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 (Review of TA611) ID4069

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (Review of TA611) ID4069

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Pharmaad:
   a. Full submission
   b. Summary of Information for Patients (SIP)

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

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

4. **External Assessment Report** prepared by BMJ Technology Assessment Group

5. **External Assessment Group response to factual accuracy check of EAR**

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost comparison

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (Review of TA611) [ID4069]

Document B

Company evidence submission

pharma& confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

19 December 2023

File name	Version	Contains confidential information	Date
ID4069_pharma&_Rucaparib_Document B_19Dec2023_FINAL [redacted]	v1.0	Yes	19 December 2023

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Tables and figures

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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 well as the full population for the comparator, 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 relapsed, platinum-sensitive high-grade epithelial ovarian, fallopian tube or primary 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	-
Intervention	Rucaparib	Generic name: rucaparib Brand name: Rubraca®	-
Comparator(s)	At least 1 of the following treatments, according to NICE guidance: • Niraparib • Olaparib (only for people who have a BRCA mutation)	For people who have a BRCA mutation and have had 2 or more courses of platinum-based chemotherapy • Olaparib • Niraparib For people who do not have a BRCA mutation and have had 2 or more courses of platinum-based chemotherapy • Niraparib	-
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free 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	The outcome measures that will be considered include: • Overall survival • Progression-free survival • Progression-free survival 2 • Chemotherapy-free interval • Time to next line of therapy • Adverse effects of treatment • Health-related quality of life	-

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	This technology has been selected to be appraised as a cost-comparison The time horizon should be sufficient to reflect any differences in costs between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any commercial arrangements for the intervention and comparator technologies will be taken into account.	It is expected that rucaparib provides similar health benefits at similar or lower cost than technologies in the same therapeutic class previously recommended in published NICE technology appraisal guidance for this indication. Therefore, a cost comparison is proposed.	-
Subgroups to be considered	-	Patients with BRCA mutated and non-BRCA mutated disease are the only relevant subgroups for this submission and will be addressed in the pharmacoeconomic analysis	-
Special considerations including issues related to equity or equality	-	No equity or equality issues are anticipated for this submission	-

BRCA, BReast CAncer gene

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B.1.2 Description of the technology being evaluated

A summary description of rucaparib is provided in Table 2.

Table 2. Technology being evaluated[1]

UK approved name and brand name	Rucaparib (Rubraca®)
Mechanism of action	Rucaparib is an inhibitor of PARP enzymes, including PARP1, PARP2, and PARP3, which play a role in DNA repair. In vitro studies have shown that rucaparib-induced cytotoxicity involves inhibition of PARP enzymatic activity and the trapping of PARP-DNA complexes resulting in increased DNA damage, apoptosis, and cell death. Rucaparib has been shown to have in vitro and in vivo anti-tumour activity in BRCA mutant cell lines through a mechanism known as synthetic lethality, whereby the loss of two DNA repair pathways is required for cell death. Increased rucaparib-induced cytotoxicity and anti-tumour activity was observed in tumour cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Rucaparib has been shown to decrease tumour growth in mouse xenograft models of human cancer with or without deficiencies in BRCA.
Marketing authorisation/CE mark 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. On 19 June 2023 the marketing authorisation of rucaparib was transferred from Clovis Oncology Ireland Ltd. to pharmaand GmbH (pharma&).
Indications and any restriction(s) as described in the 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 600 mg (two 300 mg tablets) taken orally twice daily with or without food (1,200 mg total daily dose). Interruption of treatment or dose reduction (600 mg to 500 mg [two 250 mg tablets] to 400 mg [two 200 mg tablets] to 300 mg [one 300 mg tablet]) can be considered for AE management.
Additional tests or investigations	No additional tests or investigations are needed to prescribe rucaparib. For rucaparib, blood count testing is initiated prior to starting treatment, and monthly thereafter.
List price and average cost of a course of treatment	The list price for rucaparib is £3,562.00 per pack of 60, 300 mg, 250 mg or 200 mg tablets. The estimated average cost per year of rucaparib is £105,869 from list-price deterministic base case economic analysis, no time-preference discounting ([redacted] inclusive of a prospective [redacted] PAS[a] 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, subject to approval, is applicable to this appraisal.

AE, adverse event; BER, base excision repair; BRCA, breast cancer gene; CHMP, Committee for Medicinal Products for Human Use; DNA, deoxyribonucleic acid; EMA, European Medicines Agency; PARP, poly(ADP ribose) polymerase; PAS, patient access scheme; SmPC, summary of product characteristics.
Source: Rucaparib SmPC[1]
[a] Please note that a revised PAS discount was proposed to NICE in December 2023

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

B.1.3.1 Disease overview

B.1.3.1.1 Brief overview of disease

In 2021, 6,673 individuals were diagnosed with ovarian or fallopian tube cancer in England, of whom 60% were diagnosed with advanced disease (Stage III or IV), indicating an urgent need for treatment.[2] OC is most common in older postmenopausal women, with over 80% of patients in the UK being diagnosed at aged 50 years or older.[3]

There are different types of OC, of which epithelial OC (EOC) is the most common, accounting for approximately 90% of all cases of OC in the UK.[4,5] EOC can be further classified into different subtypes, of which serous is the most common (Table 3).[4,5]

Table 3. Summary of ovarian cancer subtypes[4,5]

Type of OC (proportion of OC diagnoses, UK)	Histologic subtypes
EOC (~90%)	• Serous carcinoma • Endometrioid carcinoma • Clear-cell carcinoma • Mucinous carcinoma • Undifferentiated or unclassified carcinoma
Fallopian tube cancer (unknown, rare)[*]	n/a
Primary peritoneal cancer (unknown, rare)[*]	n/a

EOC, epithelial ovarian cancer
[a] The incidence of primary peritoneal cancer and fallopian tube cancer are low in the UK; in the US it is estimated that primary peritoneal cancer accounts for 10% of OC cases.[6,7]

Similar to other cancer types, staging of OC assesses the size of the primary tumour and if the cancer cells have spread.[8] The International Federation of Gynecology and Obstetrics (FIGO) system is most commonly used to stage OC (Table 4).[8,9]

Table 4. FIGO Staging of Advanced OC (Stages I-IV)[9]

FIGO stage	Description
I	Tumour confined to ovaries or FTs
II	Tumour in 1 or both ovaries or FTs with pelvic extension (below pelvic brim) or peritoneal cancer
III	Tumour in 1 or both ovaries or FTs, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal LNs
IV	Distant metastasis excluding peritoneal metastases

FIGO, International Federation of Gynecology and Obstetrics; FT, fallopian tube; LN(s), lymph node(s); OC, ovarian cancer

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OC is graded on a scale of 1–3 according to the microscopic appearance of tumour cells relative to that of normal cells.[8] Tumour cells in low-grade (Grade 1) OC have a 'well-differentiated' appearance similar to that of normal cells, while tumour cells in high-grade OC look very different to normal cells and are described as 'moderately-differentiated' (Grade 2) or 'poorly-differentiated' (Grade 3).[8] High-grade tumours are more aggressive than low-grade tumours, and are more likely to grow and spread quickly.[8]

In England, 60% of patients with OC in 2021 had advanced stage disease at the time of diagnosis (Stage III or IV) indicating an urgent need for treatment.[2] The "Million Women Study", which recruited patients diagnosed with OC through National Health Service (NHS) screening in England and Scotland (1996–2001), found that 69.8% of patients had Stage III or IV disease at the time of their diagnosis and 83.1% of patients diagnosed with EOC subtypes had high-grade tumours (Grade 2+).[10]

The prognosis for advanced stage OC is poor.[11] Data for England (2016-2020) showed 5-year survival rates of patients with Stage III and Stage IV OC were 31.9% and 16.0%, respectively.[12] Results from 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 European Union 5 (36.2% in 2010–2014 compared to 43.5% for the same period in France).[13] Updated CONCORD data are imminent following an announcement in November 2023.[14] Moreover, the British Gynaecological Cancer Society have recently reported that: 5-year net survival rates across England range from 28.6% to 49.6%; and only 51% in England receive international standard of care treatment.[15] The same authors highlight that OC survival in the UK 'lags behind comparable countries'.[15]

B.1.3.1.2 Aetiology of OC

OC can affect people of any age but is most common in older postmenopausal women. Of the cases diagnosed in the UK, 81.2% are in people aged 50 years or older.[3] The majority of OC cases are sporadic, however increasing age, factors related to lifestyle and the environment (e.g., smoking, being overweight, exposure to asbestos), hormone replacement therapy and certain medical conditions (e.g., endometriosis, diabetes) have all been associated with elevated risk of OC development.[16]

OC can also be caused by inherited faulty genes.[16] Compared with people who have no family history, individuals who have a first degree relative with OC are at 2.7–3.5 times greater risk of developing the disease themselves.[17] This risk may be further increased if the

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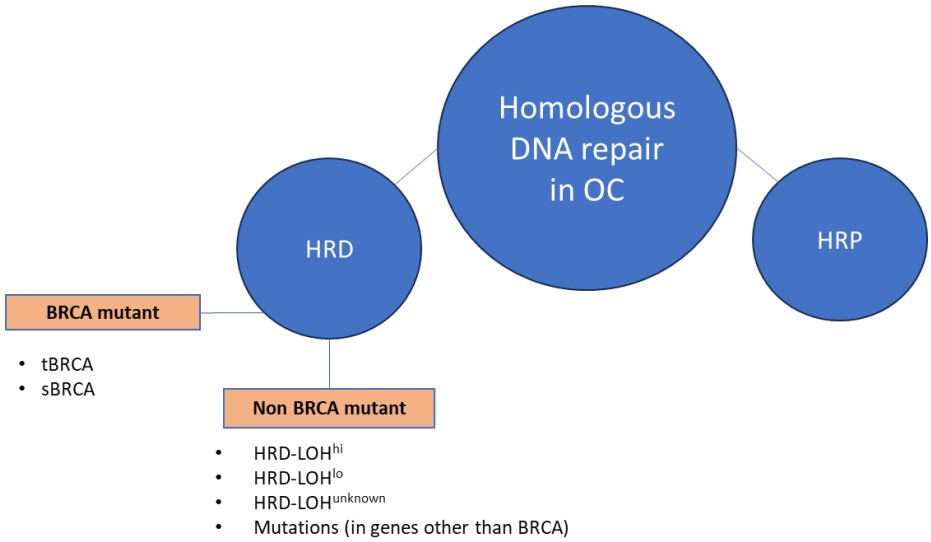
family relative was diagnosed at a younger age.[17] Inherited genes that increase the risk of OC include faulty versions of deoxyribonucleic acid (DNA) repair (or 'homologous recombination repair') genes; an analysis of The Cancer Genome Atlas estimated that approximately 50% of patients with high-grade serous OC have homologous recombination deficiency (HRD).[18] Specific drivers of HRD (summarised in Figure 1) 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[19,20]
- Somatic mutations in the BRCA1 or BRCA2 genes, estimated to account for between 6% and 8% of cases of high-grade serous OC[18,21]
- Mutation in a homologous recombination gene other than BRCA1 or BRCA2, estimated to account for approximately 16% of cases of high-grade serous OC[18]
- 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[18]

Figure 1. Drivers of homologous recombination repair deficiency in OC[a]



BRCA, breast cancer gene; DNA, deoxyribonucleic acid; HRD, homologous recombination deficiency; HRP, homologous recombination repair proficiency; LOH, loss of heterozygosity; OC, ovarian cancer; sBRCA, somatic cell BRCA mutation; tBRCA, tumour BRCA mutation
[a]tBRCA refers to somatic (tumour cell) *or* germline mutation in BRCA1/2 genes, while sBRCA refers exclusively to somatic (tumour cell) mutation of BRCA1/2 genes.

B.1.3.1.3 Symptoms of OC

People with OC may experience unpleasant or debilitating symptoms such as bloating, early satiety, loss of appetite, persistent pain in the abdomen or lower abdomen, increased need

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to urinate, changes in bowel habits, symptoms of irritable bowel syndrome (IBS), unexplained fatigue and unexplained weight loss.[22]

In the UK, National Institute of Health and Care Excellence (NICE) Clinical Guideline 122 states women who experience symptoms of IBS for the first time at age ≥50 years should receive appropriate testing for OC.[23] Investigation into the possibility of OC is also triggered if the following symptoms are experienced relatively frequently (particularly 12 or more times per month and especially in women aged ≥50 years):[23]

- Persistent abdominal distension
- Early satiety
- Pelvic or abdominal pain
- Increased urinary urgency and/or frequency

Changes in global health, physical and physiological functioning, symptoms (including fatigue, pain and appetite loss) and health-related quality of life (HRQoL) can be further exacerbated in patients with disease progression following initial response to treatment.[24] Moreover, side effects of chemotherapy have a significant negative impact on HRQL.[25,26] 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.[27] 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.[26]

Target Ovarian Cancer is working to raise awareness of the symptoms of OC, and campaigning for diagnostic pathways to be shortened in the UK to allow diagnosis of OC at an earlier stage, increasing the chance of survival.[28]

B.1.3.2 Clinical pathway of care for advanced OC

Primary debulking surgery (before chemotherapy or after neoadjuvant chemotherapy) is recommended by the current NICE and European Society for Medical Oncology (ESMO) guidelines for patients with advanced OC (Figure 2); the aim of primary surgery is complete resection of all macroscopic disease.[23,29]

First-line (1L) chemotherapy with a platinum-based compound (cisplatin or carboplatin) with or without paclitaxel is considered standard of care in the UK for patients with advanced OC.[29-31] Treatment objectives following 1L chemotherapy include complete response (CR,

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defined as ‘malignant disease not detectable for ≥4 weeks’) and a partial response (PR, defined as ‘tumour size reduced by at least 50% for >4 weeks’).[31] However, responses to platinum-based therapy are often short-lived in the absence of maintenance therapy, with up to 75% of patients relapsing within 2 years of initial response.[31] A retrospective study conducted in the UK determined the rate of relapse among 354 patients with OC after 1L surgery and chemotherapy was 71% over >5 years.[32] The risk of relapse is higher in patients with a suboptimal response to initial treatment; it is estimated that 60–70% of patients with residual disease <1cm and 80–85% of patients with large-volume residual disease experience recurrence.[33]

B.1.3.3 Pathway of care for relapsed platinum-sensitive advanced OC

In the relapsed setting, NICE and ESMO guidelines recommend platinum-rechallenge for those patients most likely to benefit (Figure 2).[29-31] Specifically, patients with relapsed OC should receive platinum-based chemotherapy if they are able to tolerate the treatment, have no contraindications to platinum and showed prior response to platinum-based chemotherapy (i.e. no progression during or shortly after treatment).[30] Patients who respond to platinum rechallenge with a platinum-based doublet should then receive maintenance treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor provided they have not been previously exposed to PARP inhibitors.(see Section B.1.3.4).[30]

For patients with platinum-sensitive advanced OC who experience multiple relapses, the duration of response and length of the platinum treatment-free interval between rounds of platinum-based chemotherapy usually becomes progressively shorter;[31,34] the eventual emergence of platinum resistance occurs in almost all patients with relapsed OC.[29,34] Platinum-resistance is defined as ‘progression during platinum therapy’ or ‘early symptomatic progression post-platinum, with response to challenge unlikely’.[30] Patients for whom further platinum-based therapy is not an option may be treated with single agent paclitaxel, topotecan, gemcitabine, pegylated liposomal doxorubicin hydrochloride (PLDH) or oral metronomic cyclophosphamide.[30] Trabectedin-PLDH is an option if the treatment-free interval since last platinum exceeds 6 months.[30] Paclitaxel, PLD or topotecan may be given in combination with bevacizumab if not previously received and not contraindicated.[30] Despite these options, patients with platinum-resistant OC have an extremely poor prognosis, with an estimated progression-free survival (PFS) ranging from 3 to 4 months and overall survival (OS) of only 12 months when treated with non-platinum-based chemotherapy.[34]

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B.1.3.4 The importance of maintenance therapies

Maintenance therapies can prolong PFS and chemotherapy-free interval (CFI), thereby delaying subsequent chemotherapy in patients with platinum-sensitive advanced OC (see ARIEL3 outcomes for rucaparib in Section B.3.6).[35,36] ESMO guidelines recommend olaparib, niraparib and rucaparib as maintenance therapies for patients who respond to platinum rechallenge, regardless of BRCA mutation or HRD status.[30] ESMO recommendations are in-line with the clinical pathway of care for platinum-sensitive advanced OC in the UK, with the exception that olaparib is restricted to patients with a BRCA mutation (Figure 2).

