	
1. Is the population of ARIEL3 broadly representative of UK clinical practice?	**Yes, but currently tumour testing (at entry to ARIEL 3) is not routine. It should become so and there will be clinical pressure to bring this into routine care for all ovarian cancer patients**
2. Is the proportion of patients in partial and complete response in ARIEL3 representative of UK clinical practice?	**Yes. This reflects UK practice**
3. Is the population of Study 19 comparable to ARIEL3 and representative of UK clinical practice?	**The population of patients in ARIEL 3 differs from study 19 in two respects. In study 19 it turned out retrospectively that 50 % patients had a BRCA mutation. In Ariel 3 it was 35%. The number of BRCA mutated patients in ARIEL3 was capped deliberately. Approximately 66% patients in ARIEL 3 were entered post 2nd line. For Study 19 the population had been a little more heavily pretreated, 46% had only 2 prior lines of chemotherapy**

4. Is the response to rucaparib influenced by the type of BRCA mutation?	**There was no evidence to suggest that patients with a BRCA1 or BRCA2 mutation behaved significantly differently, or that patients with somatic or germline BRCA mutations had different response/outcome**
5. To what extent is testing for somatic BRCA mutations done in the UK?	**Currently this is not routine but there is a strong clinical wish to implement this. Otherwise 6-7 % of all ovarian cancers will not benefit from PARP inhibitors. In other words, 1/3 of BRCA positive patients will be denied access to PARP inhibitors. With the delayed implementation of Genetic hubs and funding streams, the environment has not been conducive to implementing such changes.**
Issue 3: Most relevant populations	
Is it relevant to separate the population into subgroups or is it more appropriate to focus on the ITT population from the trial?	**In this trial, there was no separation of sBRCA and gBRCA. Whilst the primary outcome effect was greatest in this subgroup, a significant overall benefit was seen in the ITT population. Currently, sensitivity to platinum-based chemotherapy remains the best overall predicator of HRD, and susceptibility to PARP inhibitors**
Issue 4: Uncertainty around the relative treatment effect of rucaparib compared to olaparib in BRCA 3L+	

1. Is the company's assumption of clinical equivalence in PFS for rucaparib and olaparib for the BRCA 3L+ population appropriate in light of the level of data available?	Yes, there is a similar magnitude of benefit. As stated previously, it is probably the degree of HRD that influences the outcome, and this may not be affected by the number of prior lines of therapy. In the poster at ESMO 2018 (Lorusso et al) the HR in the ITT population was 0.42 for 2L and 0.28 for ≥3L. for the BRCA population it was 0.24 and 0.21 respectively
2. What conclusion can be made of the relative treatment effect of olaparib vs rucaparib given the ITC results?	I think there is little to distinguish the drugs in terms of activity. However, the number of patients treated in Study 19 without a BRCA is much smaller than patients treated with rucaparib. The Study 19 analysis of the $BRCA^{wt}$ group was retrospective in a randomised phase II trial. Thus, the rucaparib data in the ITT population is more robust- a randomised phase III trial with stratification on BRCA at the outset
a. Which study (Study 19 or SOLO2) is the most appropriate for informing outcomes for olaparib in the NMA?	Study contains a population of patients with BRCA mutation and BRCA wild-type (approx. 50% of each). SOLO2 has only patients with a BRCA mutation, so Study 19 is more similar to the rucaparib data
3. Would additional data from ARIEL3 reduce uncertainty in the current NMA?	The PFS2 data gives an indication of post-progression survival, less confounded by cross-over and post-progression chemotherapies than overall survival. These values show significant benefit for rucaparib using the HR across BRCA and ITT cohorts. Also, there is little change in either the HR or median PFS2 at the 15 April 2017 analysis and the one 8 months later on 31 Dec 2017.

4. Is it appropriate to conduct a cost-minimisation for the BRCA 3L+ population?	No. The drug has been shown to be effective for any patient responding to platinum-based therapy (the ITT population). Thus, isolating a BRCA+ group in 3rd line is not of value. (This group was defined for NICE evaluation of olaparib a few years ago. It is not the prime population for PARP inhibitor therapy. Significant benefit is seen after 2L therapy, and in BRCA-wild type
Issue 5: Post progression and overall survival calculation	

1. Which approach to modelling post-progression survival is most appropriate?	The problem with modelling is knowing how many patients in the placebo arm are going to receive a PARP inhibitor post progression. This will increase year on year as PARP inhibitors become more widely available. Secondly, it is important to take note of the tail of the OS curve in study 19; it flattens after 3 years and 11% patients (BRCA and non BRCA) are long-term survivors. There is no reason to suspect that rucaparib will behave differently
a. Do the results of the company's comparison of PFS in ARIEL3 and Study 19, which appears to be a naïve comparison, justify its methods?	Not sure why it is thought to be a 'naïve' comparison. The long-term outcome data from study 19 are all that exist now, and the population, 50% BRCA + is closest to the ARIEL3 population
b. Is the assumption of equivalence in PPS across PARP inhibitors maintenance treatments plausible?	The results of the PFS2 analysis, or TSST show continuing benefit of rucaparib over placebo, although the separation of the curves is less than in PFS. The continuing benefit of rucaparib suggests that post progression therapy in the control arm, even allowing for some cross over to a PARP inhibitor does not annul the effect of rucaparib. The advantage is made up to at least the PFS2
2. What would be considered a plausible PFS:OS ratio?	This is a difficult figure to calculate and it is not clear what this ratio would mean. From the data in Study 19, there is a tail on the survival curve, around 11 % long-term survival (in spite of cross over to a PARP inhibitor) and this small but hugely meaningful effect might not be seen if PFS:OS ratios are used to quantify outcome benefit
Issue 6: Survival extrapolation for the non-BRCA and BRCA 2L subgroups	

1. For the non-BRCA population, are the company's estimates of PFS and TTD ([redacted] difference between mean PFS and mean TTD) or the ERG's (0.3 months difference between mean PFS and mean TTD) the most plausible?	In ARIEL 3 patients stopped treatment on progression (unlike olaparib were some continued). Thus, it is difficult to understand why there should be a large difference between the mean PFS and mean TTD. 0.3 months would be more plausible
2. For the BRCA 2L population, is the company's estimate of PFS ([redacted] of patients in PFS at 10 years) or the ERG's (all patients have progressed after 10 years) most plausible?	It is possible that there may be more than [redacted] non-progressing at 10 years, if the behaviour of patients on rucaparib is similar to olaparib. There is likely to be a tail on the curve that persists (there are patients in Study 19 coming up to their 10th anniversary on olaparib without any sign of progressison)
Issue 7: Subsequent therapy cost calculation	
1. Is the company's estimation of subsequent therapy costs based on selected treatments given in ARIEL3 appropriate and representative of clinical practice (see appendix 1 of the technical report)?	
2. The ERG re-estimated subsequent therapy costs based on all subsequent therapies given in Study 19. Is this more appropriate and representative of clinical practice (see appendix 1 of the technical report)?	
3. Would subsequent therapies differ according to BRCAm status and number of previous chemotherapy regimens?	
4. Are patients expected to receive more than one PARP inhibitor in their treatment pathway (e.g. patient who received rucaparib as 2L maintenance could receive olaparib as 3L maintenance)?	
Issue 8: Cancer Drugs Fund	

1. Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?	Yes. This would provide real world data on outcome, length of treatment, dose reductions etc. It could if properly set up collect data on further lines of therapy, their timing and survival
2. Is rucaparib a good candidate for use in the Cancer Drugs Fund?	Yes. A well tolerated active drug

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

ERG review of company's response to technical engagement report

June 2019

This report was commissioned by the NIHR HTA Programme as project number 128204

BMJ Technology Assessment Group

1 SUMMARY

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of rucaparib for maintenance treatment of recurrent platinum-sensitive epithelial ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (GID-TA10383).

Each of the issues outlined in the technical report are discussed in further detail in Section 3. In addition, the company has provided a revised patient access scheme (PAS) discount of [redacted]. No further changes have been made to the company's base case analysis from those presented in the company's clarification response.

2 UPDATED COMPANY AND ALTERNATIVE ERG BASE CASE ANALYSES

In response to the technical engagement report, the company presented updated analyses for the intention-to-treat (ITT) population and for breast cancer susceptibility gene (BRCA) patients who have had three or more lines of platinum-based chemotherapy (hereafter, BRCA 3L+ population) with the revised PAS discount of [redacted] However, the ERG considers it is important that the committee are presented with the company's subgroup analyses for the non-BRCA and BRCA 2L population with revised PAS discount applied (Table 1 and Table 2).

Table 1. Deterministic results of company's non-BRCA subgroup analysis (updated PAS)

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]	**£24,037**
Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

Table 2. Deterministic results of company's BRCA 2L subgroup analysis (updated PAS)

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]	**£42,372**
Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, Quality-adjusted life year.							

As mentioned previously, the company has not made any further changes to their base case assumptions from those outlined in their clarification response. In addition, the ERG considers that the company has provided no evidence that requires changes to any of the assumptions made for the ERG alternative base case analyses. Table 3 to Table 6 presents the ERG's alternative base case analyses for the ITT, non-BRCA, BRCA2L and BRCA3L+ analyses including the revised PAS discount. For further information on these assumptions, please refer to Section 6 of the main ERG report.

Table 3. ERG's preferred model assumptions – ITT population (updated PAS)

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Corrected company base-case	*6.1*	[redacted]	[redacted]	**£37,832**
Post-progression survival modelled as the residual of ARIEL3 PFS and Study 19 OS	*4.2.5.1*	[redacted]	[redacted]	**£43,898**
Use of subsequent therapy proportions from Study 19	*4.2.8.1, 6.2 & 6.3*	[redacted]	[redacted]	**£43,669**
PFS off maintenance costs for routine surveillance	*4.2.8.1*	[redacted]	[redacted]	**£44,787**
Removal of oral therapy administration costs	*4.2.8.1*	[redacted]	[redacted]	**£43,292**
Extension of time horizon to 50 years	*4.2.4.1*	[redacted]	[redacted]	**£41,103**
Abbreviations: ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.				

Table 4. ERG's preferred model assumptions – non-BRCA population (updated PAS)

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Corrected company base-case	*6.1*	[redacted]	[redacted]	**£25,157**
Using the lognormal distribution for PFS for the non-BRCA population	*4.2.5.1, 6.2 & 6.3*	[redacted]	[redacted]	**£30,276**
Post-progression survival modelled as the residual of ARIEL3 PFS and Study 19 OS	*4.2.5.1*	[redacted]	[redacted]	**£33,861**
Use of subsequent therapy proportions from Study 19	*4.2.8.1, 6.2 & 6.3*	[redacted]	[redacted]	**£42,708**
PFS off maintenance costs for routine surveillance	*4.2.8.1*	[redacted]	[redacted]	**£43,792**
Removal of oral therapy administration costs	*4.2.8.1*	[redacted]	[redacted]	**£42,373**
Extension of time horizon to 50 years	*4.2.4.1*	[redacted]	[redacted]	**£38,035**
Abbreviations: BRCA, breast cancer susceptibility gene mutation; PFS, progression-free survival; OS, overall survival.				

Table 5. ERG's preferred model assumptions – BRCA2L population (updated PAS)

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Corrected company base-case	*6.1*	[redacted]	[redacted]	**£42,957**
Using the Weibull distribution for PFS for the BRCA2L population	*4.2.5.1, 6.2 & 6.3*	[redacted]	[redacted]	**£38,836**
Post-progression survival modelled as the residual of ARIEL3 PFS and Study 19 OS	*4.2.5.1*	[redacted]	[redacted]	**£44,479**
Use of subsequent therapy proportions from Study 19	*4.2.8.1, 6.2 & 6.3*	[redacted]	[redacted]	**£45,494**
PFS off maintenance costs for routine surveillance	*4.2.8.1*	[redacted]	[redacted]	**£46,444**
Removal of oral therapy administration costs	*4.2.8.1*	[redacted]	[redacted]	**£44,926**
Extension of time horizon to 50 years	*4.2.4.1*	[redacted]	[redacted]	**£41,831**

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

Table 6. ERG's preferred model assumptions – BRCA3L+ population (updated PAS)

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.

3 ERG REVIEW OF ISSUES

3.1 Issue 1: Immature clinical trial evidence - overall survival

The ERG agrees with the company that Study 19 has the most mature overall survival (OS) dataset for a PARP inhibitor (PARPi; olaparib) available at present and therefore provides the only longer-term data to inform the long-term outcomes of the PARPi rucaparib.

The ERG highlights that OS is expected to vary according to subgroup (BRCA, non-BRCA) as BRCA mutation status is a key prognostic factor and a treatment effect modifier for a PARPi such as rucaparib. For example, estimated life years gained for rucaparib are 3.52 in the non-BRCA subgroup and 5.61 in the BRCA2L subgroup. This is explored further under Issue 3.

3.2 Issue 2: Generalisability of the clinical evidence to UK clinical practice

The ERG agrees with the company that the population of ARIEL3 are broadly representative of patients in UK clinical practice, although, patients in ARIEL3 are slightly younger and fitter (better performance status) than those seen in UK practice. The ERG also agrees with the company that the proportion of patients in partial and complete response in ARIEL3 is representative of UK clinical practice, based on input from the ERG's clinical experts.

However, there is a difference between the ARIEL3 ITT population and patients in UK clinical practice in the proportion of patients with a BRCA mutation. Of patients in ARIEL3, 35% had either a germline or somatic BRCA mutation whereas the proportion of patients with a germline BRCA mutation is up to 15% among ovarian cancer patients in clinical practice and around 20% in patients with high-grade serous ovarian cancer.[1,2] According to the ERG's clinical experts, the response to rucaparib is unlikely to be influenced by the type of BRCA mutation (germline or somatic) but the different proportions of BRCA mutation is important as BRCA is a treatment effect modifier for a PARPi, as indicated by the larger effect size of rucaparib in the BRCA subgroup compared with the non-BRCA subgroup (see Table 7 and ERG report Table 9 and Table 10). The ERG considers that the efficacy of rucaparib may be overestimated in the ITT population of ARIEL3 compared with its expected efficacy in clinical practice.

The ERG also notes that there is a difference in the proportion of patients with a BRCA mutation in the ITT populations of Study 19 compared with ARIEL3 and UK clinical practice. In Study 19, 54% of patients had a germline or somatic mutation in the olaparib arm and 48% in the placebo arm. As such, the ITT population of Study 19 is likely to overestimate the efficacy of olaparib compared to clinical practice. More importantly, as there is a higher proportion of BRCA mutation patients in the olaparib arm of Study 19 compared to the rucaparib arm of ARIEL 3 (54% vs 35%, respectively), using the ITT

population for Study 19 to inform the overall survival for the ITT population for rucaparib will lead to an over-estimation of rucaparib OS. The ERG does, therefore, not consider the ITT population of Study 19 comparable to ARIEL3 or representative of UK clinical practice. However, the subgroups based on BRCA status overcome the confounding of OS by different proportions of patients having BRCA mutation in the ITT populations.

3.3 Issue 3: Most relevant populations

The company maintains that the ITT population is still the most relevant population to use for the assessment of the cost-effectiveness of rucaparib. The ERG agrees with the company that methodologically it is more robust to use the ITT population from ARIEL3 than any subgroups from the trial. However, as pointed out under Issue 2, the ERG considers there are differences in terms of survival for the BRCA and non-BRCA subgroups, which have a direct impact on cost-effectiveness. Based on the ERG's preferred assumptions for its alternative base case analyses, Table 7 presents the estimated life years for each of the subgroups. Life years estimated by the model for the BRCA2L population are substantially greater compared to the non-BRCA population.

Table 7. Life years for patients by BRCA status and line of therapy - ERG assumptions

Subgroup	Rucaparib	Routine surveillance	Olaparib	Incremental life years
Non-BRCA	3.52	2.12	-	1.79
BRCA2L	5.61	3.33	-	2.28
BRCA3L	2.46	-	2.46	0
Abbreviations: BRCA, breast cancer susceptibility gene mutation.				

Moreover, the ERG considers that for the committee to make an informed decision that is consistent with other technology appraisals (TA528, GID-TA10342) of PARPis for the same indication, subgroup analyses by BRCA status and line of therapy is necessary. For this appraisal, as well as for TA528 and GID-TA10342, the main comparator for patients with a BRCA mutation who have had three or more prior therapies is currently olaparib capsules. Patients at this position in the treatment pathway, who are eligible for olaparib, are unlikely to receive routine surveillance (RS). Inappropriately including this patient group in a comparison with RS will inflate the efficacy of rucaparib compared with RS and provide inaccurate cost-effectiveness results.

Further detail on the importance of the subgroup analyses can be found in the main ERG report (Sections 3.3.1, 3.3.4, 4.2.2 and 4.2.5.1).

The ERG acknowledges that the non-BRCA subgroup in ARIEL3 is a "pure" non-BRCA group compared with the equivalent group in clinical practice, which includes people with a somatic BRCA mutation, as these are not routinely tested for in clinical practice. However, the ERG does not advocate assessing patients with a somatic BRCA mutation in a separate subgroup, but merely highlights that results for the non-BRCA subgroup for ARIEL3 may be conservative compared with clinical practice.

3.4 Issue 4: Uncertainty around the relative treatment effect of rucaparib compared to olaparib in BRCA 3L+

The company has provided extensive analyses exploring the assumption of progression-free survival (PFS) equivalence between rucaparib and olaparib in the BRCA 3L+ subgroup. However, the company has not been able to provide robust evidence to support this assumption.

Although not statistically significant, the results when comparing rucaparib with olaparib capsules (the formulation currently available for routine commissioning in this patient population) the mean estimate favours olaparib. This result is consistent whether analysed as a network meta-analysis (NMA) ([redacted]) or as an anchored matching adjusted indirect comparison (MAIC) ([redacted]), in which differences in baseline characteristics have been adjusted for. Assuming equivalence of PFS between rucaparib and olaparib in the BRCA 3L+ subgroup is likely to be an optimistic assumption, whereas using the mean estimate from the NMA provides a more conservative estimate in light of the limitations of the data. The ERG would like to stress that lack of statistical significance alone is not evidence of no difference in treatment effect.