Olaparib, niraparib and rucaparib are currently available through NHS England for maintenance therapy in patients with platinum-sensitive advanced OC (Figure 2).[37-42] Specifically:

- Olaparib is recommended for the maintenance treatment of advanced OC if patients have responded to platinum-based chemotherapy, have a BRCA mutation AND have received ≥2 courses of platinum-based chemotherapy.[40]
- Niraparib is recommended for the maintenance treatment of advanced OC if patients have responded to platinum-based chemotherapy, have a BRCA mutation AND have received 2 courses of platinum-based chemotherapy OR do not have a BRCA mutation AND have received ≥2 courses of platinum-based chemotherapy.[41]
- Rucaparib is recommended as an option for maintenance treatment of relapsed platinum-sensitive advanced OC within the Cancer Drugs Fund (CDF).[42]
- In the 1L setting, olaparib and niraparib are also available through the CDF for maintenance therapy after response to 1L platinum-based chemotherapy.[37-39]

On 15 November 2023, the European Medicines Agency approved an extension of the rucaparib product label to include an indication for first-line maintenance treatment in advanced OC.[43]

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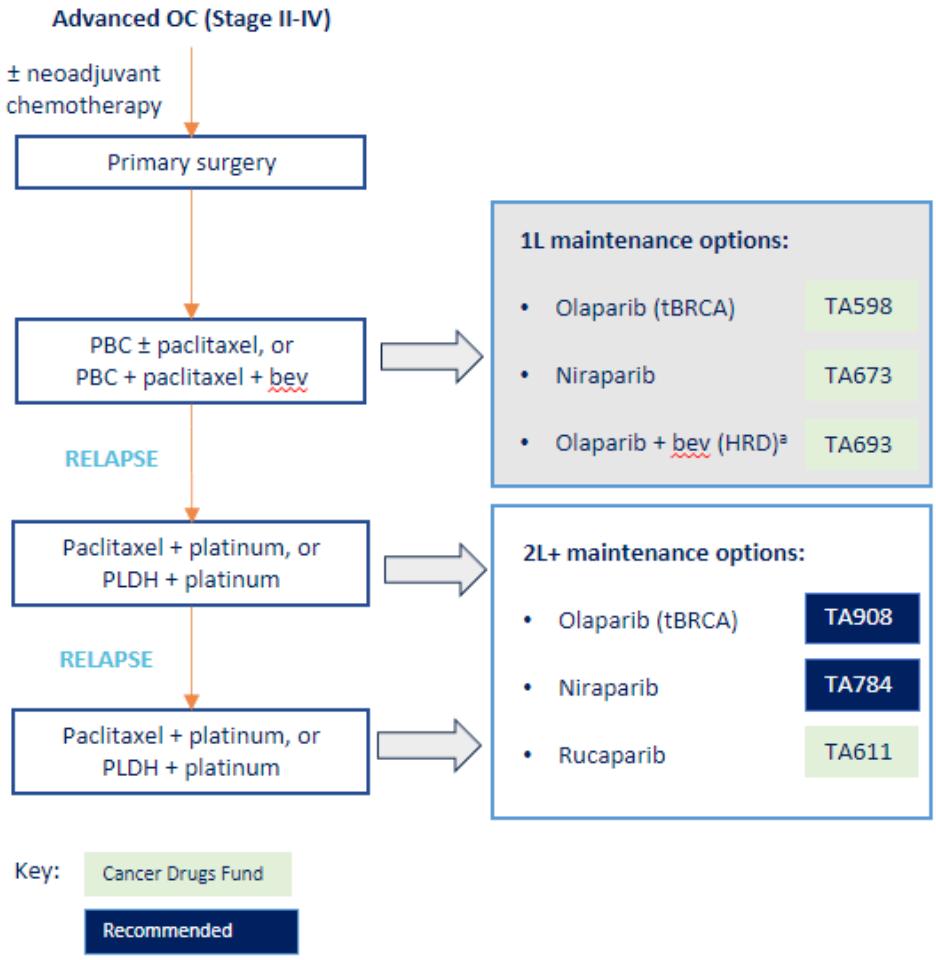
Figure 2. Clinical pathway of care for platinum-sensitive advanced OC and options for maintenance therapy in NHS England



2L+, second or later-line; bev, bevalizumab; OC, ovarian cancer; PBC, platinum-based chemotherapy; PLDH, pegylated liposomal doxorubicin hydrochloride; STA, single-technology appraisals; tBRCA, tumour with BRCA mutation

Recommendations for maintenance therapy based on the following NICE STAs TA55[31], TA389[44], TA908[40] TA784[41] and TA611[42]

B.1.3.5 Unmet medical need

Advanced OC is an aggressive disease with a poor prognosis, particularly for patients in the UK where survival expectations are low.[15] Despite 70%-80% of patients responding to 1L platinum-based chemotherapy, 71% of patients will relapse ≥5 years after initial chemotherapy in the absence of maintenance therapy.[31,32] In particular, the risk of relapse is greater for patients with a suboptimal response to initial treatment.[33] While patients often benefit from further platinum-based chemotherapy, responses shorten with each relapse and most patients eventually develop platinum resistance.[31,34] Patients with platinum-resistant OC have limited treatment options and are not expected to survive beyond 12 months.[34]

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Maintenance therapies can extend the treatment response, prolong PFS and CFI and potentially increase the subsequent response to further platinum-based chemotherapy.[34-36] Maintenance therapy also extends other clinical outcomes such as PFS2, time to first subsequent anticancer treatment (TFST) and time to second subsequent anticancer treatment (TSST) (see ARIEL3 outcomes for rucaparib in Section B.3.6). ESMO guidelines state that PARP inhibitor therapies offer a non-platinum maintenance treatment option in the setting of platinum-sensitive relapsed OC, with demonstrated efficacy in patients with and without BRCA mutation.[29,30,36,40,41]

As currently recommended by ESMO, maintenance therapy with a PARP inhibitor should be given to patients with platinum-sensitive relapsed OC, provided they have no prior exposure to a PARP inhibitor.[30] In NHS England, the maintenance treatments available through routine commissioning and funding in the 2L+ setting (and therefore considered as relevant comparators in accordance with NICE criteria) are olaparib (TA908) and niraparib (TA784).[40,41] The use of olaparib is limited to patients with BRCA mutations, while niraparib is18ecommendded for the treatment of patients with BRCA mutation (if they have received 2 courses of platinum-base chemotherapy) and without BRCA mutation (if they have had ≥2 courses of platinum-based chemotherapy).[40,41] Moreover, the EMA indication for niraparib in relapsed OC is restricted to high-grade serous histology, while the rucaparib and olaparib labels have no histology restrictions.[1,45,46] Key differences between rucaparib, olaparib and niraparib are summarised in Table 5.

Rucaparib offers a maintenance therapy for patients with relapsed OC with favourable efficacy outcomes among all molecular subgroups as well as versatile drug performance in pivotal trials regardless of biomarker status (Section B.3.6).[35,36] It also has manageable tolerability and safety profile that differs from the safety profile of other PARP inhibitor maintenance treatments (Section B.3.10).[1,45,46] In case of adverse events (Aes) during treatment, a flexible 3-step dose-reduction can be applied, whereby a two week pack size allows for flexible dosing adaptation.[1] Due to the consistent and manageable safety profile of rucaparib,[35] no starting dose adjustment is required for elderly patients (≥ 65 years of age) or for patients with mild or moderate hepatic or renal impairment.[1]

Moreover, potentially burdensome weekly blood counts are not required for patients treated with rucaparib.[1] Complete blood counts are monitored weekly during the first month of treatment with niraparib, and blood pressure is monitored weekly for the first two months.[45] Complete blood counts and blood pressure are then monitored monthly for the next 10 months and 12 months of treatment, respectively, and periodically after this period.[45]

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Within the current treatment pathway, rucaparib would provide an individual PARP inhibitor maintenance option independent of biomarker status and an individual profile which differs to those of other PARP inhibitors, thereby allowing clinicians to focus on a patient specific maintenance therapy and select the most suitable PARP inhibitor.[1,47,48] Rucaparib addresses an unmet medical need in current clinical practice, and could further advance the incorporation of PARP inhibitor maintenance treatment within the standard of care for people with platinum-sensitive relapsed OC.

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Table 5. Key SmPC differences between rucaparib, olaparib and niraparib as maintenance therapies in the 2L+ setting

	Rucaparib – film-coated tablets[1]	Olaparib – film-coated tablets[46]	Niraparib – hard capsules[49]	Key differences
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 advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy • 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 in combination with bevacizumab is indicated for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based	Zejula is indicated as monotherapy for the: • maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy • maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy	• Rucaparib is currently indicated for patients with relapsed OC only while niraparib and olaparib are indicated in the 1L setting as well as the relapsed setting • The niraparib indication for patients with relapsed epithelial OC is restricted to those with serous pathology while indications for rucaparib and olaparib do not specify pathological subtypes of epithelial OC • Olaparib is also indicated in combination with bevacizumab while niraparib and rucaparib are indicated as monotherapy only

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	Rucaparib – film-coated tablets[1]	Olaparib – film-coated tablets[46]	Niraparib – hard capsules[49]	Key differences
		chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status defined by either a BRCA1/2 mutation and/or genomic instability.		
NICE recommendations	Not applicable.	Olaparib is recommended as an option for the maintenance treatment of relapsed, platinum-sensitive, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer in adults whose cancer has responded to platinum-based chemotherapy, only if[40]: • They have a BRCA1 or BRCA2 mutation • They have had 2 or more courses of platinum-based chemotherapy	Niraparib is recommended as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults, only if[41]: • They have a BRCA mutation and have had 2 courses of platinum-based chemotherapy, or • They do not have a BRCA mutation and have had 2 or more courses of platinum-based chemotherapy	• Olaparib is only recommended for patients with BRCA1/2 mutation • Niraparib is recommended in patients with and without BRCA mutation • We do not anticipate any restrictions to rucaparib based on BRCA mutation status
Dosing and administration	600 mg (two 300 mg film-coated tablets) taken orally twice daily with or without food. Doses should be taken 12 hours apart.	300 mg (two 150 mg tablets) taken orally twice daily without regard to meals	300 mg (three 100 mg hard capsules) taken orally one daily without regard to meals. The dose should be taken at approximately the same time each day. Bedtime administration may be a potential method for managing nausea.	Minimal differences in dosing and administration are noted.
Monitoring requirements	This medicinal product is subject to additional monitoring. Patients with moderate hepatic impairment should be carefully	Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to	Testing complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after	• Rucaparib is subject to additional monitoring • Olaparib and niraparib both require monthly monitoring

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	Rucaparib – film-coated tablets[1]	Olaparib – film-coated tablets[46]	Niraparib – hard capsules[49]	Key differences
	monitored for hepatic function and adverse reactions. Patients with moderate or severe renal impairment should be carefully monitored for renal function and adverse reactions.	monitor for clinically significant changes in haematological toxicity during treatment. Patients should be monitored for clinical signs and symptoms of venous thrombosis and pulmonary embolism.	this time is recommended to monitor for clinically significant changes in any haematologic parameter during treatment. Blood pressure should be monitored at least weekly for two months, monitored monthly afterwards for the first 12 months and periodically thereafter during treatment. Patients with moderate hepatic impairment and should be carefully monitored.	of complete blood counts during the first 10-12 months of treatment. In the case of niraparib, blood counts are monitored weekly during the first month • Niraparib requires regular monitoring of blood pressure during the first 12 months of treatment
Special warnings and precautions for use	<u>Haematological toxicity</u> During treatment with rucaparib, events of myelosuppression may be observed. <u>MDS/AML</u> MDS/AML, including cases with fatal outcomes, have been reported. <u>Photosensitivity</u> Photosensitivity has been observed. <u>Gastrointestinal toxicities</u> Gastrointestinal toxicities are frequently reported with rucaparib but are generally low grade. <u>Intestinal obstruction</u> Cases of intestinal obstruction have been observed in clinical trials. <u>Embryofoetal toxicity</u>	<u>Haematological toxicity</u> Cases of mild or moderate anaemia, neutropenia, thrombocytopenia and lymphopenia have been reported. <u>MDS/AML</u> MDS/AML have been reported in a small number of patients; the majority of cases were fatal. <u>Venous thromboembolic events</u> Venous thromboembolic events, predominantly events of pulmonary embolism, have occurred. <u>Pneumonitis</u> Pneumonitis has been reported in a patients receiving olaparib, with some cases having been fatal. <u>Embryofoetal toxicity</u>	<u>Haematological toxicity</u> Cases of thrombocytopenia, anaemia and neutropenia have been reported. <u>MDS/AML</u> Cases of MDS/AML, including cases with fatal outcomes, have been reported. <u>Hypertension/hypertensive crisis</u> Cases of hypertension and hypertensive crisis have been reported. <u>PRES</u> Cases of PRES have been reported. <u>Pregnancy/contraception</u> Niraparib should not be used during pregnancy or in women of childbearing potential who are	• Special warnings that appear only the rucaparib label: photosensitivity, gastrointestinal toxicities and intestinal obstruction • Special warnings that appear only on the olaparib label: venous thromboembolic events and pneumonitis • Special warnings that appear only on the niraparib label: hypertension/hypertensive crisis, PRES, hepatic impairment, lactose, tartrazine

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	Rucaparib – film-coated tablets[1]	Olaparib – film-coated tablets[46]	Niraparib – hard capsules[49]	Key differences
	Rucaparib can cause foetal harm when administered to a pregnant woman. Pregnancy/contraception Pregnant women should be informed of the potential risk and are advised to use effective contraception during treatment and for 6 months following the last dose of rucaparib.	Olaparib can cause foetal harm when administered to a pregnant woman. Pregnancy/contraception Olaparib should not be used during pregnancy or in women of childbearing potential who are not using reliable contraception.	not using highly effective contraception. Hepatic impairment Hepatic impairment may increase niraparib exposure. Lactose Niraparib should not be taken by patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption. Tartrazine Tartrazine in niraparib hard capsules may cause an allergic reaction.	