The ERG agrees with the company that no further indirect treatment comparison (ITC) work can currently address the lack of direct evidence comparing rucaparib with olaparib in the BRCA 3L+ population or the immaturity of the OS data in ARIEL3.

3.5 Issue 5: Post progression and overall survival calculation

In the company's response, it is stated that for two previous TAs, which have not been referenced, the ERG's preferred approach would have been to assume similar post-progression survival (PPS) across PARPis. The ERG assumes that one of the TAs the company refers to is TA528 (niraparib), as this is referenced in the main company submission as the justification for their approach to modelling PPS. As such, the ERG considers the company's statement is factually incorrect as the ERG for TA528 recommended that to overcome the lack of mature OS data and the company's means-based modelling approach, the company could have performed a partitioned survival analysis and conducted an adjusted ITC to estimate a hazard ratio for niraparib vs olaparib for PFS, assuming proportional hazards hold for niraparib vs routine surveillance and olaparib vs routine surveillance. Then, if the ITC showed that the mean HR for PFS was ≥1 in favour of niraparib, then the longer-term OS data from Study 19 could

have been used to provide OS estimates of niraparib vs routine surveillance, by assuming niraparib and olaparib have the same OS.

The company's approach to modelling PPS is reliant on the underlying assumption, stated in the company's clarification response, that in absolute terms the median PFS for rucaparib is longer in ARIEL3 than for olaparib in Study 19 and as such, patients on rucaparib would be dying with a hazard rate of that later time point. However, as explored in Section 4.2.5.1 of the main ERG report, the ERG assumed that this analysis was based on a naive comparison of PFS Kaplan Meier curves from each of the trials. The company have stated that extensive analyses were conducted, through NMA and MAICs and that this justifies their modelling approach of PPS. However, the company's ITCs of rucaparib vs olaparib indicate that rucaparib treatment may result in shorter PFS compared with olaparib in the BRCA 3L+ subgroup, as discussed under Issue 4, and either no or a small benefit in PFS for rucaparib in the ITT population (Company submission Table 25). Although, no ITC results, whether NMA or MAIC, reached statistical significance.

Study 19 is the only trial to provide mature OS data for a PARPi. However, the company states that, "*it was reasonable and appropriate to assume that PPS will not be less for rucaparib patients than what was observed for a given population in Study 19*", but then also state that in reference to Study 19, "*these results were not replicated in any other trial, this begs the question as to what should be the most appropriate methodological approach*". The ERG considers that its approach to modelling PPS as the residual of ARIEL3 PFS and Study 19 OS given the lack of robust evidence that PFS is longer for rucaparib and that OS data from ARIEL3 is immature, is appropriate and conservative. The ERG's approach uses the mature data available from each trial and doesn't disconnect the PFS informing the analysis from the calculation of PPS, so the patient population is maintained throughout the model. Furthermore, it does not produce OS benefits which could be considered implausible. Further information on the ERG's critique of the company's approach to modelling PPS can be found in the ERG main report Section 4.2.5.1.

For TA528 and GID-TA1296, the committee discussed the relationship between PFS and OS for patients in this indication. These discussions resulted in an assessment of what would and wouldn't be considered a plausible OS based on a PFS:OS ratio, where there is a lack of OS data available. The ERG does not endorse the use of a PFS:OS ratio, as there is very little evidence to suggest that a consistent ratio exists for ovarian cancer. However, the ERG considers that it is informative for committee to appreciate the implicit ratio based on the company's methods for estimating OS. For the ITT population, the company's base case approach results in a PFS to OS ratio of [redacted]. Further information on this issue can be found in Section 4.2.5.1 of the main ERG report.

3.6 Issue 6: Survival extrapolation for the non-BRCA and BRCA 2L subgroups

The ERG considers that the company's justification for the [redacted] difference in PFS and TTD for the non-BRCA population to be based on speculation and the ERG considers that it is implausible – that is, the difference being potentially due to patient discontinuation due to adverse events but remaining progression-free. As TTD and PFS are modelled independently, the company should have considered the correlation between the two outcomes as part of the clinical plausibility of their extrapolations. Further critique of this issue as outlined in Section 4.2.5.1 of the main ERG report.

3.7 Issue 7: Subsequent therapy cost calculation

The ERG maintains that as OS is being informed from Study 19, subsequent therapy usage and costs should also be reflective of Study 19. Further critique of this issue is outlined in Section 4.2.8.1 of the main ERG report.

4 REFERENCES

1. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012; 30: 2654-63.

2. NHS England E01/P/b. Clinical Commissioning Policy: Genetic Testing for BRCA1 and BRCA2 Mutations. 2015. Accessed 21/06/2019. Available from: https://www.england.nhs.uk/commissioning/.../e01pb-brca-ovarian-cancer-oct15.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report – Updated after technical engagement

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

1. Summary of the technical report

1.1 This document is the post-engagement technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. A draft version of this technical report was sent out for consultation between May 17th and June 14th, 2019. The draft report included a list of issues that have an impact on the uncertainty of the company's estimates of clinical or cost-effectiveness. The aim of the consultation was to seek feedback from consultees dans commentators on these issues to help inform the technical team's favoured modelling assumptions.

The aim of the post-engagement version of the technical report is to:

- Summarise the feedback that was received on the issues that were identified originally
- Explain how the feedback has or has not been helpful in resolving areas of uncertainty

Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1.2 After technical engagement the technical team has collated the comments received and, if relevant, updated the scientific judgement by the technical team and rationale. The issues that were considered at technical engagement are described in detail in section 2 below, along with the feedback that was received. The following table summarises the current status of each issue in terms of the technical team's view on the level of outstanding uncertainty.

Issue title, number and issue status following engagement	Issues identified pre-engagement	Response to consultation	Technical team scientific judgement after engagement
Issue 1 – Immature clinical trial evidence **For discussion**	The benefit of rucaparib in terms of overall survival (OS) is not currently known because ARIEL3 data are immature. Therefore, the company assumes that rucaparib has the same OS benefit as olaparib capsules using data from Study 19. Clinical opinion was sought on whether it is appropriate to assume the same OS as for olaparib.	PARPis are broadly similar in terms of efficacy. Survival in ARIEL3 is expected to be longer than in Study 19, because rucaparib in ARIEL3 was used in earlier treatment lines than olaparib in Study 19.	In the absence of mature overall survival from ARIEL3, Study 19 provides the best source for estimates of overall survival
Issue 2- Generalisability of the clinical trial evidence to UK clinical practice **For discussion**	The technical team sought clinical opinion on whether the population of ARIEL3 and Study 19 were representative of UK clinical practice especially the composition of the BRCA/non-BRCA groups.	ARIEL3 trial reflects clinical practice in the UK especially in terms of tumour burden. The magnitude of benefits appears to be similar in germline and somatic mutations. although somatic BRCA testing is not routinely funded. In Study 19 there was a higher proportion of patients having treatment at later treatment lines.	ARIEL3 is representative of UK clinical practice. However, there are some differences between clinical practice (BRCA/non-BRCA composition) and Study 19 (rucaparib used in earlier treatment lines, more BRCA-mutated patients in Study 19).

Issue 3 – Most relevant populations **For discussion**	It was unclear whether ITT population or subgroups (BRCA 3L+, BRCA 2L or non-BRCA) were the most appropriate to focus on.	ITT is the most robust population. There are differences in effectiveness between BRCA and non-BRCA however some non-BRCA patients have the capacity to gain long-term benefits from PARPis. It is usually more robust to follow the trial population when possible, unless subgroup analyses are very robust.	ITT and subgroup analyses will be presented at the committee meeting.
Issue 4- Uncertainty around the relative treatment effect of rucaparib compared to olaparib in BRCA 3L+ **For discussion**	The NMA did not demonstrate any statistically significant differences between rucaparib and olaparib in PFS, although the direction of effect varied according to whether data from Study 19 or SOLO 2 were used to inform the outcomes for olaparib.	PARPi are similar in terms of efficacy but there are differences in terms of tolerance. It is reasonable to assume PFS equivalence between PARPIs. It is appropriate to conduct a cost-minimisation in the BRCA 3L+.	In the absence of a reliable comparison, and given the comments from clinical experts, a cost minimisation approach for the BRCA 3L+ population may be reasonable.
Issue 5 – Post progression and overall survival calculations **For discussion**	The approach used to calculate post-progression and overall survival has a big impact on the results and the preferred approach is different between the ERG and the company.	The company tried to avoid the PFS:OS ratio because it was criticised in previous appraisals. The ERG believes the OS:PFS ratio is useful to show the plausibility of the results. Clinical experts reported that populations were different between ARIEL3 and Study 19 which may explain differences in results.	The ERG's approach is conservative but may underestimate the benefit in OS for rucaparib, while the company's approach seems to overestimate the overall survival for rucaparib.

Issue 6 – Survival extrapolation for the non-BRCA and BRCA 2L subgroups **Agreed**	The long-term extrapolation of PFS is one of the main drivers of the model. Non-BRCA: The company's choice leads to an overestimate of the benefits in terms of PFS compared to the time on treatment and associated treatment costs. BRCA 2: The company's choice lead to some patients still in PFS at 10 years.	Non-BRCA: It is not plausible to have such a discrepancy between PFS and TTD because patients in ARIEL 3 stopped treatment at progression. BRCA 2L: It is plausible to have patients in PFS at 10 years, as observed in Study 19.	In the non-BRCA, the ERG's approach (lognormal) is the most plausible because it is more aligned with TTD. In the BRCA 2L, the company's approach (lognormal) is the most plausible because it is more aligned with what was observed in Study 19 trial at 6 years.
Issue 7- Subsequent therapy cost calculation **For discussion**	Clinical opinion was sought on whether the subsequent therapies received in ARIEL3 and Study 19 were representative of clinical practice, and whether subsequent therapies would differ according to BRCA mutation status.	Availability of treatments in the UK for progressed disease can be different from other parts of the world. Using Study 19 distribution instead of ARIEL3 distribution increases the ICER for the non-BRCA population.	The subsequent therapies costs impact the ICER in the non-BRCA population only.
Issue 8 – Cancer Drugs Fund **For discussion**	One of the main uncertainties in the evidence base is about the long-term overall survival benefit of rucaparib compared with routine surveillance. More mature data from ARIEL3 trial could address this uncertainty.	OS is the main uncertainty in the submission. Company is expecting OS to be mature by [redacted].	Rucaparib is a plausible candidate for the CDF if it is shown to have the plausible potential to be cost-effective.

1.3 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical trial evidence is very immature and median overall survival has not been met
- The subgroup analyses for the non-BRCA and BRCA 2L populations were *post hoc* analyses with small sample sizes and heavy censoring
- Patients in the placebo arm of ARIEL3 and Study 19 received subsequent treatment with a PARP inhibitor outside the trials ([redacted]% in ARIEL3 and 13.5% in Study 19), which may confound and bias the OS results in favour of placebo.

1.4 The cost-effectiveness results include an agreed commercial arrangement (patient access scheme) for rucaparib. The company proposed an updated commercial arrangement during the technical engagement.

1.5 Taking these aspects into account, the technical team's favoured assumptions result in an incremental cost-effectiveness ratio (ICER) of £42,175 per QALY gained for the ITT population, £41,288 per QALY gained for the non-BRCA population and £56,994 per QALY gained for the BRCA 2L population (see table 1). For the BRCA 3L+ population, rucaparib is dominated by olaparib. These estimates include the updated commercial arrangement for rucaparib submitted during technical engagement.

1.6 Rucaparib is not likely to meet the end-of-life criteria (see Other issues for information).

1.7 Innovation: Rucaparib is unlikely to be considered innovative because NICE has already appraised two other PARP inhibitors for this indication. Technology appraisal 381 recommends olaparib for the maintenance treatment of BRCA 1 or 2 mutated, relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer who have had three or more courses of platinum-based chemotherapy. Technology appraisal 528 recommends niraparib for use within the Cancer Drugs Fund for the maintenance treatment of relapsed platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who have germline BRCA mutation and had 2 courses of platinum-based chemotherapy or in

patient who do not have germline BRCA mutation and have had two or more courses of platinum-based chemotherapy.

1.8 No equality issues were identified.

2. Key issues for consideration

Issue 1 – Immature clinical trial evidence - overall survival

Background/description of issue	• At the data cut-off for the primary endpoint analysis of ARIEL3 (15 April 2017), OS data for rucaparib and routine surveillance were very immature 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 at this timepoint and there was no statistically significant difference between the treatment arms. • No updated analyses of OS were performed at the updated safety data cut-off date (31 December 2017) as the OS data were still immature. • ARIEL3 OS data could not be used in the cost-effectiveness analysis. As a result, OS data from Study 19 were used to model long-term outcomes of rucaparib maintenance and routine surveillance. • Study 19 provides mature OS data with over 6 years follow-up of olaparib (capsule formulation) as a maintenance treatment for ovarian cancer. It is the only trial available to inform the long-term outcomes of PARP inhibitors maintenance therapy and of routine surveillance. • The ERG considers Study 19 to provide the most robust data available but acknowledges that there is limited evidence to demonstrate whether the assumption of equivalence between olaparib and rucaparib in terms of OS is conservative or optimistic. • Additionally, there is 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 different populations.
Why this issue is important	Immature overall survival data introduce uncertainty into the clinical and cost-effectiveness evidence.
Questions for engagement	1. Is rucaparib expected to increase overall survival? If so, is it appropriate to assume the same overall survival as for olaparib? 2. Is OS expected to vary according to subgroups (BRCA 2L, BRCA 3L+, non-BRCA)? 3. When is the company expecting a new data cut-off for efficacy?

Technical team preliminary scientific judgement and rationale	In the absence of mature data for rucaparib, Study 19 appears to provide the most robust data available, if it can be assumed there is a class effect for PARP inhibitors.
Summary of comments	Comments received from the clinical experts: • PARP inhibitors are broadly similar in terms of efficacy. • Survival in ARIEL3 is expected to be longer than in Study 19, because rucaparib in ARIEL3 was used in earlier treatment lines than olaparib in Study 19. As a result, a more promising PFS is already observed. • There is likely to be an increase in overall survival. However, the likelihood of cross over in ARIEL 3 will reduce the magnitude of difference. The degree of crossover for ARIEL 3 will be greater than previous trials with olaparib or niraparib as the availability of PARP inhibitors (worldwide) is greater. There is no reason to believe the potency/effectiveness of rucaparib is different from olaparib or niraparib. • The greatest benefit seen to date with all PARP inhibitors is in patients with a BRCA mutation (germline or somatic). For OS, differences in 2L or 3L may be less clear cut. It is more the magnitude of HRD that will be responsible for the biggest OS difference and this is more likely to be tumour-dependent rather than time-dependent. Comments received from the ERG: • The ERG agrees that Study 19 has the most mature OS data available for PARP inhibitors. • OS is expected to vary according to BRCA status, as BRCA mutation is a prognostic factor and a treatment effect modifier for PARP inhibitors such as rucaparib.
Technical team scientific judgement after engagement	In the absence of mature overall survival from ARIEL3, Study 19 provides the best source for estimates of overall survival.

Issue 2 – Generalisability of the clinical evidence to UK clinical practice

Background/description of issue	The clinical effectiveness estimates in the company's cost-effectiveness model are informed by the data from ARIEL3 (for PFS) and Study 19 (for OS). *Generalisability of ARIEL3 evidence to UK clinical practice* • Although only [redacted]% of the ARIEL3 trial patients were enrolled and treated in the UK, the ERG's clinical experts consider the full trial population largely representative of people in England eligible for rucaparib maintenance treatment. • 66% of the patients in ARIEL3 had a partial response to last platinum-based therapy and 34% had a complete response. • Patients in ARIEL3 were slightly younger and had better performance status. Also, the proportion of patients with a BRCA mutation and who had prior bevacizumab was higher than what would be expected in UK clinical practice. • The BRCA group of ARIEL3 includes germline and somatic BRCA mutations and is therefore slightly different from the BRCA group in clinical practice which would not include somatic BRCA mutations because somatic BRCA testing is not widely available in England. *Generalisability of Study 19 evidence and comparability with ARIEL3* • The ERG highlighted several differences between ARIEL3 and Study 19 in terms of both trial design and patients' characteristics. • ARIEL3 is a phase III trial while Study 19 is phase II. Moreover, BRCA status was a stratification factor in the randomisation process of ARIEL3, while in Study 19 BRCA status

	was confirmed retrospectively and ancestry (Jewish vs non-Jewish) was used as a proxy for BRCA status. As a result, the BRCA subgroup in Study 19 is *post hoc*. • No comparison of the baseline characteristics could be made for the BRCA 2L subgroup between Study 19 and ARIEL3 given that baseline characteristics were not available for this subgroup in Study 19. • Only limited baseline characteristics were available for the BRCA 3L+ population across the trials, with imbalances both within and between trials, due to the *post hoc* nature and the small sample size of these subgroups. • For the ITT and non-BRCA populations of ARIEL3 and Study 19, patient characteristics were balanced within and between the trials. • In TA381, the ERG noted that the Study 19 population might differ from clinical practice in England given that the BRCA-mutated subgroup included germline and somatic mutations while somatic testing might not be possible in England.
Why this issue is important	The generalisability of the clinical trial evidence to UK clinical practice is an important consideration for decision making.
Questions for engagement	1. Is the population of ARIEL3 broadly representative of UK clinical practice? 2. Is the proportion of patients in partial and complete response in ARIEL3 representative of UK clinical practice? 3. Is the population of Study 19 comparable to ARIEL3 and representative of UK clinical practice? 4. Is the response to rucaparib influenced by the type of BRCA mutation? 5. To what extent is testing for somatic BRCA mutations done in the UK?
Technical team preliminary scientific judgement and rationale	The ITT population of ARIEL3 is largely representative of UK clinical practice according to the ERG's clinical expert. There is uncertainty around the influence of somatic BRCA mutations on the clinical and cost-effectiveness evidence.