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	Rucaparib – film-coated tablets[1]	Olaparib – film-coated tablets[46]	Niraparib – hard capsules[49]	Key differences
Interaction with other medicinal products	**Caution** should be used for concomitant use of: • Strong CYP3A4 inhibitors or inducers; • Strong P-gp inhibitors • Warfarin • CYP3A substrates with a narrow therapeutic index • Metformin • UGT1A1 substrates (i.e. irinotecan) in patients with UGT1A1*28 (poor metaboliser) **Dose adjustments** may be considered when co-administering: • CYP1A2 substrates • CYP2C9 substrates (e.g., warfarin and phenytoin) • CYP3A substrates	The recommended (monotherapy) dose of olaparib is not suitable for combination with myelosuppressive anticancer medicinal products. **Caution** should be used for concomitant use of: • CYP3A substrates • Statins • Vaccines or immunosuppressant agents **Appropriate clinical monitoring** is recommended when co-administering: • CYP3A substrates • P-gp substrates **Dose adjustments** are required when co-administering: • Moderate to strong CYP3A inhibitors Concomitant use of the following is **not recommended**: • Moderate to strong CYP3A inducers • Moderate to strong CYP3A inhibitors	**Caution** should be used for concomitant use of: • Vaccines, immunosuppressant agents or other cytotoxic medicinal products • Substrates of CYP3A4 • Substrates of CYP1A2 • Substrates of BCRP • Substances that underdo an uptake transport by OCT1	• Patients receiving olaparib in combination with CYP3A and P-gp substrates may require additional clinical monitoring • There are strong recommendations on concomitant use of olaparib with moderate to strong CYP3A inducers (do not use olaparib) and strong CYP3A inhibitors (olaparib dose adjustment is required) • Caution is recommended when co-administering either olaparib or niraparib with any myelosuppressive or cytotoxic medicinal products • There is no recommendation on the generalised avoidance of myelosuppressive or cytotoxic medicinal products for rucaparib; however caution when co-administering rucaparib with the cytotoxic agent irinotecan is specified

1L, first-line; AML, acute myeloid leukaemia; BRCA, breast cancer gene; CR, complete response; CYP, cytochrome P450; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; HRD, homologous recombination deficiency; MDS, myelodysplastic syndrome; OC, ovarian cancer; OCT1, organic cation transporter 1; P-gp, p-glycoprotein; PR, partial response; PRES, posterior reversible encephalopathy syndrome; SmPC, summary of product characteristics; UGT1A1, UDP-glucuronosyltransferase 1A1
Source: Niraparib SmPC[45]; Olaparib SmPC[46]; Rucaparib SmPC[1].

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B.1.4 Equality consideration

Not applicable.

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B.2 Key drivers of the cost effectiveness of the comparators

B.2.1 Clinical outcomes and measures

The comparators for rucaparib in this appraisal are the PARP inhibitors olaparib and niraparib, which are also licensed in this indication. Both therapies have been previously evaluated by NICE and recommended for patients in this setting as part of appraisals TA908 (managed access review of TA620) and TA784 (managed access review of TA528), respectively (Table 6, see Section B.1.3.4).

Three key measures of clinical effectiveness in the economic modelling of the TA908 and TA784 submissions were OS, PFS and time-to-treatment discontinuation (TTD). These outcomes were drivers of cost-effectiveness in both submissions (Table 7). Other clinical measures included in the appraisals were AEs and utilities.

Table 6. Summary of comparator trials and appraisals

Comparator	Appraisal	Pivotal study and population	Source
Olaparib	TA908	SOLO2 (N=295): Randomised (2:1), double-blind study comparing olaparib with placebo after platinum-based chemotherapy in people with a BRCA mutation	Pujade-Lauraine et al., 2017[50]
Niraparib	TA784	NOVA (N=553): Randomised (2:1) double-blind, placebo-controlled trial in patients with relapsed, platinum-sensitive ovarian cancer, with and without a BRCA mutation	Mirza et al., 2016[51]

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Table 7. Clinical outcomes and measures appraised in published NICE guidance for the comparators[40,5042,49]

Appraisal	Outcome	Measurement scale	Used in cost-effectiveness model?	Committee's comments
NICE TA908 Olaparib (SOLO2)[40,50]	PFS	Time to event in months • INV-PFS (according to modified RECIST v1.1); radiologic scans performed at baseline then every ~12 weeks up to 72 weeks, then every ~ 24 weeks thereafter until objective radiological disease progression • IRR	Yes	Concluded that olaparib extends PFS compared with placebo
	OS	Survival assessed every 4 weeks until treatment discontinued, then every 12 weeks. Assessed up to a maximum of 75 months	Yes	Noted that the OS data from SOLO2 was mature, and more relevant. Concluded that olaparib extends OS compared with placebo. To reflect the pathway at CDF entry, unadjusted OS data for the placebo arm was preferred. CDF lead said that PARP inhibitors have the same MoA, so they could be expected to have similar efficacy and tolerability to olaparib
	TTD	Further details not reported	Yes	The committee did not discuss this
	HRQoL	Further details not reported	No	The committee did not discuss this
	AEs	Graded according to CTCAE v4	Yes	The committee did not discuss this, but the EAG updated the company model with AE data from the final data cut
NICE TA784 Niraparib (NOVA)[41,51]	PFS	Time between randomisation and disease progression or death from any cause • CT or MRI to assess disease progression was performed at baseline, every 8 weeks through cycle 14, and then every 12 weeks until treatment discontinuation. The objective assessment of disease progression was determined by means of central radiologic and clinical review, according to RECIST v1.1, which was performed in a blinded fashion. PD is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study	Yes	Noted that PFS results differed by assessment: • The committee was aware that the company model used PFS results assessed by IRC. • The committee noted that any difference in benefit accrued could have a significant impact on the cost-effectiveness results because time on treatment (and so the related cost) was IA, the preferred assumption from the original appraisal of niraparib • Noted niraparib increased PFS vs placebo in both treatment groups using INV-PFS or IRR-PFS

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Appraisal	Outcome	Measurement scale	Used in cost-effectiveness model?	Committee's comments
	OS	From treatment randomisation to date of death by any cause, up to 7 years, 7 months and 4 days	Yes	Noted that NOVA was not powered to test for statistical significance for OS Moreover, placebo OS results were confounded by missing data and subsequent PARP use Concluded that niraparib may improve OS for people with a BRCA mutation but survival benefit with niraparib for people without a BRCA mutation is uncertain Concluded that OS data from the SACT database is less useful for decision making than updated survival data from NOVA
	TTD	Further details not reported	Yes	Concluded that the company's estimation of TTD from the NOVA trial was more reflective of clinical practice than the ERGs preferred based case of TTD=PFS and therefore the most appropriate. SACT TTD data were used in a scenario
	HRQoL	HRQoL data from EQ-5D-3L was used to map treatment-specific utility values from NOVA	Yes	Clinical expert and CDF lead noted that utilities may improve on niraparib as it may improve clinical response for people with partial response to treatment Committee noted that progression-based utility values increased cost-effectiveness estimates but concluded that treatment-specific utility values are appropriate for decision making
	AEs	Graded according to CTCAE v4.02	No	The committee did not discuss this

AEs, adverse events; CDF = cancer drug fund; CT, Computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; EQ-5D-3L, EuroQoL five-dimension three-levels; HRQoL, health-related quality of life; INV-PFS, investigator-assessed progression-free survival; IRR, independent radiology review; MRI, magnetic resonance imaging; NICE, National Institute of Health and Care Excellence; OS, overall survival; PARP, Poly (ADP-ribose) polymerase; PD, progressive disease; PFS, Progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumours; SACT, Systemic Anti-Cancer Therapies; TTD, time to treatment discontinuation

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B.2.2 Resource use assumptions

As both TA784 and TA908 are managed access reviews, there is limited information provided in the committee papers on costs and resource use (Table 8). We have assumed that resource use and cost items included remained unchanged; however, it is likely unit costs were updated to the most recent values. For TA908, the original information from TA620 has been removed from the NICE website and so limited information were available. For TA784, the original data from TA528 are still available on the NICE website. Resource use considered in the relevant NICE appraisals include:

- Drug acquisition
- Treatment administration
- Health state related resource use and cost
- Subsequent treatment costs
- Adverse event costs

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Table 8. Resource use items for comparators in NICE scope[40,41,45,52]

Comparator evaluation	Key resource costs associated with comparator(s)	Committee's preferred assumptions in NICE evaluation of comparator(s)	Uncertainties
Niraparib as maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer that has responded to platinum-based chemotherapy (CDF review of TA528)[41]	• Drug acquisition costs for 56 x 100mg capsules and 84 x 100mg capsules of niraparib at a starting dose of 300 titrated to 200 mg daily (if required, or to manage AEs). For olaparib costs for 448 x 58mg capsules with mean daily dose taken from Study 19 as reported in TA381.[52] Wastage was applied to both niraparib and olaparib. • No oral initiation cost was included. • Adverse event resource use and costs were included for nausea, thrombocytopenia, fatigue, anaemia, vomiting, neutropenia, and hypertension. • PFD health state and treatment were specific to the cycle of treatment (by cycle 1, cycle 2-14 and cycle 15+). • A single PD health state resource use is applied to all comparators. Health state resource use includes CT scan, blood monitoring and outpatient visit with consultant oncologist. • Monitoring resources use olaparib NICE TA381[52], the draft niraparib SmPC[45] and expert clinical opinion. • Subsequent treatment acquisition and administration costs were applied in PD health state. Subsequent treatment regimens reports in >3% of patients in NOVA trial and used in UK clinical practice were used for niraparib and RS, and from STUDY 19 for olaparib • Source for unit costs for NHS reference costs • Source for drug costs BNF	Company amended mean cost for niraparib based on updated dose data from 2020 NOVA data-cut and updated dose data based on actual dose consumed (dispensed dose minus returned dose per cycle). ERG prefer to use prescribed dose, however the clinical expert explained that clinicians favour starting treatment with a lower 200 mg daily dose of niraparib as it is associated with reduced toxicity and treatment stopping rates. The company explained that the NORA clinical trial which used lower doses showed equal efficacy to the NOVA study and results are therefore expected to be sustained and similar to the 300 mg daily higher dose in clinical practice. The committee concluded that actual dose data for niraparib from NOVA is appropriate to use in the economic model.	Appropriate dosing of niraparib to apply in analysis

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Comparator evaluation	Key resource costs associated with comparator(s)	Committee's preferred assumptions in NICE evaluation of comparator(s)	Uncertainties
Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer after 2 courses of platinum based chemotherapy CDF exit review of TA620 – ACM2[40]	• Drug acquisition costs • Administration costs • BRCA testing costs. Testing cost per patient was calculated as number tested per patient treated with cost of genetic testing derived from TA381.[52] • Health state and treatment specific monitoring resource use includes CT scan, blood monitoring and consultation (office visit) • Adverse event costs for anaemia, neutropenia, abdominal pain and fatigue • End of life care resource use and costs assuming 51.28% of patients will receive end-of-life care. • Unit costs for NHS reference costs	No comments were made on resource use	N/A

AE, adverse event; BNF, British National Formulary; BRCA, BReast CAncer gene; CT, computerised tomography; ERG, Evidence Review Group; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; PD, progressive disease; PFD, progression-free disease; RS, routine surveillance; SmPC, Summary of Product Characteristics; UK, United Kingdom

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B.3 Clinical effectiveness

B.3.1 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.3.2 List of relevant clinical effectiveness evidence

The pivotal regulatory evidence to support rucaparib, and the focus of this submission, is the randomised, double-blind, placebo-controlled, phase III ARIEL3 study.[35] This study was completed on 7 July 2022 with a final visit data cut of 4 April 2022 and reports direct data for the comparison of rucaparib with routine surveillance (represented by placebo).[53,54]

A summary of ARIEL3 is presented in Table 9,[55] with further details of its design provided in Section B.3.3.

Details of additional studies relevant to this appraisal are provided in Appendix D. The publications for these additional studies report clinical evidence for active comparator technologies (olaparib and niraparib), which were used to inform indirect treatment comparison (ITC) estimates presented in Section B.3.9.

Table 9. Clinical effectiveness evidence[55]

Study	**ARIEL3; NCT01968213**				
Study design	ARIEL3 is a randomised, international, double-blind, placebo-controlled, multicentre, phase III study that evaluated rucaparib vs. placebo as maintenance therapy in relapsed, platinum-sensitive ovarian carcinoma.				
Population	Adult patients with platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, who had received at least two previous platinum-based chemotherapy regimens and had achieved CR or PR 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	• PFS • OS • PFS2 • CFI • TFST • AEs of treatment				

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Study	ARIEL3; NCT01968213
	• HRQoL
All other reported outcomes	• FOSI-18 • TSST • QA-PFS and Q-TWiST • Response in patients with measurable disease • CA-125

AE, adverse event; CA-125, cancer antigen 125; CFI, chemotherapy-free interval; CR, complete response; EQ-5D VAS, EuroQol 5 dimensions visual analogue scale; FOSI-18, Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18; HRQoL, health-related quality of life; OS, overall survival; PFS(2), progression-free survival (2); PR, partial response; QA-PFS, quality-adjusted progression-free survival; Q-TWiST, quality-adjusted time without symptoms or toxicity; TFST, time to start of first subsequent anticancer treatment/time to next line of therapy; TSST, time to start of second subsequent anticancer treatment
Source: ARIEL3 CSR[55]

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 ARIEL3 study

Further details of the methodology of the ARIEL3 study are presented in Table 11.[35,55]

B.3.3.1.1 Trial design

The ARIEL3 study comprised 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.[55] ARIEL3 was completed on 7 July 2022 with a final visit data cut of 4 April.[54,56]

Upon formal closure of the study, individual patients who continued to benefit from treatment with rucaparib, and who did not meet any of the criteria for withdrawal, had the option to enter an open-label extension protocol and continue to receive rucaparib.[55]

B.3.3.1.2 Randomisation

Eligible patients (N=564) were randomised in a 2:1 ratio to receive oral rucaparib (n=375; 600mg twice daily) or matching placebo (n=189). A minimum of 180 and a maximum of 200 patients with a deleterious tumour BRCA mutation were to be enrolled. Enrolment of patients with a known deleterious germline BRCA mutation documented in their medical record was not to exceed 150. There was no minimum number of patients required for each of the non-BRCA HRD and biomarker negative subgroups. However, no more than 360 total patients were to be randomized for stratification into these subgroups combined. Randomisation was carried out within 8 weeks of completing a course of platinum-based chemotherapy and was

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conducted through a central randomisation procedure using Interactive Voice Response System/Interactive Web Response System. To ensure that treatment groups were balanced, the criteria in Table 10 were included as randomisation stratification factors.[55]

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[55]:

- 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

In the final patient population, 196 (34.8%) of patients had BRCA mutations and 130 (23.0%) patients had germline BRCA mutations. Baseline patient characteristics are presented in Table 13.[55]

Table 10. Randomisation stratification factors for ARIEL3[55]

Randomisation stratification factor	Categories

HRD classification by the CTA, developed by FMI, which identifies mutations in 30 genes involved in HRD through analysis of tumour tissue	• 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 CA-125 was in the ULN	• CR, defined as complete radiological response by RECIST v1.1 • PR, defined as PR by RECIST v1.1 and/or a GCIG CA-125 response.