Summary of comments	Comments received from the clinical experts: • The population of ARIEL3 very much reflects clinical UK practice, especially because ARIEL3 did not exclude patients based on the extent of residual disease contrary to the niraparib trial (NOVA). • The magnitude of benefit appears to be similar in people with germline and somatic BRCA mutations, but there is no funding for testing of somatic BRCA mutations in the UK. There is a strong clinical wish for somatic testing to be implemented because currently some patients are denied access to PARP inhibitors. • Around 20% of patients have germline or somatic mutations in the UK (6-7% have somatic). • In Study 19, there was a higher proportion of patients in later lines of therapies. Approximately 63% of patients in ARIEL3 had 2 prior lines of chemotherapy. For Study 19 the population had been a little more heavily pre-treated, 46% had only 2 prior lines of chemotherapy. • Additionally, the distribution of BRCA and non-BRCA was slightly different. Study 19 included more patients with BRCA mutations (50%) than in ARIEL3 (35%). The number of BRCA mutated patients in ARIEL3 was capped deliberately. • The survival in ARIEL3 is expected to be longer because rucaparib was used earlier in treatment lines. Comments received from the ERG: • ERG agrees that ARIEL3 patients are broadly representative of patients in UK clinical practice. • However, there are differences in terms of the proportion of patients with a BRCA mutation. In ARIEL3, 35% had a BRCA mutation whereas in clinical practice there are 15 to 20% with a BRCA mutation. • As a result, the efficacy of rucaparib in ITT population may be overestimated compared with its expected efficacy in clinical practice. • Additionally, there is a higher proportion of BRCA mutated patients in Study 19 compared to ARIEL3 and to clinical practice (50% in Study 19), so Study 19 ITT is likely to overestimate

	the efficacy of olaparib compared to clinical practice. Therefore, using Study 19 to model OS for ITT population for rucaparib may overestimate rucaparib OS. • However, analyses by subgroups based on BRCA status overcome the confounding of OS by different proportions of patients having a mutation in the ITT population. • The non-BRCA group in ARIEL3 is a "pure" subgroup as it does not include somatic BRCA mutations, only non-BRCA patients. • As a result, the efficacy in non-BRCA in the ARIEL3 trial is conservative compared to clinical practice where patients would do a bit better. Comments received from the company: • The company believes that the population in ARIEL3 is broadly representative of UK clinical practice. • Importantly, the inclusion in ARIEL3 was not restricted based on the extent of residual disease at study entry while the NOVA trial for niraparib excluded patients with bulky disease. • A subgroup analyses of ARIEL3 in patients with any lesion ≥ 2 cm (i.e., bulky disease) was conducted to assess the benefit of rucaparib in this subgroup, however clinical advice received by the company suggested that the full population in ARIEL3 better reflected UK clinical practice. • The company believes that the proportion of patients in partial and complete response in ARIEL3 is representative of UK clinical practice.
Technical team scientific judgement after engagement	ARIEL3 is broadly representative of UK clinical practice. However, there are some differences between ARIEL3 and clinical practice (BRCA/non-BRCA composition) and Study 19 (rucaparib used in earlier treatment lines, more BRCA-mutated patients in Study 19).

Issue 3 – Most relevant populations

Background/description of issue	• The company's base case is the ITT population compared with routine surveillance and the BRCA 3L+ population compared with olaparib. • However, the ERG considers the most relevant populations for the decision problem are the non-BRCA, BRCA 2L analyses (compared with routine surveillance) and BRCA 3L+ analysis (compared with olaparib) provided by the company because treatment options vary for these groups. • At clarification stage, the company provided additional analyses for the non-BRCA and BRCA 2L subgroups highlighting the fact that ARIEL3 trial was not designed to assess the efficacy of rucaparib in these subgroups. • As a result, the analyses for the non-BRCA and BRCA 2L populations are *post hoc* and based on small sample sizes resulting in high uncertainty. • Moreover, the treatment pathway is changing due to new treatments currently being appraised and recommended.
Why this issue is important	The effectiveness estimates for the non-BRCA and BRCA 2L populations are highly uncertain. The population of interest for the appraisal is key for decision-making
Questions for engagement	Is it relevant to separate the population into subgroups or is it more appropriate to focus on the ITT population from the trial?
Technical team preliminary scientific judgement and rationale	The post hoc subgroup analyses are insufficiently robust for estimating clinical effectiveness. Therefore, the ITT population provides the most reliable evidence to appraise rucaparib.
Summary of comments	Comments received form clinical experts: • Olaparib capsules will no longer be available in the next future and olaparib will also become available earlier in the treatment pathway. This means that olaparib being a comparator in BRCA 3L+ will no longer be an issue in the future. • The primary outcome effect was greatest in BRCA subgroup; however, a significant overall benefit was seen in the ITT population. Currently, sensitivity to platinum-based chemotherapy remains the best overall predicator of HRD, and susceptibility to PARP inhibitors. • Rucaparib has been shown to be effective for any patient responding to platinum-based therapy (the ITT population). Thus, isolating a BRCA+ group in 3rd line is not of value. This

	group was defined for NICE evaluation of olaparib a few years ago, but it is not the prime population for PARP inhibitor therapy. Significant benefit is seen after 2L therapy, and in BRCA-wild type. Comments received from ERG: • The ERG agrees that the ITT population is the most robust data set. • The ERG considers there are differences in terms of survival for the BRCA and non-BRCA subgroups that have direct impact on cost-effectiveness. Life years estimated by the model for the BRCA 2L are substantially greater compared to the non-BRCA population. • The ERG considers that for the committee to make an informed decision consistent with TA528 and GID-TA10342 (PARP inhibitors for the same indication), analyses by BRCA mutation status and treatment line are necessary. • The main comparator for BRCA 3L+ is olaparib capsules and patients at this stage in the treatment pathway are unlikely to receive routine surveillance. As a result, including the BRCA 3L+ in a comparison with routine surveillance is inappropriate and will inflate the efficacy of rucaparib vs routine surveillance providing inaccurate cost-effectiveness results. Comments received from the company: • The company believes that the ITT provides the most complete reliable and robust evidence. ARIEL3 was not designed or powered to detect differences in efficacy or safety between the BRCA and non-BRCA cohort at different treatment lines. • The subgroups analyses provided at clarification stage are post-hoc analyses comprising small sample sizes are cannot be considered robust enough for decision-making. • By separating the population in non-BRCA and BRCA, two other clinically relevant issues arise: somatic BRCA would not be identified in practice because it is not tested, so the BRCA subgroup would only include germline BRCA mutation and somatic BRCA may not be able to benefit from rucaparib. Additionally, Study 19 indicates that long-term responders include non-BRCA patients, which reinforces that ITT is the appropriate population.
Technical team scientific judgement after engagement	The ITT population provides the most robust evidence, but both the ITT and subgroup analyses based on BRCA mutation status will be presented at the committee meeting.

Issue 4 – Uncertainty around the relative treatment effect of rucaparib compared to olaparib in BRCA 3L+

Background/description of issue	• A network meta-analysis (NMA) and matching adjusted indirect comparison (MAIC) were conducted to assess the comparative effectiveness of rucaparib and olaparib in the BRCA 3L+ population in absence of head-to-head trials.
	• Both Study 19 (olaparib capsules) and SOLO2 (olaparib tablets) provide data for PFS, but only Study 19 provides data for OS as SOLO2 data are very immature. However, OS data from the ITC do not inform the model as they were considered too unreliable because of the immaturity of the ARIEL3 data.
	• The ERG agreed that the value of an ITC for OS is limited because of the immaturity of ARIEL3 OS data.
	NMA
	• NMA on PFS
	  ○ The company pooled the two studies of olaparib (SOLO2 and Study 19) in the NMA to compare rucaparib to olaparib.
	  ○ The ERG commented that there is currently little evidence to support or refute whether the olaparib formulations are equivalent in terms of safety and efficacy.
	  ○ 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 formation currently used in routine commissioning and reports long term outcomes. Additionally, as Study 19 is used for OS data it is preferable to use only Study 19 for PFS in order to use the same dataset to inform OS and PFS.
	• In their response to ERG's clarification question, the company provided NMA results for PFS based on SOLO2 and Study 19 individually: No statistical difference between rucaparib and olaparib was demonstrated, irrespective of which study was informing the data. However, the point estimate varied substantially. The HR for PFS of rucaparib vs olaparib was [redacted] when using SOLO2 and [redacted] when using Study 19, while including both olaparib studies produced a HR of [redacted]. The ERG considers that the difference in results is likely to be due to

	differences between Study 19 and SOLO2 trials, especially the differences in olaparib formulations, as well as the enrolment of BRCA patients only in SOLO2. • Based on the NMA results, the company assumed clinical equivalence between rucaparib and olaparib for the BRCA 3L+ population. As a result, PFS for olaparib is modelled using the ARIEL3 PFS data for rucaparib, and OS for rucaparib is modelled using Study 19 OS data for olaparib. • The ERG considers that the non-statistically significant results do not justify the company's assumption of equivalence. Instead, the ERG believes that the ITC results may suggest that the olaparib capsule formulation provides longer PFS than rucaparib. • The ERG noted that by assuming equivalence between olaparib and rucaparib, the cost-effectiveness analysis for BRCA 3L+ is reduced to a cost minimisation. **MAIC** • The company conducted a MAIC in addition to the NMA in order to adjust for potential treatment effect modifiers within and between trials. • However, the ERG didn't consider that conducting a MAIC adjusting for these factors demonstrated a more robust estimate than a NMA approach. The NMA and MAIC produced very similar results, with no statistically significant differences between rucaparib and olaparib, and the point estimates varying according to whether the data for olaparib were from Study 19 or SOLO2.
Why this issue is important	The clinical equivalence assumption made by the company is very uncertain and is used in the base-case analysis to inform the cost-effectiveness of rucaparib.
Questions for engagement	1. Is the company's assumption of clinical equivalence in PFS for rucaparib and olaparib for the BRCA 3L+ population appropriate in light of the level of data available? 2. What conclusion can be made of the relative treatment effect of olaparib vs rucaparib given the ITC results? a. Which study (Study 19 or SOLO2) is the most appropriate for informing outcomes for olaparib in the NMA? 3. Would additional data from ARIEL3 reduce uncertainty in the current NMA? 4. Is it appropriate to conduct a cost-minimisation for the BRCA 3L+ population?

Technical team preliminary scientific judgement and rationale	Because of the lack of direct trial evidence comparing rucaparib and olaparib, there is uncertainty about the extent to which outcomes may differ for the 2 drugs. The technical team does not believe that additional data would reduce the current uncertainty in the ITC. The ITC for OS is of limited value because of the immaturity of ARIEL3 OS data.
Summary of comments	Comments received from clinical experts: • PARP inhibitors are broadly the same in terms of efficacy but there are differences in how they are tolerated. It is probably the degree of HRD that influences the outcome, and this may not be affected by the number of prior lines of therapy. • Clinical experts believe it is reasonable to assume PFS equivalence between the PARP inhibitors. • The difference in effectiveness between Study 19 and SOLO2 is mainly due to different patients included and different formulations. SOLO2 only included patients with a BRCA mutation, so Study 19 is more like the rucaparib trial. • PFS2 data gives an indication of post-progression survival, given that it is less confounded by cross-over and post-progression chemotherapies than overall survival. PFS2 results show significant benefit for rucaparib using the HR across BRCA and ITT cohorts. Also, there is

	little change in either the HR or median PFS2 at the 15 April 2017 analysis and the one 8 months later on 31 Dec 2017. Comments received from the ERG: • Although not statistically significant, the results of the comparison of rucaparib with olaparib capsules (formulation currently available and recommended for routine commissioning) favours olaparib. • This result is consistent whether the NMA or the MAIC is used. • The assumption of PFS equivalence between rucaparib and olaparib in the BRCA 3L+ population is likely to be an optimistic assumption, and the lack of statistical significance alone is not evidence of no difference in treatment effect. Comments received from the company: • The company has undertaken extensive work to explore the relative efficacy between rucaparib and olaparib in BRCA 3L+, with both NMA and MAIC. • Results were not statistically significant and did not provide any evidence against equivalence of PFS in the BRCA 3L+ population. • It is acknowledged that available data to assess relative efficacy between rucaparib and olaparib in BRCA 3L+ were limited. • Although the company has conducted ITC from a number of different perspectives, these have limitations and further ITC work cannot currently address the lack of direct evidence and the immaturity of OS data.
Technical team scientific judgement after engagement	In the absence of a reliable comparison, and given the comments from clinical experts, a cost minimisation approach for the BRCA 3L+ population may be reasonable.

Issue 5 – Post progression and overall survival calculation

Background/description of issue	Company's approach and rationale • Given that the company assumed clinical equivalence in PFS for rucaparib and olaparib in the BRCA-3L+ population (see issue 3), the company also assumed equivalence in post-progression outcomes. • For the other populations (ITT, non-BRCA and BRCA 2L), the company did not calculate the PPS as the difference between Study 19 OS and ARIEL3 PFS as this would produce shorter PPS outcomes for rucaparib. • This rationale is based on what the ERG assumes is a naïve comparison, which showed that PFS was longer in ARIEL3 than in Study 19. Therefore, using the same OS irrespective of any PFS gain would imply that patients who progress later on a treatment providing PFS gain will have higher mortality hazard leading to shorter PPS outcomes. • Therefore, the company calculated PPS using Study 19 PFS and OS outcomes, and then used PPS outcomes from Study 19 to model PPS for rucaparib in the model, assuming that PPS outcomes for rucaparib are equivalent to olaparib in Study 19. • The company's clinical expert stated that assuming PPS equivalence across PARP inhibitors maintenance treatments was plausible. ERG's critique • The company's approach results in an implied PFS:OS ratio of [redacted]. This is highly optimistic according to the ERG, given that the appraisal committee in previous appraisals of niraparib (TA528) and olaparib (GID1296) considered the PFS:OS ratio of 1:2 to be optimistic. • Moreover, the ERG considers that the company's approach is unconventional as the calculation of PPS is disconnected from the PFS informing the analyses. • The ERG's preferred approach is to calculate PPS as the residual of ARIEL3 PFS and Study 19 OS for the ITT, non-BRCA and BRCA 2L populations as this makes the most of the mature data available. • During the clarification stage, the ERG requested the company to calculate PPS using this approach. The company believes that the ERG's preferred approach is not appropriate because assuming same OS irrespective of any PFS gain will results in higher mortality hazard and shorter PPS outcomes and the company is not aware of any clinical rationale

	supporting this assumption. Also, the company referred to the long-term data of Study 19 which showed a continued benefit of olaparib for OS and time to second subsequent therapy (TSST), supporting the fact that benefits beyond PFS are seen in responders to PARP inhibitors. The company also reported that the assumption of equivalence in PPS outcomes across PARP inhibitors was considered plausible by clinical experts. • However, the company presented a scenario analysis of the ERG's preferred approach in its clarification response. This showed a large impact on the ICER increasing from £50,681 to £59,078 per QALY gained in the ITT population, from £33,340 to £45,217 per QALY gained in the non-BRCA population and from £58,054 to £79,007 per QALY gained in the BRCA 2L population. • The ERG's preferred approach results in a PFS:OS ratio greater than 1:2 for the ITT population, but less than [redacted]. For the non-BRCA and BRCA 2L populations, the ERG's preferred approach results in a PFS:OS ratio greater than 1:1, which was considered too conservative by the committee for the appraisals of niraparib and olaparib (TA528 and GID1296 respectively) but less than 1:2. • The ERG acknowledges that this alternative approach has several limitations including: using different sources for PFS and OS, assuming that OS outcomes for rucaparib are equivalent to olaparib, assuming that patients in the routine surveillance arm for ARIEL3 and Study 19 are similar and data for the BRCA 2L subgroup from Study 19 includes all BRCA patients regardless of number of lines of platinum-based chemotherapy.
Why this issue is important	The approach used to calculate PPS has a large impact on the ICER, with ICERs varying from £50,681 to £59,078 per QALY gained in the ITT population, from £33,340 to £45,217 per QALY gained in the non-BRCA population and from £58,054 to £79,007 per QALY gained in the BRCA 2L population.
Questions for engagement	1. Which approach to modelling post-progression survival is most appropriate? a. Do the results of the company's comparison of PFS in ARIEL3 and Study 19, which appears to be a naïve comparison, justify its methods? b. Is the assumption of equivalence in PPS across PARP inhibitors maintenance treatments plausible? 2. What would be considered a plausible PFS:OS ratio?

Technical team preliminary scientific judgement and rationale	The approach proposed by the company uses the absolute PPS outcomes obtained in Study 19. However, the rationale for using this approach is based on what appears to be a naïve comparison of PFS in Study 19 and ARIEL3 which is not methodologically appropriate. In addition, the company's approach leads to a highly optimistic implied PFS:OS ratio of [redacted] which is not supported by evidence. In light of this, the technical team believes that the ERG's more conservative approach is justified.
Summary of comments	Comments received from the clinical experts: • It is important to remember that the populations between studies are different so it may appear that the PFS in ARIEL3 is longer than in Study 19 but it may be due to a higher proportion of patients being in later lines of treatment in Study 19. • The issue is also to identify how many patients in the placebo arm will receive a PARP inhibitor in post progression. This will increase year on year as PARP inhibitors become more widely available. • It is important to underline that the tail of the OS curve in Study 19 flattens after 3 years and 11% of patients (BRCA and non-BRCA) are long-term survivors. There is no reason to suspect that rucaparib would behave differently. • Although the separation of the curves is less than in PFS, the results of the PFS2 analysis or TSST (time to second anti-cancer treatment) demonstrate a continuing benefit of rucaparib over placebo. This suggests that post progression therapy in the control arm, even allowing for some cross over to a PARP inhibitor does not annul the effect of rucaparib. The advantage is made up to at least the PFS2. • It is difficult to calculate a PFS:OS ratio and unclear what this would mean. The tail of the OS curve from Study 19 and the 11% of long-term responder patients are small but a hugely meaningful benefit that would not be seen if a ratio PFS:OS was used to estimate the benefit provided. Comments received from the ERG: • In the company's responses, it is stated that the ERG's preferred approach would have been to assume similar PPS in two appraisals. Although the two previous TA are not stated, the ERG assumes that one of the TA the company refers to is TA528. As such, the ERG

	considers that the company's statement is factually incorrect as the ERG for TA528 did not recommend assuming similar PPS between treatments. • The company's approach relies on the underlying assumption that in absolute terms the median PFS for rucaparib in ARIEL3 is longer that median PFS for olaparib in Study 19 and as such, patients on rucaparib would die with a hazard rate of that later timepoint. • The ERG assumes that this analysis was based on a naïve comparing of the PFS Kaplan-Meier curves from each trial. Although the company have stated that extensive analyses were conducted through NMA and MAICs, the company's ITC of rucaparib vs olaparib in BRCA 3L+ indicate that rucaparib treatment may results in shorter PFS compared with olaparib. • The ERG considers that its approach to modelling PPS is appropriate and conservative given the lack of robust evidence that PFS is longer for rucaparib and that ARIEL3 OS is immature. The ERG's approach uses mature data available and does not disconnect the PFS informing the analysis from the PPS calculation, so the population is maintained throughout the model. Additionally, it doesn't produce OS benefits which could be considered implausible (more than 100% patients coming out of the model with the company's approach). • The reference to a PFS:OS ratio was based on previous TA in which the committee discussed the relationship between PFS and OS in this indication. • The ERG doesn't endorse the use of a PFS:OS ratio as there is little evidence to support that a consistent ratio exists for ovarian cancer. However, the ERG considers it is informative for the committee to appreciate the implicit ratio based on the company's methods for estimating OS. Comments received from the company: • The company tried to stay away from the PFS:OS relationship because it was criticised in previous appraisals. The assumption of PPS equivalence was the preferred approach in two previous ERG reports. • Based on previous appraisals and clinical advice, the company concluded that it was appropriate to assume that PPS for rucaparib patients will not be less than what was observed in Study 19.