BRCA, BReast CAncer gene; CA-125, cancer antigen 125; CR = complete response; CTA, clinical trial assay; FMI, Foundation Medicine, Incorporated; GCIG, Gynaecologic Cancer Group; HRD, homologous recombination deficiency; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal
Source: ARIEL3 CSR[55]

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Table 11. Summary of methodology of ARIEL3[35,55]

Trial number (acronym)	NCT01968213 (ARIEL3)
Location	This global study was 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 a randomised, double-blind, placebo-controlled, multicentre, phase III study, that evaluated the efficacy and safety of rucaparib vs. 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 2L or later platinum-based chemotherapy. This study was completed on 7 July 2022 with a final visit data cut of 4 April.[54,56]
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 o For mixed histology, >50% of the primary tumour must be confirmed to be high-grade serous or endometrioid o 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) o 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 o 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 o If both neoadjuvant and adjuvant treatment were administered pre/post any debulking surgery, this was considered one treatment regimen o 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 o 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 o 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 o 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*. o 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 o CA-125 must also have been <ULN for all responses classified as a PR

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Trial number (acronym)	NCT01968213 (ARIEL3)
	○ 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 PS 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 × 109/L ▪ Platelets >100 × 109/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 PARP inhibitor, 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.

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Trial number (acronym)	NCT01968213 (ARIEL3)
	• 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. o Ongoing hormone treatment for previously treated breast cancer was permitted, o 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 Q2 Solutions' central laboratory (exact location depending on region of the investigational site). • Analysis of PK samples from all sites was performed at Q2 Solutions (formerly Quintiles BioScience Inc [Ithaca, New York, USA]) for analysis. • Analysis of CA-125 and AAG analysis from all sites was performed at Q2 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 IRR. • 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: o Liver function tests were monitored weekly until resolution to ≤ Grade 2

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Trial number (acronym)	NCT01968213 (ARIEL3)
	○ 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.

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Trial number (acronym)	NCT01968213 (ARIEL3)
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 IRR, 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) • OS, 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 INV-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 IRR, in patients who have measurable disease at study entry • DOR as per RECIST v1.1, as assessed by both the investigator and IRR • PRO as measured by the total score on the EQ-5D • CFI, calculated in months as the time since the last dose of the most recent chemotherapy regimen to the date of the first dose of a subsequent chemotherapy after study drug + 1 day • TSFT, calculated in months as the time from randomisation to the date of the first dose of the first subsequent anti-cancer treatment regimen after study drug + 1 day • TSST, calculated in months as the time from randomisation to the date of the first dose of the second subsequent anti-cancer treatment regimen after study drug + 1 day
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 unknown) • Measurable disease at baseline (yes, no) • Bulky disease at baseline (yes, no)

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Trial number (acronym)	NCT01968213 (ARIEL3)
	• 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.

2L, second-line; AAG, alpha-1 acid glycoprotein; AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BCRP, breast cancer resistance protein; BRCA1, breast cancer 1 gene; BRCA2, breast cancer 2 gene; CA-125, cancer antigen 125; CFI, chemotherapy-free interval; 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 PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; EQ-5D, Euro-Quality of Life 5 Dimensions; 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; INV-PFS, investigator-assessed progression-free survival; IRB, Institutional Review Board; IRR, independent radiology review; LOH, loss of heterozygosity; NCI, National Cancer Institute; ORR, overall response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; 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; TFST, time to first subsequent anticancer treatment; TSST, time to second subsequent anticancer treatment; ULN, upper limit of normal.
Source: Coleman et al. 2017;[35] ARIEL3 CSR.[55]

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B.3.3.1.3 Genomic testing

The population enrolled in ARIEL3 were stratified at the time of randomisation into BRCA mutant and BRCA wild type (non-BRCA HRD and biomarker negative) through identification of mutations in 30 HRD genes (tumour-based clinical trial assay [CTA] testing) (Table 10). Further testing was conducted in order to group patients into pre-specified efficacy analysis cohorts and patient subgroups.[55]

Patients identified through tumour-based CTA testing as having mutations in the BRCA1 or BRCA2 gene were further grouped by mutation type (germline vs. somatic vs. unknown [not tested]) through blood-based germline mutation testing (Myriad Genetics, Salt Lake City, Utah).[55]

Patients identified through tumour-based CTA testing as BRCA wild type were further grouped by the extent of loss of heterozygosity (LOH; low [<16%] vs. high [≥16%] vs. unknown [not evaluable]) through tumour-based T-5 next-generation sequencing, developed by Friedrich Miescher Institute.[55] LOH is a proposed marker of HRD and thus PARP inhibitor activity. LOH thresholds were informed by data from Part 1 of the ARIEL2 trial – a phase II study that evaluated 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.[57]

The results of the CTA, germline mutation, and LOH testing in the intent-to-treat (ITT) population, were used to categorise patients into predefined subgroups and pre-specified efficacy analysis cohorts, detailed in Section B.3.4. Data for the pre-specified BRCA mutated and HRD efficacy analysis cohorts are presented alongside results for the ITT population in Section B.3.6.[55] However, the HRD cohort was not considered interest to the decision problem in this submission, as agreed with NICE in the final scope (Section B.1.1).

B.3.3.1.4 Endpoints

The primary efficacy endpoint in the ARIEL3 study was investigator-assessed (INV)-PFS, defined as time from randomisation to disease progression (according to investigator assessment using Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) or death from any cause. 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. The primary efficacy endpoint was assessed at the 15 April 2017 data cut.[55]

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Table 12. Overview of secondary efficacy endpoints and key exploratory endpoints in ARIEL3[55,56]

Endpoint	Definition	Data cut
Secondary efficacy endpoints		
IRR-assessed PFS	Time from randomisation to disease progression + 1 day (according to blinded, independent radiologist assessment of tumor progression using RECIST v1.1) or death from any cause	15 April 2017
FOSI-18, a subscale of the (NCCN FACT)	• Time to worsening of the DRS-P subscale of the FOSI-18 was defined as time from randomisation to a 4-point reduction in the DRS-P subscale • Time to worsening of the total FOSI-18 score was defined as the time from randomisation to an 8-point reduction in the total score	15 April 2017
OS	Time from randomisation to date of death due to any cause	15 April 2017 and 4 April 2022
Exploratory endpoints relevant to this submission		
CFI	Time since the last dose of the most recent chemotherapy regimen to the date of the first dose of a subsequent chemotherapy after study drug + 1 day	15 April 2017 and 4 April 2022
TFST	Time from randomisation to the date of the first dose of the first subsequent anti-cancer treatment regimen after study drug + 1 day	15 April 2017 and 4 April 2022
PFS2	Time from randomisation to the second event of disease progression as assessed by the investigator or death due to any cause	15 April 2017 and 4 April 2022
TSST	Time from randomisation to the date of the first dose of the second subsequent anti-cancer treatment regimen after study drug + 1 day	15 April 2017 and 4 April 2022
EQ-5D visual analogue scale	Analyses of changes and/or percent changes from baseline were analysed for each scheduled post-baseline visit and for the final visit for EQ-5D visual analogue scale	15 April 2017

CFI, chemotherapy-free interval; DRS-P, Disease-related Symptoms – Physical; EQ-5D, Euro-Quality of Life 5 Dimensions; FOSI-18, Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18; IRR, independent radiology review; NCCN FACT, National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent anti-cancer treatment; TSST, time to second subsequent anti-cancer treatment;
Source: ARIEL3 CSR[55]; ARIEL3 CSR addendum[56]

B.3.3.2 Baseline demographics

Baseline characteristics for patients in the ITT population of the ARIEL3 study are presented in Table 13. Baseline characteristics of the ITT population in ARIEL3 and in Appendix I; they were generally well balanced between the treatment arms.[35,55,56] All patients were female, with an overall median age of 61.0 years and, in accordance with the study inclusion criteria (see Table 11), all had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 at baseline.[55]

The majority of patients had high-grade EOC and serous histology. Overall, less than 10% of patients had either fallopian tube cancer or primary peritoneal cancer. 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.[55]

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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 vs. 15.3% placebo) at baseline. Notably, 66.3% of patients enrolled in ARIEL3 had PR to previous platinum therapy and 33.7% of patients had CR.[55,56] By comparison, the proportion of patients with PR in the SOLO2, Study 19, NOVA and NORA trials ranged from 48% to 58% (Table 30).[35,50,51,58,59]

See Appendix D for the number of participants eligible to enter the ARIEL3 trial and the CONSORT flow chart for patient disposition.[55,56,60]

Table 13. Baseline characteristics of the ITT population in ARIEL3[35,55]

	Rucaparib (n=375)	**Placebo (n=189)**	**Total (n=564)**
Median age, years (range)	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 PS, n (%)			
0	280 (74.7)	136 (72.0)	416 (73.8)
1	95 (25.3)	53 (28.0)	148 (26.2)
Type of OC, n (%)			
EOC	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)
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)
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)

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	Rucaparib (n=375)	Placebo (n=189)	Total (n=564)
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)
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)
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)
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)

BRCA, breast cancer gene; CA-125, cancer antigen 125; CR, complete response; CSR, clinical study report; CTA, clinical trial assay; ECOG PS, Eastern Cooperative Oncology Group performance status; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; ITT, intent-to-treat; LOH, loss of heterozygosity; OC, ovarian cancer; 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;[35] ARIEL3 CSR[55]; ARIEL3 CSR addendum[56]

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B.3.4 Study groups and statistical analysis

B.3.4.1 Analysis populations

The predefined analysis populations used to analyse the ARIEL3 trial data (ITT and safety populations) are defined in Table 14.[55]

As described in Section B.3.3, the results of the CTA, germline mutation and LOH testing in the ITT population were used to categorise patients into two further pre-specified efficacy analysis cohorts (nested cohorts; BRCA mutated and HRD).[55]

Figure 3 presents the number of patients in each of the pre-specified and post-hoc analysis populations.[35,55]

Table 14. Description of the analysis populations in ARIEL3[55]

Population	Description	Relevant section of the submission
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 unknown)	Section B.3.6
Safety population	The safety population consisted of all patients who received at least one dose of protocol-specified treatment	Section B.3.10
BRCA mutated cohort	The BRCA mutant cohort consisted of all BRCA mutant patients irrespective of germline mutation status (germline, somatic, germline/somatic status unknown)	Section B.3.6
HRD cohort	The HRD cohort consisted of all BRCA mutant patients (germline, somatic, germline/somatic status unknown) and BRCA wild type LOH high patients	Not applicable
Non-BRCA mutated cohort	The non-BRCA mutant cohort consisted of all patients without tumour BRCA mutation; this was not a pre-specified subgroup	Section B.3.7

BRCA, breast cancer gene; HRD, homologous recombination deficiency; ITT, intent-to-treat; LOH, loss of heterozygosity
Source: ARIEL3 CSR[55]

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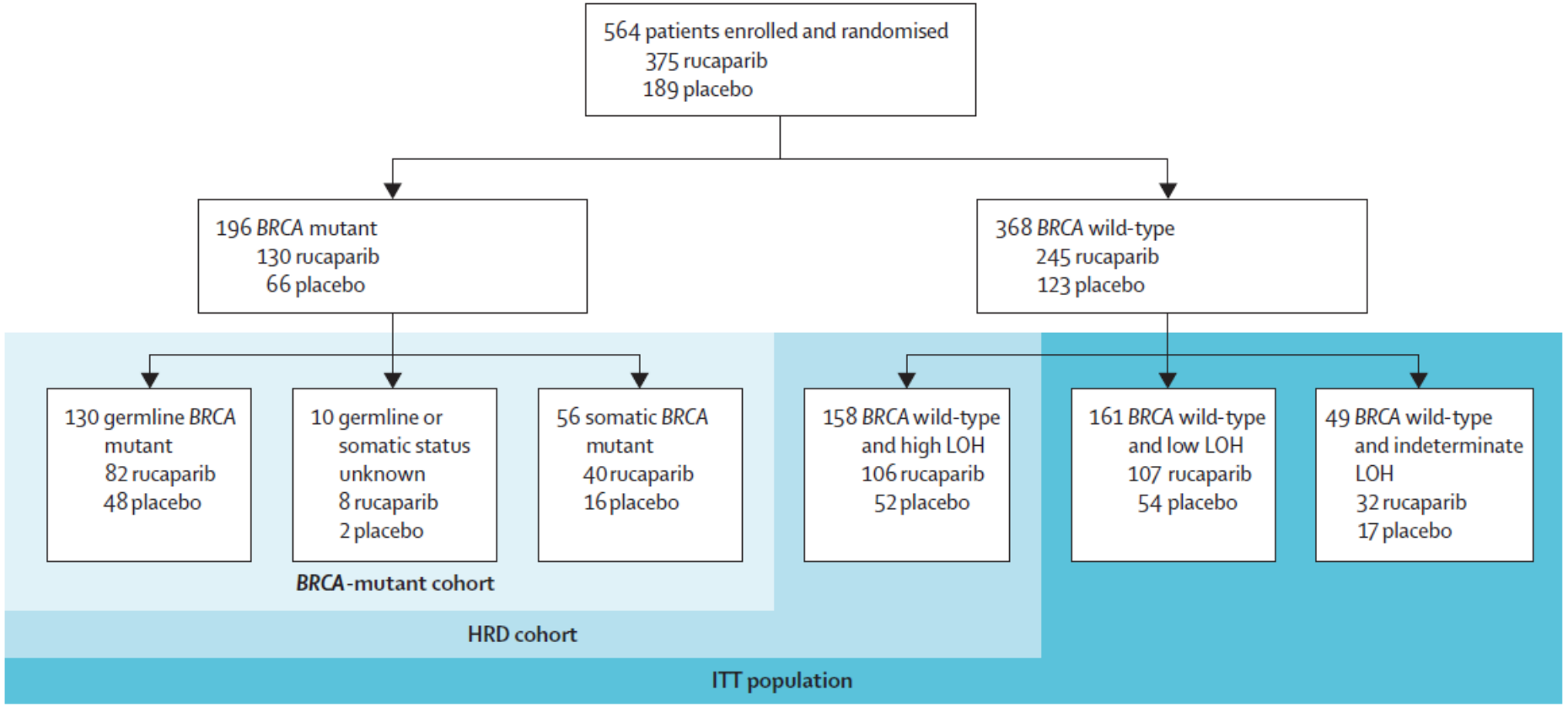
Figure 3. Efficacy analysis cohorts[35]



BRCA, breast cancer gene; HRD, homologous recombination deficiency; ITT, intention-to treat; LOH, loss of heterozygosity.
Source: Coleman et al. 2017[35]

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B.3.4.2 Multiple comparison step-down procedure for the prespecified analyses of ARIEL3

The primary and key secondary endpoints were tested among the BRCA mutated cohort, HRD cohort, and ITT population, using an ordered step-down multiple comparisons procedure, illustrated in Figure 4.[55]

INV-PFS in the BRCA mutated cohort was tested first at a one-sided 0.025 significance level. If the INV-PFS in the BRCA mutated cohort was statistically significant, then the INV-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 mutated 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.[55]

To ensure the results in the HRD cohort and ITT population were not solely driven by the results in the BRCA mutated cohort, the primary and secondary efficacy endpoints were also evaluated in the three predefined BRCA wild type subgroups: LOH high, LOH low, and LOH unknown. 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 mutated or HRD cohorts, the size of the estimated effect in the BRCA wild type LOH low and unknown 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.[55]

An additional post-hoc subgroup was defined to assess outcomes in patients without BRCA mutation to provide evidence for the effectiveness of rucaparib in the non-BRCA mutated cohort for this submission. Standard parametric distributions were fitted to INV-PFS, TTD PFS2 and OS outcomes in the BRCA and non-BRCA mutated cohort in ARIEL3 for extrapolation purposes .