	• In light of this, the ERG's assumption that there is greater post-progression mortality hazard associated with one PARP inhibitor over another is not justified. The company do not think it is helpful to discuss whether there is a plausible OS:PFS ratio. • The challenge here is how to translate the PFS benefits into OS benefits if any. The company considered that the best way to calculate PPS and keep the PFS benefits from ARIEL3 is to use Study 19 data. • The company acknowledge that the "implied" ratio PFS:OS is large, however note that it is a consequence of the long tail of the OS splines distribution that was validated by clinicians.
Technical team scientific judgement after engagement	The ERG's approach is conservative but may underestimate the benefit in OS for rucaparib, while the company's approach seems to overestimate the overall survival for rucaparib.

Issue 6 – Survival extrapolation for the non-BRCA and BRCA 2L subgroups

Background/description of issue	• In order to model progression-free and overall survival, the company extrapolated Kaplan-Meier data by selecting survival curves based on lowest AIC/BIC statistics, visual inspection and clinical plausibility of the extrapolation. • For the ITT and BRCA 3L+ populations, the ERG considers that the approach used to extrapolate OS, PFS and TTD for these 2 populations is appropriate. • For the non-BRCA and BRCA 2L populations, the ERG considers that the extrapolation for PFS is not satisfactory. **Non-BRCA population** • For the non-BRCA population, the ERG noted that the company's preferred curve choices for PFS led to a modelled mean PFS being markedly longer than modelled mean TTD (about [redacted]). • This difference in means leads to treatment costs being substantially lower than the benefit obtained. • Moreover, SmPC for rucaparib states that treatment should be given until disease progression or unacceptable toxicity. In ARIEL3, [redacted] of patients receiving rucaparib discontinued treatment due to toxicity. Therefore, there is no clear rationale why mean PFS would be so much longer than mean TTD. • The ERG considers that the company's extrapolation for TTD is reasonable, but the company's extrapolation for PFS using the generalised gamma distribution results in poor fit to the Kaplan-Meier data from ARIEL3. The ERG considers extrapolation using the lognormal distribution to be a better fit for PFS, which results in a modelled PFS that is better aligned with the modelled mean TTD (only [redacted] months difference between mean PFS and mean TTD). When considering AIC/BIC statistics, the lognormal distribution is the second best-fitting curve. **BRCA 2L population** • For the BRCA 2L population, the company used a lognormal curve, but the ERG preferred the Weibull curve as it considers that it is a better fit to the Kaplan-Meier data and gives more clinically plausible results. With the ERG's preferred curves, all patients have progressed

	after 10 years while the company's preferred choice results in [redacted] of patients still in PFS at 10 years.
Why this issue is important	The long-term extrapolation of PFS is one of the main drivers of the model. The company's choice leads to an overestimate of the benefits in terms of PFS compared to the time on treatment and associated treatment costs, particularly in the non-BRCA population.
Questions for engagement	1. For the non-BRCA population, are the company's estimates of PFS and TTD ([redacted] difference between mean PFS and mean TTD) or the ERG's ([redacted] months difference between mean PFS and mean TTD) the most plausible? 2. For the BRCA 2L population, is the company's estimate of PFS ([redacted] of patients in PFS at 10 years) or the ERG's (all patients have progressed after 10 years) most plausible?
Technical team preliminary scientific judgement and rationale	There is no clear rationale why mean modelled PFS would be much longer than TTD in the non-BRCA population, and the approach proposed by the ERG seems to be more representative of what would happen in clinical practice. The ERG's approach using the Weibull distribution to extrapolate PFS in BRCA 2L seems more plausible.

Summary of comments	**1. Non-BRCA population** Comments received from clinical experts: • Regarding the discrepancy between mean PFS and TTD, it is not plausible to have such a difference between mean PFS and mean TTD, given that patients in ARIEL3 stopped treatment after progression. Comments received from ERG: • The ERG considers that the company's justification for the difference between PFS and TTD is not plausible. • Given that TTD and PFS are modelled independently, the company should have considered the correlation between the two outcomes as part of the clinical plausibility of their extrapolations. Comments received from the company: • The difference in the means in non-BRCA was due to the long tail at the end of extrapolation. The 12 months difference arises from the best-fitting survival function fitted to the patient level data from ARIEL3. • Lognormal was not the best fit to the data for non-BRCA therefore the company didn't choose this curve. • The 12 months difference may be due to patients discontinuing treatment due to adverse events but still remaining progression-free. It should be noted that the 12 months difference occurs over a 30-year time horizon, which the company does not believe to be clinically implausible. **2. BRCA 2L population** Comments received from clinical experts: • In Study 19 there were still 6% of patients in PFS and on treatment at 6 years so it is wrong to assume that all the patients would have progressed at 10 years. Also, some patients are coming to their 10th anniversary with olaparib without progressing.
Technical team scientific judgement after engagement	In the non-BRCA population, the ERG's approach (lognormal instead of generalised gamma distribution) is the most plausible because it is more aligned with TTD. In the BRCA 2L population, the company's approach (lognormal distribution) is the most plausible because it is more aligned with what was observed at 6 years in Study 19 trial.

Issue 7 – Subsequent therapy cost calculation

Background/description of issue	• There is a lack of clarity around the selection of subsequent therapies from ARIEL3 included in the cost calculation, as some therapies that are not commonly used in the UK such as cisplatin plus paclitaxel were costed while some therapies that are used in the UK such as radiotherapy and tamoxifen were excluded. • Given that Study 19 OS data is used in the model, it would be more appropriate to use the subsequent therapies received in Study 19. • Additionally, given that ARIEL3 OS data are highly immature, there will potentially be more subsequent therapies received, and the current cost estimate of subsequent therapies based on ARIEL3 is potentially underestimated. • In their ERG clarification question's response, the company provided a scenario including subsequent therapies from Study 19. However, the company didn't justify why some therapies received in Study 19 were omitted and why some therapies from ARIEL3 were carried over. • Therefore, the company's scenario results in a substantially reduced proportion of patients receiving subsequent therapies. A scenario including all subsequent therapies in Study 19 was ran by the ERG, which markedly impacts the ICER for the non-BRCA population. • The company assumed subsequent therapies were the same regardless of BRCA status and number of previous chemotherapy regimen received.
Why this issue is important	The subsequent therapy cost is a driver of the cost-effectiveness in the model when running deterministic sensitivity analyses, especially for the non-BRCA population.

Questions for engagement	1. Is the company's estimation of subsequent therapy costs based on selected treatments given in ARIEL3 appropriate and representative of clinical practice (see Appendix 1 – Subsequent therapy data? 2. The ERG re-estimated subsequent therapy costs based on all subsequent therapies given in Study 19. Is this more appropriate and representative of clinical practice (see Appendix 1 – Subsequent therapy data)? 3. Would subsequent therapies differ according to BRCAm status and number of previous chemotherapy regimens? 4. Are patients expected to receive more than one PARP inhibitor in their treatment pathway (e.g. patient who received rucaparib as 2L maintenance could receive olaparib as 3L maintenance)?
Technical team preliminary scientific judgement and rationale	Given that OS in the model is based on Study 19, it would be more appropriate to use subsequent therapies from the same study. Moreover, using subsequent therapies from ARIEL3 to calculate costs may underestimate subsequent therapy costs as ARIEL3 data are immature.
Summary of comments	Comments received from clinical experts: • The availability of treatments for progressed disease in the UK can be different from other parts of the world. Comment received from the ERG: • The ERG maintains that as OS is informed from Study 19, subsequent therapy usage and costs should be reflective of Study 19. Comments received from the company: • Deriving subsequent therapies that are reflective of clinical practice is challenging given the data available. The company tried to combine both the evidence from ARIEL3 and current UK clinical practice. • The company costed all therapies given as subsequent therapies in ARIEL3, if they are available in the UK. • Many patients received multiple therapies, so only a few patients who received exclusively non-NHS treatments were excluded from the calculation. • In the non-BRCA population, the original ICERs versus routine surveillance varied from £50,681 to £58,224 per QALY and remained unchanged in the ITT and BRCA 2L

	populations. The subsequent therapies costs impact the ICER in the non-BRCA population only.
Technical team scientific judgement after engagement	Given that OS in the model is based on Study 19, it would be more appropriate to use subsequent therapies from the same study. Moreover, using subsequent therapies from ARIEL3 to calculate costs may underestimate subsequent therapy costs as ARIEL3 data are immature.