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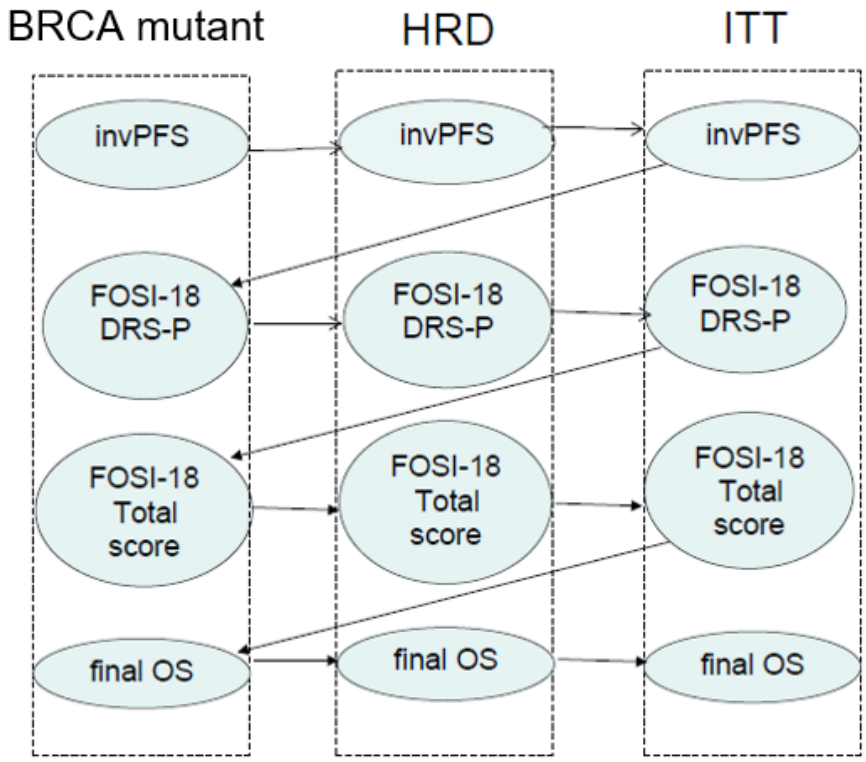
Figure 4. Ordered step-down procedure for ARIEL3[55]



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.[55]

B.3.4.3 Data cuts for analysis of ARIEL3 outcomes

B.3.4.3.1 15 April 2017 data cut

Data analysis for the primary endpoint in the ARIEL3 study was to be conducted after 70% of patients in the BRCA mutated cohort had an observed event of investigator-assessed disease progression or death. The target number of progression events in the BRCA mutated 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. Data presented for this analysis include all data up to and including 15 April 2017 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).[55]

Analyses of secondary and exploratory endpoints occurred alongside the primary endpoint. However, at the time of the 15 April 2017 data cut, data for OS, PFS2 and TSST were immature.[55]

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B.3.4.3.2 31 December 2017 safety data cut

An additional database lock for updated safety data occurred on 31 December 2017. An updated analysis of PFS2 was also provided with the data cut for updated safety data, but OS data were still heavily censored (>70% of patients), and no updated analyses were performed.[36]

B.3.4.3.3 04 April 2022 final analysis

In accordance with the statistical analysis plan for ARIEL3, the final analysis of OS was to be conducted after 70% of patients in the ITT population had died. The target number of OS events was achieved as of 4 April 2022, with 72.7% of events in the ITT population (rucaparib: 72.0%; placebo: 74.1%). As of this date, there were 15 patients remaining on treatment, all of whom were in the rucaparib group. Updated pre-specified analyses of PFS2, CFI, TFST and TSST were also provided with the final data cut, along with updated safety evaluations.[56]

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Table 15. Summary of statistical analysis of INV-PFS, the primary outcome of ARIEL3[35,55,61]

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 INV-PFS within each of the efficacy analysis cohorts (BRCA mutated, HRD and ITT population).	The time to INV-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 INV-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 mutated cohort, HRD cohort, and ITT population using an ordered step-down multiple comparison procedure, illustrated in Figure 4. INV-PFS in the BRCA mutated cohort was tested first at a one-sided 0.025 significance level. If INV-PFS in the BRCA mutated cohort was statistically significant, then INV-PFS was tested in the all HRD cohort, followed by the ITT population.	Approximately 540 patients were randomised (2:1) to receive either rucaparib or placebo. A minimum of 180 and a maximum of 200 BRCA mutated patients were to be enrolled, which included no more than 150 germline BRCA mutated 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 median INV-PFS for each efficacy analysis cohort: • BRCA mutated cohort: 12.0 months in the rucaparib arm vs. 6.0 months in the placebo arm; HR 0.5 • HRD cohort: 10.0 months vs. 6.0 months; HR 0.6 • 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.	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 of INV-PFS. 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.

BRCA, breast cancer gene; CTA, clinical trial assay; HR, hazard ratio; HRD, homologous recombination deficiency; INV-PFS, investigator-assessed progression-free survival; ITT, intention-to-treat; RECIST, Response Evaluation Criteria in Solid Tumors.
Source: Coleman et al. 2017;[35] ARIEL3 CSR[55]; ARIEL3 statistical analysis plan[61]

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B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

A complete quality assessment in accordance with the NICE recommended checklist for randomised controlled trial (RCT) assessment of bias is presented in Appendix D. During the previous assessment of TA611, the Evidence Review Group (ERG) agreed with the overall risk of bias being low for ARIEL3 in the full trial population but noted that results for the subgroups are at a higher risk of bias than those reported for the full population.[62]

B.3.5.1 Conduct of ARIEL3

ARIEL3 was conducted in accordance with Good Clinical Practice Guidelines of the International Council for Harmonisation,[63] with a single protocol to promote consistency across sites, and measures taken to minimise bias.[55] As outlined in Appendix D.3, the ARIEL3 trial met all quality related criteria of an appropriate RCT as described by the International Council for Harmonisation. Sponsor personnel (with the exception of individuals responsible for the clinical supply chain), investigators, clinical site staff and patients were all blinded to study treatment to avoid bias in the interpretation of the efficacy and safety results. To avoid bias between treatment groups, patients were randomised with stratification according to HRD classification (based on gene mutation), interval between completion of penultimate platinum-based regimen and disease progression by radiologic assessment and best response to platinum regimen received immediately before initiation of maintenance therapy in this study. Moreover, independent radiology review-assessed PFS (IRR-PFS) was assessed alongside INV-PFS to provide objective support to the primary endpoint.[55]

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.[55]

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

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limited, and primary and secondary outcome assessments were conducted in an ordered, step-down, multiple comparison procedure.

B.3.5.2 Subsequent PARP inhibitor treatment

A potential source of bias against rucaparib is the impact of subsequent anticancer regimens in the placebo arm of the trial, specifically the use of subsequent PARP inhibitor therapies within the post-progression phase. The majority of patients in the BRCA mutated and non-BRCA mutated cohorts who were randomised to placebo received at least one subsequent anti-cancer regimen ([redacted] and [redacted], respectively); the proportion of patients randomised to placebo who received subsequent PARP inhibitors was [redacted] in the BRCA mutated cohort and [redacted] in the non-BRCA mutated cohort.[56] The frequency of subsequent PARP inhibitor use in ARIEL3 was higher than in the olaparib SOLO2 and niraparib NOVA trials (Table 20 in Section B.3.6.2.3.1).[56,64-66] This is likely due to the widespread commercial availability of olaparib and niraparib, which were available in many markets at the time ARIEL3 participants were candidates for subsequent treatment lines.[40,41,56] Use of post-progression PARP inhibitor treatment may mask the true treatment effect of rucaparib vs. placebo on OS.[56]

B.3.6 Clinical effectiveness results of the relevant studies

Clinical efficacy outcomes from the ARIEL3 trial are presented below. Data for the HRD cohort were part of the prespecified testing hierarchy and have been included alongside the ITT population and BRCA mutated cohort to provide a complete picture of ARIEL3.[35] However, the HRD cohort is not considered relevant to the decision problem for this submission (Section B.1.1).[62]

B.3.6.1 Primary endpoint: INV-PFS

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 at the 15 April 2017 data cut (Table 16).[35,55]

The INV-PFS of patients without a BRCA mutation in the ARIEL3 study was evaluated as part of a post-hoc analysis with results presented in Section B.3.7.2.

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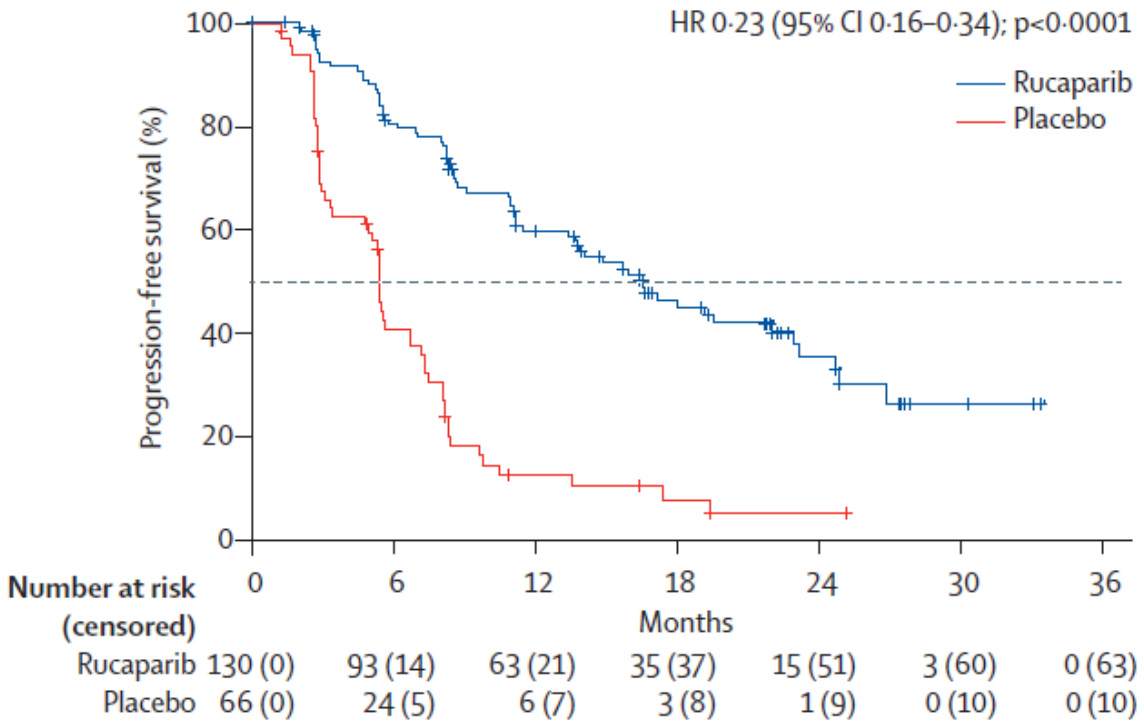
Table 16. Summary of INV-PFS (15 April 2017 data cut)[35,55]

	ITT population		HRD cohort		BRCA mutated 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

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; INV, investigator-assessed; ITT, intention-to-treat; PBO, placebo; PFS, progression-free survival.
Source: Coleman et al. 2017;[35] ARIEL3 CSR[55]

As can be observed in the Kaplan–Meier (KM) curves presented in Figure 5, Figure 6 and Figure 7, 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.[35]

Figure 5. KM estimates of PFS as assessed by the investigator in the BRCA mutated cohort (15 April 2017 data cut)[35]



BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; PFS, progression-free survival
Source: Coleman et al. 2017[35]

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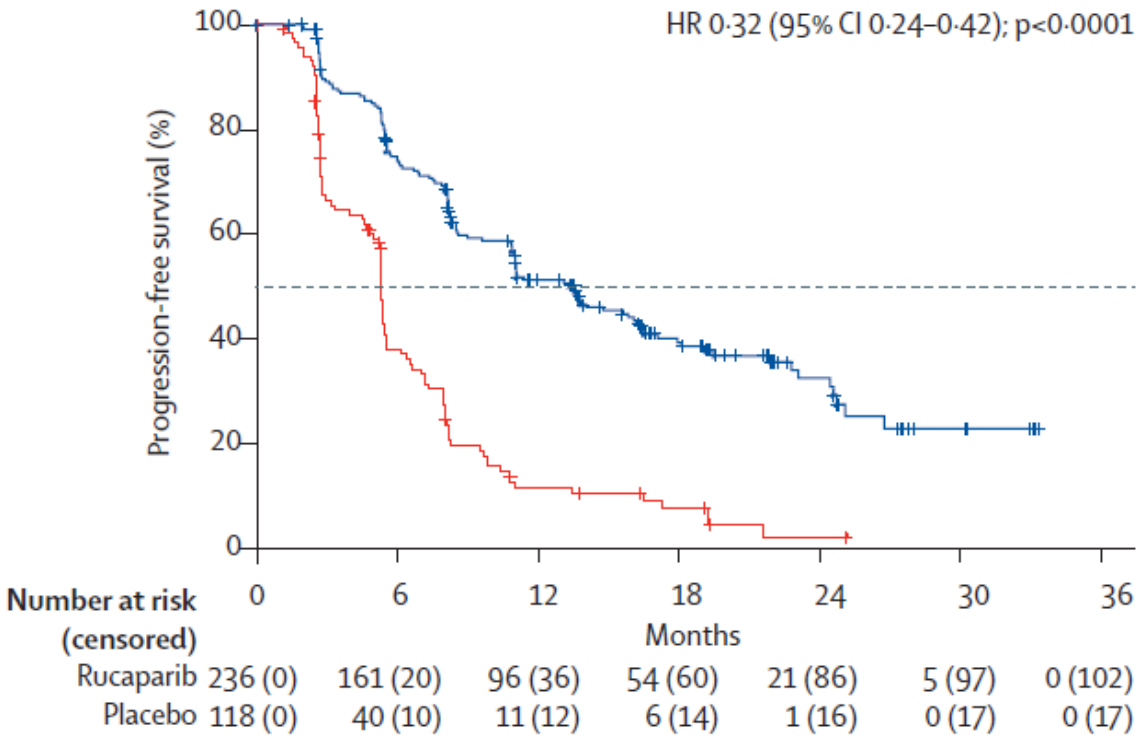
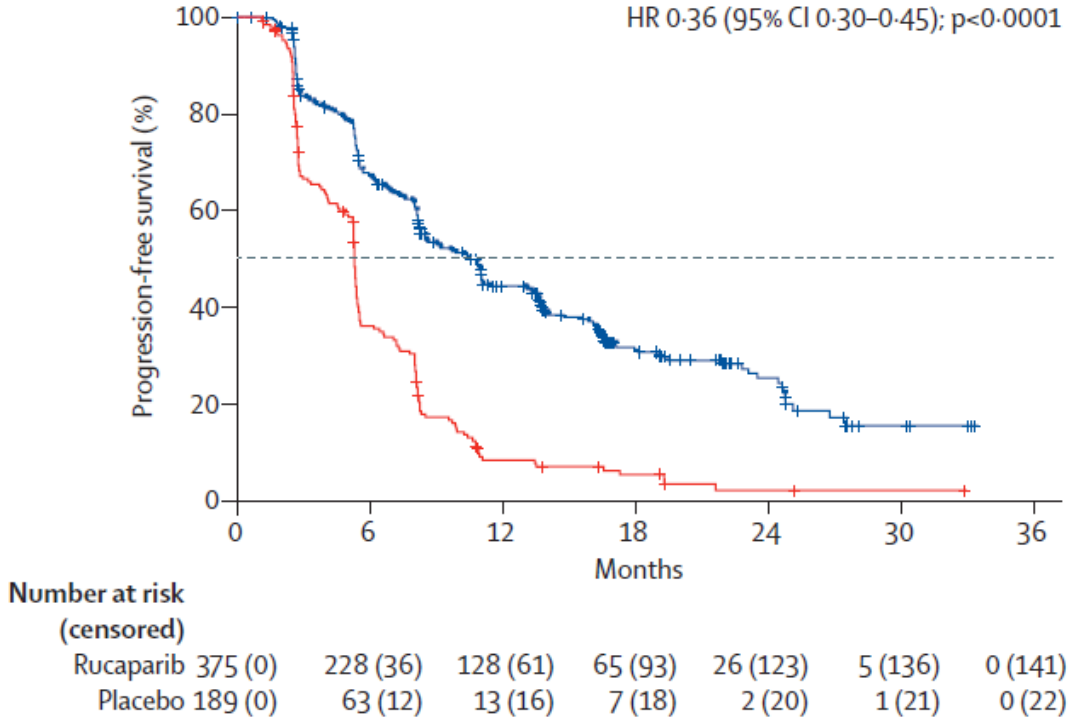
Figure 6. KM estimates of PFS as assessed by the investigator in the HRD cohort (15 April 2017 data cut)[35]



CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; KM, Kaplan–Meier; PFS, progression-free survival
Source: Coleman et al. 2017[35]

Figure 7. KM estimates of PFS as assessed by the investigator in the ITT population (15 April 2017 data cut)[35]



CI, confidence interval; HR, hazard ratio; ITT, intention to treat; KM, Kaplan–Meier; PFS, progression-free survival. Source: Coleman et al. 2017[35]

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B.3.6.2 Secondary endpoints

B.3.6.2.1 PFS as assessed by IRR

IRR-PFS using RECIST v1.1, estimated by the KM method, was used as a key standalone, secondary endpoint in support of the primary endpoint of INV-PFS.[35,55]

Across all efficacy analysis cohorts (and thus irrespective of BRCA status), rucaparib significantly reduced the risk of disease progression or death as assessed by IRR compared with placebo at the 15 April 2017 data cut, as summarised in Table 17.[35,55]

Table 17. Summary of PFS as assessed by IRR (15 April 2017 data cut)[35,55]

	ITT population		HRD cohort		BRCA mutated 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: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; IRR, independent radiology review; ITT, intention-to-treat; NR, not reached; PBO, placebo; PFS, progression-free survival
Source: Coleman et al. 2017[35]; ARIEL3 CSR[55]

As can be observed in the KM curves presented in Figure 8, Figure 9 and Figure 10 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.[35]

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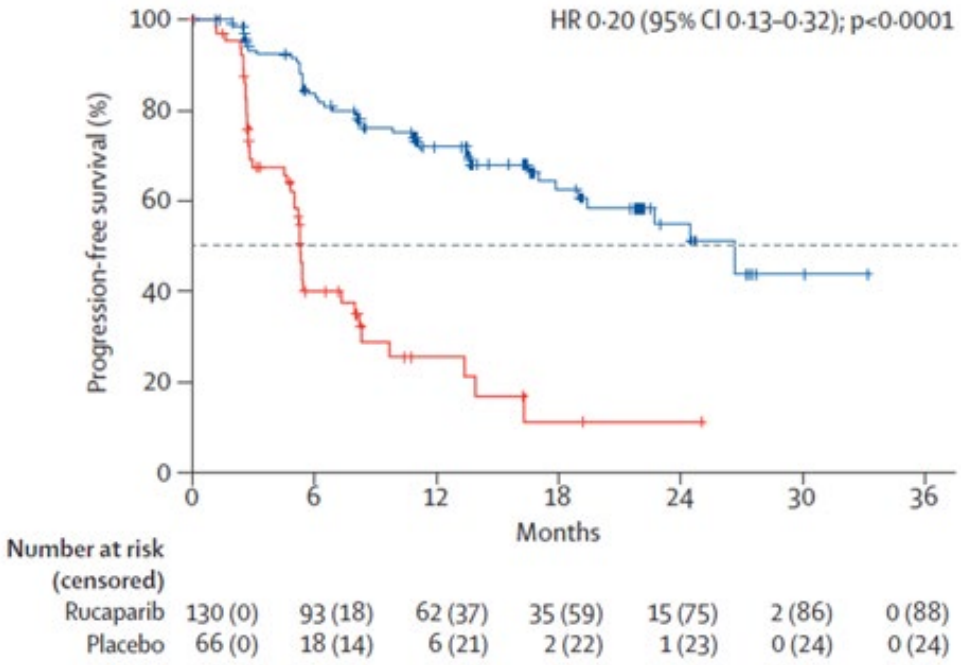
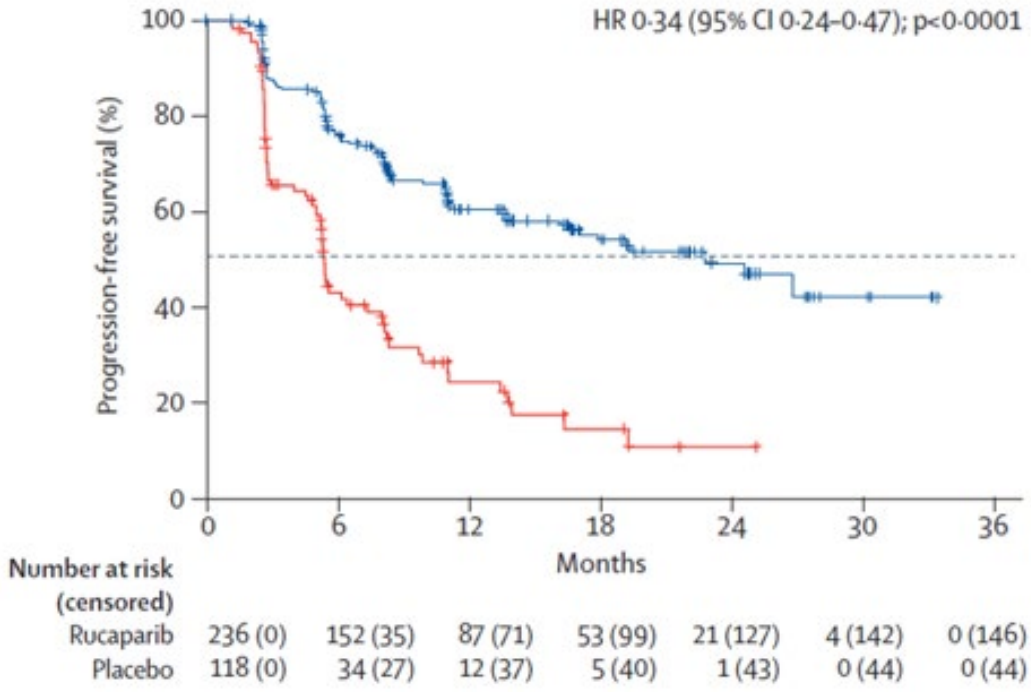
Figure 8. Kaplan–Meier estimates of PFS as assessed by IRR in the BRCA mutated cohort (15 April 2017 data cut)[35]



BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; IRR, independent radiology review; PFS, progression-free survival
Source: Coleman et al. 2017.[35]

Figure 9. Kaplan–Meier estimates of PFS as assessed by IRR in the HRD cohort (15 April 2017 data cut)[35]



CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; IRR, independent radiology review; PFS, progression-free survival.
Source: Coleman et al. 2017.[35]

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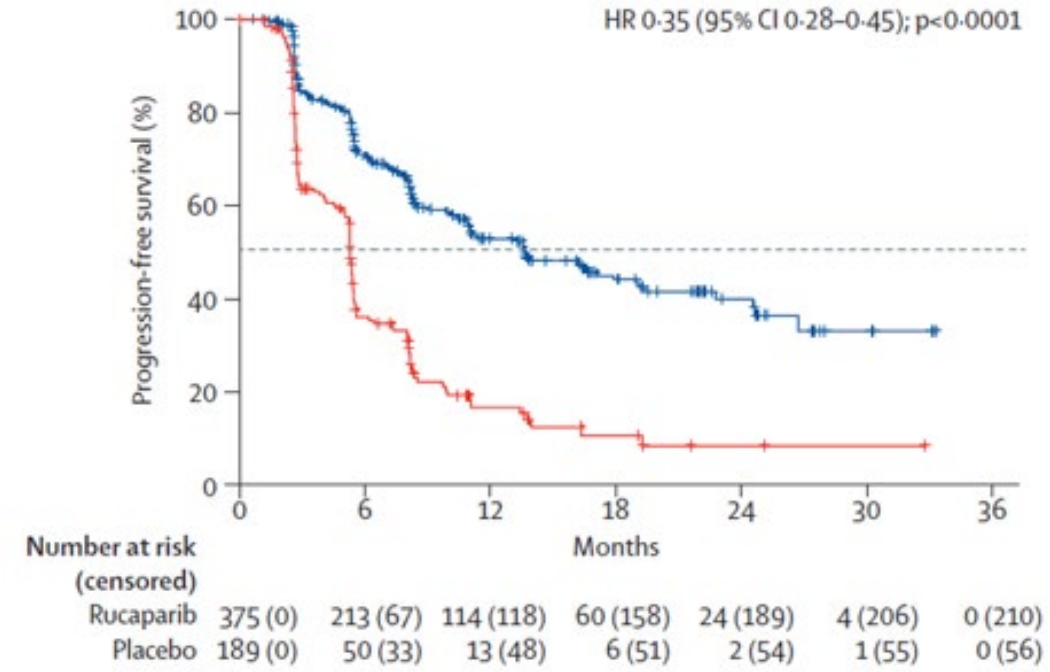
Figure 10. Kaplan–Meier estimates of PFS as assessed by IRR in the ITT population (15 April 2017 data cut)[35]



CI, confidence interval; HR, hazard ratio; IRR, independent radiology review; ITT, intention to treat; PFS, progression-free survival
Source: Coleman et al. 2017.[35]

Overall, results for IRR-PFS were consistent with, and supportive of, the INV-PFS result. While the HRs were consistent between investigator- and IRR-PFS, the median point estimates with 95% confidence intervals of IRR-PFS were longer than those of the INV-PFS in the rucaparib arm for the primary analysis cohorts.

According to ARIEL3 study protocol, scans were sent for IRR until progression or death as assessed by the investigator, therefore, there was a higher censoring rate in IRR analyses (with no further scans sent for IRR once the investigator had assessed progression) that could be contributing to the differences observed. A higher median IRR-PFS as compared to INV-PFS has been observed in other clinical studies of PARP inhibitor maintenance treatments within the relapsed OC setting.[50,51,67] Factors which may influence INV-PFS (but not IRR-PFS) include the detection of worsening symptoms and deteriorating physical condition of the patient, and increasing trends in cancer antigen 125 values. This also reflects the point in time of IRR-PFS data collection, which is delayed compared to INV-PFS data collection in this time-sensitive indication.

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B.3.6.2.2 Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18 (FOSI-18)

As summarised in Table 18, there was a shortening of time to worsening in the FOSI-18 disease-related symptoms-physical subscale (DRS-P) subscale (defined as ≥4 point decrease) and total score (defined as ≥8 point decrease) in patients treated with rucaparib at the 15 April 2017 data cut. However, no significant differences in self-reported HRQoL 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.[55]

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.3.10).

Table 18. Summary of FOSI-18 outcomes (15 April 2017 data cut)[55]

	ITT population		HRD cohort		BRCA mutated 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]†	

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.
*, defined as ≥4 point decrease; †, p-values are presented descriptively but are not representative of significance; ‡, defined as ≥8 point decrease.
Source: ARIEL3 CSR[55]

In accordance with the pre-specified hierarchical step-down procedure used for adjusting for multiplicity testing in ARIEL3 (see Section B.3.4), 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).

B.3.6.2.3 Final OS

OS data were immature at the 15 April 2017 data cut, with only 22% of events in the ITT population, and no updated analyses of OS were performed at the updated safety data cut-off date (31 December 2017).[35,36]

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At the final analysis (4 April 2022; median follow-up 77.0 months), OS data were mature, having reached 72.7% of events in the ITT population.[53,68] As can be observed in the KM curves presented in Figure 11, Figure 12 and Figure 13, the 95% confidence bands for rucaparib and placebo are highly overlapping, indicating no significant differences in final OS between treatment groups in ARIEL3 (Table 19).[53,56,68]

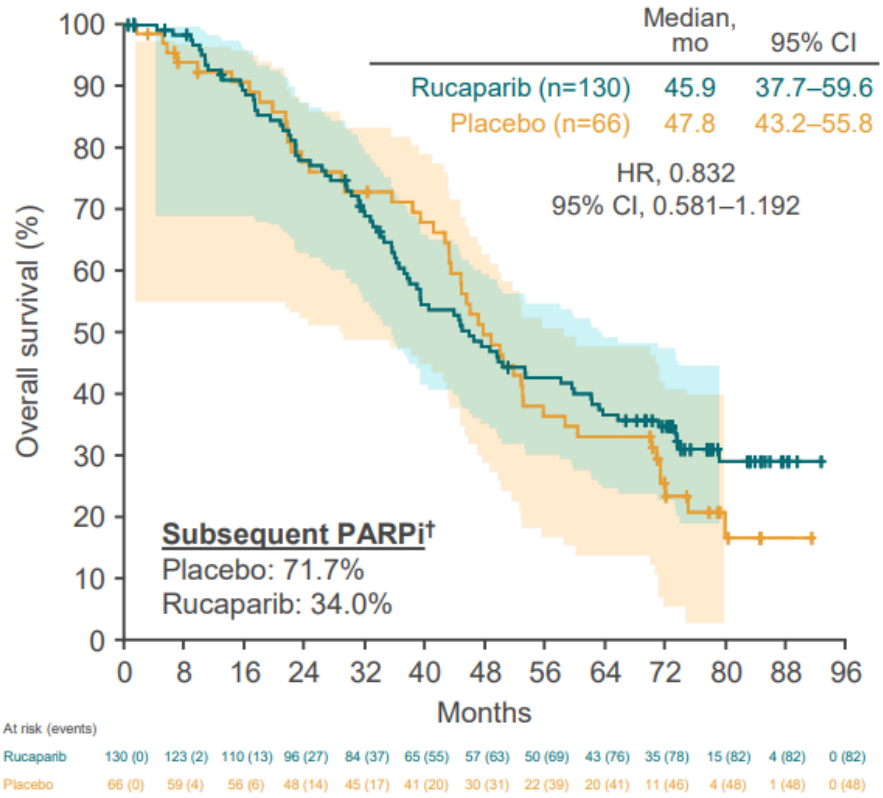
Data on the OS survival of patients with non-BRCA mutated OC who received rucaparib or placebo in ARIEL3 are presented in Section B.3.7.1.2.