Issue 8 – Cancer Drugs Fund

Background/description of issue	• At the data cut-off for the primary endpoint analysis of ARIEL3 (15 April 2017), OS data for rucaparib and routine surveillance were very immature 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 at this timepoint and there was not statistically significant difference between the treatment arms. • As a result, ARIEL3 OS data could not be used in the cost-effectiveness analysis. OS and PPS outcomes for olaparib from Study 19 were used instead, for which several assumptions have been made and introduced uncertainty in the analysis.
Why this issue is important	If rucaparib is not recommended for routine use, but the committee thinks that there is plausible potential for rucaparib to be cost effective the committee could recommend it for use in the Cancer Drugs Fund while additional data are collected that address the uncertainties in the evidence base.
Questions for engagement	1. Would additional data collection in the Cancer Drugs Fund reduce the uncertainty? 2. Is rucaparib a good candidate for use in the Cancer Drugs Fund?
Technical team preliminary scientific judgement and rationale	The main uncertainty is the long-term overall survival benefit of rucaparib compared with routine surveillance, for which additional data collection though ARIEL3 trial could address this uncertainty.
Summary of comments	Clinical experts commented that additional data collection within the CDF would provide real world data on outcome, length of treatment, dose reductions etc. It could if properly set up collect data on further lines of therapy, their timing and survival. The company reported that OS is not expected to be mature before [redacted] and that OS was the main uncertainty in the submission. The company believes rucaparib is a suitable candidate for use in the CDF.
Technical team scientific judgement after engagement	Rucaparib is a plausible candidate for the CDF if it is shown to have the plausible potential to be cost-effective.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the Technical Report comments table provided.

Table 1: Technical team favoured assumptions and impact on the cost-effectiveness estimate

Scenario	Incremental costs	Incremental QALYs	ICER
Company base case - ITT	[redacted]	[redacted]	**£36,319/QALY**
ERG's preferred assumptions - ITT			
ERG correction of minor errors	[redacted]	[redacted]	£37,832/QALY
PPS modelled as difference between Study 19 OS and ARIEL3 PFS	[redacted]	[redacted]	£43,898/QALY
Subsequent therapies from Study 19	[redacted]	[redacted]	£43,669/QALY
PFS off maintenance costs for routine surveillance	[redacted]	[redacted]	£44,787/QALY
Remove administration costs for oral therapies	[redacted]	[redacted]	£43,292/QALY
Extension of time horizon to 50 years	[redacted]	[redacted]	£41,103/QALY
Technical team's preferred assumptions- ITT*	[redacted]	[redacted]	**£42,175/QALY**
Company subgroup analysis - Non-BRCA	[redacted]	[redacted]	**£24,037/QALY**

Scenario	Incremental costs	Incremental QALYs	ICER
ERG's preferred assumptions – Non-BRCA			
ERG correction of minor errors	[redacted]	[redacted]	£25,157/QALY
Using the lognormal distribution for PFS for the non-BRCA population	[redacted]	[redacted]	£30,276/QALY
PPS modelled as difference between Study 19 OS and ARIEL3 PFS	[redacted]	[redacted]	£33,861/QALY
Subsequent therapies from Study 19	[redacted]	[redacted]	£42,708/QALY
PFS off maintenance costs for routine surveillance	[redacted]	[redacted]	£43,792/QALY
Remove administration costs for oral therapies	[redacted]	[redacted]	£42,373/QALY
Extension of time horizon to 50 years	[redacted]	[redacted]	£38,035/QALY
Technical team's preferred assumptions- Non-BRCA*	[redacted]	[redacted]	£41,288/QALY
Company subgroup analysis- BRCA 2L	[redacted]	[redacted]	£42,372/QALY
ERG's preferred assumptions – BRCA 2L			
ERG correction of minor errors	[redacted]	[redacted]	£42,957/QALY
Using the Weibull distribution for PFS for the non-BRCA population**	[redacted]	[redacted]	£38,836/QALY
PPS modelled as difference between Study 19 OS and ARIEL3 PFS	[redacted]	[redacted]	£44,479/QALY

Scenario	Incremental costs	Incremental QALYs	ICER
Subsequent therapies from Study 19	[redacted]	[redacted]	£45,494/QALY
PFS off maintenance costs for routine surveillance	[redacted]	[redacted]	£46,444/QALY
Remove administration costs for oral therapies	[redacted]	[redacted]	£44,926/QALY
Extension of time horizon to 50 years	[redacted]	[redacted]	£41,831/QALY
Technical team's preferred assumptions- BRCA 2L*	[redacted]	[redacted]	£56,994/QALY
Company subgroup analysis – BRCA 3L+	[redacted]	[redacted]	Rucaparib dominated
ERG's preferred assumptions – BRCA 3L+	**Total costs rucaparib**	**Total costs olaparib**	**Incremental costs**
ERG correction of minor errors	[redacted]	[redacted]	[redacted]
Remove administration costs for oral therapies	[redacted]	[redacted]	[redacted]

* Assumptions in italic were not included in the technical team's preferred assumptions because of modest impact on ICER

** lognormal distribution is technical team's preferred assumption as this was considered more clinically plausible than Weibull at technical engagement

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Immature evidence base	Median overall survival in ARIEL3 has not yet been reached. The analyses are based on overall survival data for olaparib from Study 19 which introduces uncertainty into the clinical and cost effectiveness evidence	Unknown
Subsequent use of PARP inhibitors in trials	Some patients in the placebo arm of ARIEL3 and Study 19 received subsequent therapy with PARP inhibitors outside the trial ([redacted]% in ARIEL3 and 13.5% in Study 19), which may have a confounding effect and bias the OS results in favour of the placebo group	The relative efficacy of PARP inhibitors compared to placebo may be underestimated because of subsequent PARP inhibitors received in the placebo group outside of the trial. However, the ERG believes that this could potentially provide a realistic estimate of PARP inhibitors efficacy compared to routine surveillance in clinical practice, given that olaparib is available through routine commissioning for patients with a BRCA mutation after 3 or more lines of platinum-based chemotherapy

Table 3: Other issues for information

Issue	Comments
Time horizon	The time horizon used in the company's base case is 30 years but for the ITT population, the extrapolation of the clinical outcomes for rucaparib results in a small proportion (~3%) of patients still alive at 30 years. For the non-BRCA and BRCA 2L populations provided in the clarification response, around 6% of patients are alive at 30 years. Therefore, the ERG considers that a 30-year time horizon might not be enough to capture all outcomes especially for younger patients of the rucaparib cohort, and that time horizon should be 50 years instead. This would allow OS to reach 0%. Increasing the time horizon has a modest impact on the ICER, reducing it by approximately £2000 in the ITT population.

Disease management costs for routine surveillance cohort in PFS	The company assumed that the disease management costs in the PFS health state were the same for rucaparib and routine surveillance cohorts, however clinical experts advising the ERG disagreed that disease management for patients receiving routine surveillance in PFS is the same as for patients receiving PARP inhibitors. The ERG's preferred assumption is to apply the off-maintenance management costs to patients receiving routine surveillance in PFS. A scenario where off-maintenance costs were applied to patients on routine surveillance in PFS for the ITT population was provided by the company at the clarification stage, this had a minor impact on the ICER.
Administration costs for oral treatments	The company included administration costs for oral treatments while the CSR of ARIEL3 states that 'rucaparib was self-administered by patients in an outpatient setting' and administration costs were not considered in previous appraisal for PARP inhibitors. The ERG's preferred assumption is to remove administration costs for oral treatments. This had a small impact on the ICER.
Niraparib as a comparator	During the clarification phase, the company included niraparib as a comparator for the subgroup analyses of the non-BRCA and BRCA 2L groups. However, niraparib is not a comparator as it is currently in the Cancer Drugs Fund. As a result, analyses including niraparib were not considered.
HRD cohort in ARIEL3	ARIEL3 trial included HRD (homologous recombination deficiency) status as a randomisation stratification factor. However, this cohort is of limited interest as genetic testing for HRD status is currently not routinely used in UK clinical practice.
End-of-life criteria	Rucaparib is not likely to meet the end-of-life criteria which are the following: The treatment provides an extension to life of more than an average of three months compared to current NHS treatment and; The treatment is indicated for patients with short life expectancy, normally a mean life expectancy of less than 24 months The company have not made a case for end of life.

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Appendix 1 – Subsequent therapy data

The selected treatments included in the subsequent therapy costs calculation in the company's base-case, the company's response to clarification questions and the ERG's preferred approach (Study 19) are reported in the table 4 below.

Table 4 Subsequent therapy data (from ERG report, page 80)

Subsequent therapy	Company's base-case (ARIEL3)		Company's response to CQ B6 (Study 19*)		Study 19* (ERG preferred assumption)	
	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 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)