Table 19. Summary of final OS (final analysis: 4 April 2022)[53,68]

	ITT population		HRD cohort		BRCA mutated cohort	
	Rucaparib (n=375)	**PBO (n=189)**	**Rucaparib (n=236)**	**PBO (n=118)**	**Rucaparib (n=130)**	**PBO (n=66)**
Events, n (%)	270 (72.0)	140 (74.1)	159 (67.4)	85 (72.0)	82 (63.1)	48 (72.7)
Median OS, months (95% CI)	36.0 (32.8, 39.4)	43.2 (38.1, 46.9)	40.5 (36.6, 48.4)	47.8 (42.7, 53.0)	45.9 (37.7, 59.6)	47.8 (43.2, 55.8)
HR (95% CI)	0.995 (0.809, 1.223)		1.005 (0.766, 1.320)		0.832 (0.581, 1.192)	
p-value	0.96		0.97		0.32	

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; OS, overall survival; PBO, placebo.
*, p values are presented descriptively but are not representative of significance.
Source: Coleman et al. 2022 (ESGO abstract)[53]; Coleman et al. 2022 (ICGS oral presentation)[68]

Figure 11. KM estimates of final OS in the BRCA mutated cohort (final analysis: 4 April 2022)[68]



BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor. Source: Coleman et al. 2022 (ICGS oral presentation)[68]

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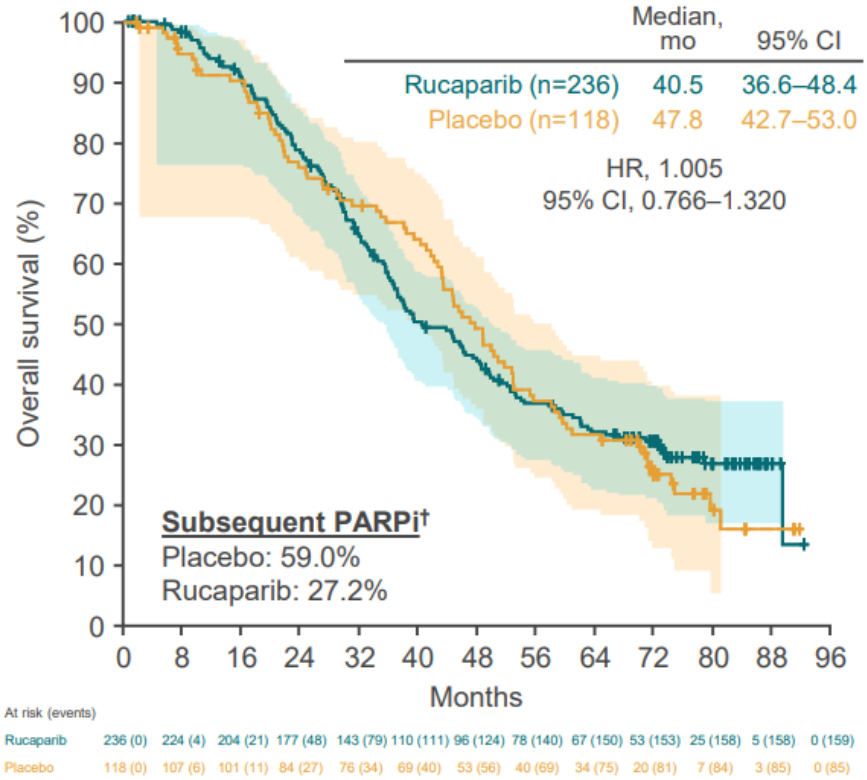
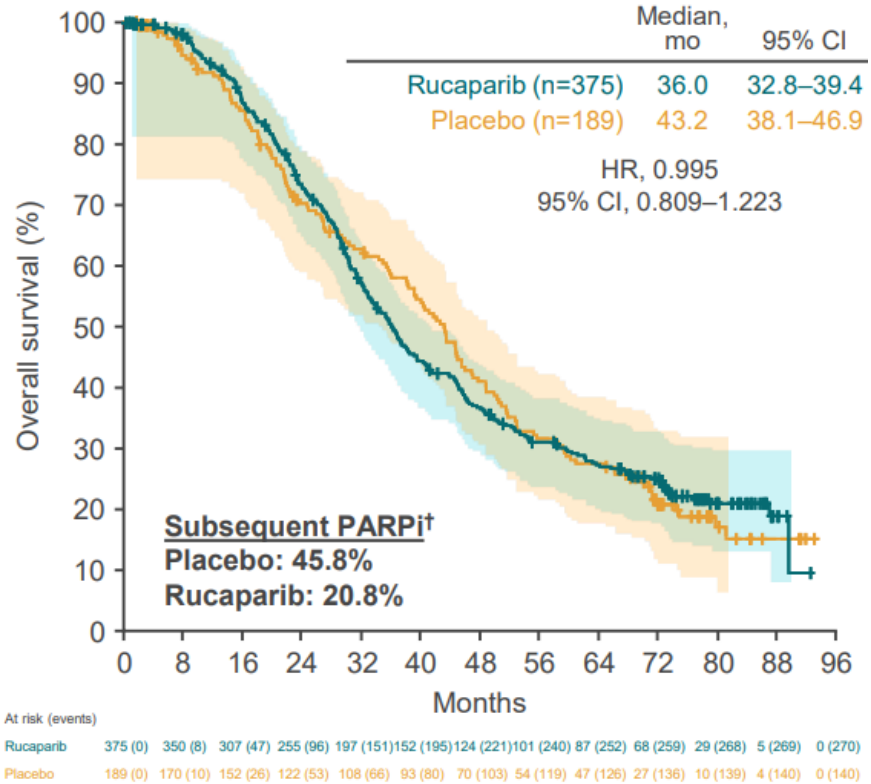
Figure 12. KM estimates of final OS in the HRD cohort (final analysis: 4 April 2022)[68]



CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; KM, Kaplan–Meier; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor. Source: Coleman et al. 2022 (ICGS oral presentation)[68]

Figure 13. KM estimates of final OS in the ITT population (final analysis: 4 April 2022)[68]



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan–Meier; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor. Source: Coleman et al. 2022 (ICGS oral presentation)[68]

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B.3.6.2.3.1 Additional analysis of OS, adjusting for subsequent treatment with PARP inhibitors in placebo patients

As discussed in Section B.3.5, there was no difference demonstrated in OS between rucaparib and placebo despite the significant difference in INV-PFS. However, a considerable proportion of patients enrolled in ARIEL3 received subsequent therapies. Since subsequent PARP inhibitor therapies were allocated outside of the clinical trial, they were non-randomised and unbalanced across treatments arms ([redacted] in the rucaparib group vs. [redacted] in the placebo group). Therefore, the impact of subsequent PARP inhibitor therapies in the post-progression phase is a potential source of bias favoring the placebo group.[56]

In addition, the frequency of subsequent PARP inhibitor use in the placebo arm of ARIEL3 was considerably higher than in the olaparib SOLO2 and niraparib NOVA trials (Table 20), likely due to the widespread commercial availability of both olaparib and niraparib at the time ARIEL3 participants were candidates for subsequent treatment lines. Therefore, the bias due to subsequent PARP inhibitor therapies in the placebo arm is assumed to be considerably less apparent within the comparator trials than in ARIEL3.[56,64-66]

Table 20. Summary of subsequent anti-cancer treatment regimens across rucaparib, olaparib and niraparib trials

	Patients treated with subsequent PARP inhibitors		Patients treated with any subsequent therapy	
	Intervention	Placebo	Intervention	Placebo
BRCA mutated cohort				
ARIEL3	[redacted]	[redacted]	[redacted]	[redacted]
SOLO2	10.2%	38.4%	66.3%	81.8%
NOVA	26.8%	49.2%	73.9%	76.9%
Non-BRCA mutated cohort				
ARIEL3	[redacted]	[redacted]	[redacted]	[redacted]
SOLO2	Not applicable	Not applicable	Not applicable	Not applicable
NOVA	6.8%	14.7%	74.8%	83.6%

BRCA, breast cancer gene; PARPi, poly (ADP-ribose) polymerase
Source: ARIEL3 CSR addendum[56]; NICE TA784[41]; NICE TA908[40]

Exploratory analyses, which were conducted to adjust for the effect of subsequent therapies on OS, found that excluding patients who received subsequent PARP inhibitors in the placebo arm resulted in significantly longer OS in the rucaparib arm than in the placebo arm within the ITT population. The median adjusted OS for patients randomised to rucaparib was [redacted] months compared to [redacted] months for patients randomised to placebo who were not treated with a subsequent PARP inhibitor (hazard ratio [HR]: [redacted]; Figure 14). Similar analyses showed adjusted OS to be numerically in favour of rucaparib for the HRD (HR: [redacted] Figure 15) and BRCA

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mutated cohorts (HR: [redacted]; Figure 16). However, a statistically significant difference was not demonstrated between treatment groups within these cohorts.[56]

Figure 14. KM analysis of adjusted OS excluding patients randomised to placebo who received a subsequent PARP inhibitor in the ITT population[56]

CI, confidence interval; ITT, intent-to-treat; KM, Kaplan–Meier; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor
Source: ARIEL3 CSR addendum[56]

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Figure 15. KM analysis of adjusted OS excluding patients randomised to placebo who received a subsequent PARP inhibitor in the HRD population[56]

CI, confidence interval; HRD, homologous recombination deficiency; KM, Kaplan–Meier; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor
Source: ARIEL3 CSR addendum[56]

Figure 16. KM analysis of adjusted OS excluding patients randomised to placebo who received a subsequent PARP inhibitor in the BRCA mutated cohort[56]

BRCA, breast cancer gene; CI, confidence interval; KM, Kaplan–Meier; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor

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Additional statistical analyses were conducted to adjust OS for the effect of placebo patients receiving subsequent PARP inhibitors. OS outcomes for the ARIEL3 BRCA mutated cohort adjusted using the Rank-Preserving Structural Failure Time Model (RPSFTM) and Inverse Probability of Censoring Weighting (IPCW) model are presented in Table 21.[56]

Both the RPSFTM and IPCW methods are subject to important limitations. The IPCW method artificially censors each placebo patient at the time they switch to a subsequent PARP inhibitor, and the remaining patients who are "similar" in terms of a specified set of baseline and time-dependent characteristics receive higher weights than 1 to replace that patient.[69] The key assumption in the IPCW method is the assumption of "no unmeasured confounders", which states that data must be available on all baseline and time-dependent prognostic factors for mortality that independently predict informative censoring, and models of censoring risk must be correctly specified. This assumption cannot be verified using trial data, and there is always a risk that some key predictors of treatment switching are not collected in a trial. Also, at high levels of switching IPCW can lead to bias.[70]

The RPSFTM method does not rely on the "no unmeasured confounders" assumption. Specifically, the RPSFTM is an instrumental variables method; and as such, it is applicable when the data available are unlikely to capture all factors that predict both treatment and outcome. The key assumption in the RPSFTM model is that the treatment effect is equal for all patients and it is the same regardless of whether the treatment is received from randomization or the time of cross-over (this is known as the "common treatment effect" assumption). In this analysis this assumption involves two components: 1) Is the experimental treatment before and after switching the same? 2) Given that treatment switching was allowed after disease progression, is it reasonable to assume that the capacity for a patient to benefit from treatment is the same compared to pre-progression?

Both assumptions are reasonable as 1) there is growing support from clinical experts that all PARP inhibitors should have similar efficacy and 2) the RPSFTM would likely remain valid if the treatment effect of subsequent PARP inhibitors can be expected at least to be similar to the effect on patients initially randomised to rucaparib. Based on these underlying assumptions of the methods described above, results from the RPSFTM are likely more robust.

The RPSFTM resulted in an acceleration factor of [redacted] in the BRCA mutated cohort, suggesting treatment with rucaparib was more efficacious for these patients. Adjustment did not substantially alter OS outcomes in the BRCA mutated cohort, likely due to relatively small patient numbers included in the analyses (130 and 66 patients on

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rucaparib and placebo, respectively) and a very high proportion of patients treated with subsequent PARP inhibitor therapy regimens.[56] Adjusted OS outcomes for the NOVA trial are presented alongside the ARIEL3 results for comparison.

Table 21. Additional analysis of OS, adjusting for subsequent treatment with PARP inhibitors in placebo patients

	Unadjusted OS analysis based on the study protocol	Intervention vs. placebo (RPSFTM) HR (95% CI)	Intervention vs. placebo (IPCW) HR (95% CI)
BRCA mutated cohort			
ARIEL3	[redacted]	[redacted]	[redacted]
SOLO2	0.740 (0.54, 1.00)	0.56 (0.35, 0.97)	Not available[a]
NOVA	0.85 (0.61, 1.20)	Not available[b]	0.66 (0.44, 0.99)
Non-BRCA mutated cohort			
ARIEL3	1.096 (0.852, 1.411)	-	-
SOLO2	Not applicable[c]	Not applicable[c]	Not applicable[c]
NOVA	1.06 (0.81, 1.37)	Not available[b]	0.97 (0.74, 1.26)

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; OS, overall survival; PARPi, poly (ADP-ribose) polymerase; RPSFTM, Rank-Preserving Structural Failure Time Model; IPCW, Inverse Probability of Censoring Weighting model
[a] Only RPSFT analysis was presented for adjustment for the SOLO2 trial
[b] Only IPCW adjustment was presented for the NOVA trial
[c] SOLO2 did not enrol any patients without BRCA mutation
Source: Matulonis et al. 2021[71]; Galbraith et al. 2020[72]

B.3.6.3 Exploratory endpoints

B.3.6.3.1 CFI and TFST

At the final analysis (4 April 2022), CFI and TFST data were mature, having reached [redacted] and [redacted] of events in the ITT population, respectively.[56] Results from the final analysis were consistent with the 15 April 2017 data cut, with significant improvements in CFI and TFST observed in patients randomised to rucaparib compared to patients randomised to placebo across all analysis cohorts.[56] These findings would suggest that rucaparib also potentially delays the deleterious effects of AEs related to further chemotherapy treatment in OC.[47] CFI and TFST results are summarised in Table 22.[55,56]

Pre-specified analysis results for CFI and TFST in the non-BRCA mutant subgroup are presented in Section B.3.7.1.2.

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Table 22. Summary of CFI and TFST (15 April 2017 data cut and 4 April 2022 final analysis)[55,56]

	ITT population		HRD cohort		BRCA mutated cohort	
	Rucaparib (n=375)	**PBO (n=189)**	**Rucaparib (n=236)**	**PBO (n=118)**	**Rucaparib (n=130)**	**PBO (n=66)**
15 April 2017 data cut						
CFI, median (95% CI) [months]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	
TFST, median (95% CI) [months]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	
4 April 2022 final analysis						
CFI, median (95% CI) [months]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	
TFST, median (95% CI) [months]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	

BRCA, breast cancer gene; CFI, chemotherapy-free interval; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; NR, not reached; PBO, placebo; TFST, time to first subsequent anti-cancer treatment.
Source: ARIEL3 CSR[55]; ARIEL3 CSR addendum[56]

B.3.6.3.2 PFS2 and TSST

At the 4 April 2022 final analysis, PFS2 and TSST data were mature, having reached 82.3% and 82.8% of events in the ITT population, respectively.[56] Results were consistent with the 15 April 2017 data cut, showing statistically significant improvements in PFS2 and TSST observed in patients randomised to rucaparib compared to patients randomised to placebo across all analysis cohorts. PFS2 and TSST results from both primary and final analyses are summarised in Table 23.[53,55,56,68,73]

Results for PFS2 and TSST among patients in the non-BRCA mutant population are presented in Section B.3.7.1.2.

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Table 23. Summary of PFS2 and TSST (15 April 2017 data cut and 4 April 2022 final analysis)[53,55,56,68,73]

	ITT population		HRD cohort		BRCA mutated cohort	
	Rucaparib (n=375)	**PBO (n=189)**	**Rucaparib (n=236)**	**PBO (n=118)**	**Rucaparib (n=130)**	**PBO (n=66)**
15 April 2017 data cut						
Median PFS2, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	
TSST, median (95% CI) [months]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	
4 April 2022 final analysis						
Median PFS2, months (95% CI)	20.6 (18.7, 23.5)	16.3 (14.6, 17.9)	24.7 (21.9, 26.8)	18.4 (15.8, 22.1)	26.1 (22.8, 32.8)	18.4 (15.7, 24.4)
HR (95% CI) p-value	0.703 (0.579, 0.854) <0.01		0.718 (0.558, 0.923) 0.01		0.672 (0.480, 0.941) 0.02	
TSST, median (95% CI) [months]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; PBO, placebo; PFS2, progression-free survival 2; TSST, time to second subsequent anti-cancer treatment.
Notes: *, median time to the start of the second subsequent anti-cancer treatment for the BRCA mutated could not be determined for patients who received rucaparib at the 15 April 2017 data cut, as only 42 of 130 patients had initiated a second subsequent anti-cancer treatment. Therefore, the degree of censoring was high.
Source: ARIEL3 CSR[55]; Summary of clinical efficacy[73]; ARIEL3 CSR addendum[56]; Coleman et al. 2022 (ESGO abstract)[53]; Coleman et al. 2022 (ICGS oral presentation)[68]

B.3.6.3.3 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 24.[55]

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Table 24. Percentage change in EQ-5D visual analogue scale from baseline to end of treatment (15 April 2017 data cut)[55]

	ITT population		HRD cohort		BRCA mutated cohort	
	Rucaparib (n=375)	PBO (n=189)	Rucaparib (n=236)	PBO (n=118)	Rucaparib (n=130)	PBO (n=66)
Baseline mean, (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference vs. placebo (95% CI) p-value	[redacted]		[redacted]		[redacted]	

BRCA, breast cancer gene; CI, confidence interval; HRD, homologous recombination deficiency; ITT, intention-to-treat; LS, least squares; PBO, placebo; SD, standard deviation.
Source: ARIEL3 CSR[55]

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.[74] These methods are fully described in the post-hoc analysis reported provided in the reference pack.[75]

A significantly longer mean quality-adjusted survival time was observed for rucaparib patients compared to placebo patients across ITT and BRCA mutated cohorts in both analyses, as summarised in Table 25.[74,75] 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 mutated cohort. When using a utility weight of [redacted] and [redacted] in Q-TWiST analysis for the ITT population and BRCA mutated 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 mutated cohort; these differences were statistically significant and in favour of rucaparib.[74,75]

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Table 25. QA-PFS and QA-TWiST (all Grade ≥3 TEAEs)[74,75]

	ITT population			BRCA mutated cohort		
	Rucaparib (n=375)	**PBO (n=189)**	**Difference**	**Rucaparib (n=130)**	**PBO (n=66)**	**Difference**
Mean QA-PFS, months (95% CI)	12.02 (10.96, 13.03)	5.74 (4.98, 6.42)	6.28 (4.85, 7.47)	15.28 (13.22, 17.45)	5.92 (4.71, 7.23)	9.37 (6.65, 11.85)
Q-TWiST health states						
Mean PFS, months (95% CI)	13.39 (12.35, 14.43)	6.45 (5.74, 7.17)	6.94 (5.67, 8.20)	16.49 (14.75, 18.22)	6.71 (5.41, 8.00)	9.78 (7.63, 11.93)
Mean TOX*, months (95% CI)	0.64 (0.49, 0.78)	0.10 (0.04, 0.16)	0.54 (0.38, 0.69)	0.64 (0.39, 0.88)	0.10 (0.02, 0.18)	0.54 (0.28, 0.79)
Mean TWiST†, months (95% CI)	12.75 (12.01, 13.50)	6.36 (5.85, 6.86)	6.40 (5.50, 7.30)	15.85 (14.61, 17.09)	6.61 (5.69, 7.53)	9.25 (7.71, 10.78)
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]

BRCA, breast cancer gene; CI, confidence interval; ITT, intention-to-treat; PBO, placebo; PFS, progression-free survival; TEAEs, treatment-emergent adverse events; TOX, toxicity; TWiST, time without symptoms or toxicity; QA-PFS, quality-adjusted progression-free survival; Q-TWiST, quality-adjusted time without symptoms or toxicity.
* The 'TOX health state' is defined as the mean duration of time that a patient experienced grade ≥3 TEAEs.
† The 'TWiST health state' is the mean duration of time without toxicity or symptoms of disease progression.
Source: ARIEL3 post-hoc analysis[75]; Oza et al. 2020[74]

B.3.7 Subgroup analysis

B.3.7.1 Pre-specified subgroup analyses

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 at the 15 April 2017 data cut, as summarised in Appendix E.[35]

B.3.7.1.1 PFS in patients with or without bulky disease

Rucaparib is the only PARP inhibitor maintenance treatment to date, reported to reduce tumour burden further in patients with bulky disease, emphasising its efficacy. Rucaparib treatment improved both PFS as assessed by the investigator, and PFS as assessed by IRR, vs. placebo in all three predefined efficacy analysis cohorts for groups of patients with and without bulky residual disease (residual tumour burden >2cm; Table 26).[76]

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Table 26. PFS in patients with or without residual bulky disease at baseline at the 15 April 2017 data cut[76]

Cohort	Rucaparib, n	Placebo, n	INV-PFS		IRR-PFS	
			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 IRR)						
Yes						
ITT population	71	29	0.40 (0.24–0.69)	8.2 vs. 2.9; p=0.0007	0.46 (0.26–0.81)	8.3 vs. 3.0; p=0.0057
HRD cohort	39	18	0.30 (0.13–0.69)	8.3 vs. 2.8; p=0.0030	0.58 (0.25–1.34)	8.3 vs. 2.9; p=0.1994
BRCA mutated cohort	21	10	0.09 (0.02–0.37)	11.1 vs. 2.8; p=0.0002	0.13 (0.03–0.55)	17.1 vs. 2.9; p=0.0028
No						
ITT population	304	160	0.36 (0.29–0.46)	11.0 vs. 5.4; p<0.0001	0.34 (0.26–0.45)	16.2 vs. 5.4; p<0.0001
HRD cohort	197	100	0.31 (0.23–0.43)	13.8 vs. 5.5; p<0.0001	0.32 (0.22–0.47)	24.7 vs. 5.6; p<0.0001
BRCA mutated 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 vs. 5.5; p<0.0001

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; INV, investigator-assessed; IRR, independent radiology review; ITT, intention-to-treat; PFS, progression-free survival.
Notes: *, stratified log-rank p value.
Source: Aghajanian et al. 2018[76]

B.3.7.1.2 Rucaparib efficacy in BRCA wild type subgroups

As part of the pre-planned analyses at the time of final data-cutoff, the efficacy of rucaparib vs. placebo was assessed in patients with wild type BRCA, i.e., 'BRCA wild type LOH+', 'BRCA wild type mutant LOH−' and 'BRCA wild type LOH unknown' subgroups (Table 27).[56] There was no significant benefit with rucaparib compared with placebo in the OS of patients with wild type BRCA. Note that data are confounded by small populations and subsequent PARP inhibitor treatment among patients randomised to the placebo arm (Section B.3.6.2.3).[56] Patients within each of the three BRCA wild type subgroups experienced significantly prolonged TFST and CFI compared with patients who received placebo (Table 27).[56]

Table 27. Pre-specified analyses in non-BRCA mutant subgroups (final data cutoff, 4th April 2022)[56]

	BRCA wild type mutant LOH+		BRCA wild type LOH−		BRCA wild type LOH unknown	
	Rucaparib (n=106)	PBO (n=52)	Rucaparib (n=107)	PBO (n=54)	Rucaparib (n=32)	PBO (n=17)
Median OS, months (95% CI)	36.8 (31.4, 46.3)	44.7 (34.4, 58.2)	28.6 (23.4, 31.9)	32.6 (22.9, 40.6)	33.9 (26.6, 41.3)	26.7 (15.2, 51.7)

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	BRCA wild type mutant LOH+		BRCA wild type LOH−		BRCA wild type LOH unknown	
	Rucaparib (n=106)	**PBO (n=52)**	**Rucaparib (n=107)**	**PBO (n=54)**	**Rucaparib (n=32)**	**PBO (n=17)**
HR (95% CI) p-value	1.280 (0.841, 1.948) 0.2490		1.153 (0.784, 1.695) 0.4703		0.673 (0.305, 1.483) 0.3256	
Median PFS2, months (95% CI)	23.6 (17.6, 25.8)	18.3 (12.1, 22.1)	15.7 (14.1, 17.8)	13.5 (11.6, 16.3)	19.1 (12.7, 26.0)	14.8 (8.3, 17.4)
HR (95% CI) p-value	0.779 (0.533, 1.138) 0.1965		0.828 (0.573, 1.196) 0.3143		0.414 (0.192, 0.893) 0.0246	
TFST, median (95% CI) [months]	11.9 (9.4, 15.7)	7.7 (6.5, 9.5)	9.7 (8.1, 11.2)	7.5 (6.0, 9.2)	9.6 (8.1, 14.0)	5.5 (3.9, 7.4)
HR (95% CI) p-value	0.590 (0.404, 0.863) 0.0066		0.628 (0.437, 0.902) 0.0118		0.268 (0.119, 0.606) 0.0016	
TSST, median (95% CI) [months]	22.6 (17.6, 26.5)	19.4 (13.7, 24.1)	17.6 (15.5, 19.1)	14.5 (12.9, 19.6)	19.0 (13.8, 26.0)	14.9 (8.5, 17.9)
HR (95% CI) p-value	0.854 (0.584, 1.249) 0.4172		0.895 (0.623, 1.287) 0.5498		0.412 (0.194, 0.875) 0.0211	
CFI, median (95% CI) [months]	13.4 (10.8, 17.6)	9.5 (7.9, 11.2)	11.7 (10.0, 13.4)	8.7 (7.6, 10.8)	10.7 (9.7, 15.0)	6.9 (5.6, 9.2)
HR (95% CI) p-value	0.627 (0.425, 0.924) 0.0184		0.584 (0.403, 0.848) 0.0046		0.328 (0.141, 0.764) 0.0098	

BRCA, breast cancer gene; CFI, chemotherapy-free interval; CI, confidence interval; HR, hazard ratio; LOH, loss of heterozygosity; OS, overall survival; PBO, placebo; PFS2 progression-free survival on a subsequent line of treatment; TFST, time to start of first subsequent treatment, TSST, time to start of second subsequent treatment.
Source: ARIEL3 CSR addendum[56]

B.3.7.2 Post-hoc subgroup analyses of non-BRCA mutant subgroup

B.3.7.2.1 PFS and TTD in non-BRCA mutant subgroups

PFS and TTD were evaluated in the non-BRCA mutated cohort (N=368, Section B.3.7.1.2) as part of a requested post-hoc analysis.[62] At the 15 April 2017 data cut, [redacted] of patients in the rucaparib group and [redacted] of patients in the placebo group had experienced a PFS event. Median PFS was significantly higher in the rucaparib group ([redacted] months) than in the placebo ([redacted] months) group (HR: [redacted]) (Figure 17).[62]

At the 15 April 2017 data cut, [redacted] of patients in the rucaparib group and [redacted] of patients in the placebo group had experienced a TTD event.[62] Median TTD was significantly higher in the rucaparib group ([redacted] months) than in the placebo ([redacted] months) group (HR: [redacted]) (Figure 18).[62]

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Figure 17. KM estimates of INV-PFS in the non-BRCA mutated cohort of ARIEL3 (post-hoc analysis; 15 April 2017 data cut)

BRCA, breast cancer gene; INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival

Figure 18. KM estimates of TTD in the non-BRCA mutated cohort of ARIEL3 (post-hoc analysis; 15 April 2017 data cut)

BRCA, breast cancer gene; KM, Kaplan–Meier; TTD, time to treatment discontinuation

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B.3.7.2.2 OS, PFS2, TFST and TSST in the non-BRCA mutant subgroup

The post-hoc analysis of OS and PFS2 in the non-BRCA mutated cohort included 368 patients (n=245 randomised to rucaparib; n=123 randomised to placebo). At the final analysis (4 April 2022), [redacted] of patients in the rucaparib group and [redacted] of patients in the placebo group had experienced an OS event (Figure 19). OS was not significantly different between the rucaparib ([redacted] months) and placebo ([redacted] months) groups [redacted]).

At the final analysis, [redacted] of patients in the rucaparib group and [redacted] of patients in the placebo group had experienced a PFS2 event (Figure 20). PFS2 was significantly higher in the rucaparib group ([redacted] months) than in the placebo ([redacted] months) group ([redacted]).

At the final analysis, [redacted] of patients in the rucaparib group and [redacted] of patients in the placebo group had experienced a TFST event (Figure 21). TFST was higher in the rucaparib group ([redacted] months) than in the placebo ([redacted] months) group. [redacted]). At the final analysis, [redacted] of patients in the rucaparib group and [redacted] of patients in the placebo group had experienced a TSST event (Figure 22). TSST was higher in the rucaparib group ([redacted] months) than in the placebo ([redacted] months) group. [redacted]).

Figure 19. KM estimates of OS in the non-BRCA mutated cohort (post-hoc analysis; final analysis: 4 April 2022)

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; OS, overall survival

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Figure 20. KM estimates of PFS2 in the non-BRCA mutated cohort (post-hoc analysis; final analysis: 4 April 2022)

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; PFS2, progression-free survival 2

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Figure 21. KM estimates of TFST in the non-BRCA mutated cohort (post-hoc analysis; final analysis: 4 April 2022)

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; TFST, time to start of first subsequent treatment

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Figure 22. KM estimates of TSST in the non-BRCA mutated cohort (post-hoc analysis; final analysis: 4 April 2022)

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; TSST, time to start of second subsequent treatment

B.3.8 Meta-analysis

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

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Identification of relevant studies

B.3.9.1.1 Published clinical trial data

As detailed in Appendix D, seven trials (reported across 89 citations) were identified through a systematic literature review that could be considered for inclusion in ITCs of interest to this appraisal; these trials investigated rucaparib, olaparib, niraparib and/or routine surveillance. Two trials were excluded during feasibility assessment (NCT01081951 and OReO/ENGOT Ov-38; see Appendix D). NCT01081951 was excluded due to the use of a treat-through design without providing baseline patient characteristics at the maintenance phase; therefore providing inadequate data to sufficiently compare patient populations. OReO/ENGOT Ov-38 was excluded due to the enrolment of patients who were previously treated with PARP

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inhibitors, resulting in a lack of comparability with other trial populations. Ultimately, five 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) and two trials comparing niraparib to placebo for the maintenance treatment of ovarian, fallopian tube or primary peritoneal cancer with predominantly high-grade serious histologic features (NOVA and NORA). Details of these studies are provided in Appendix D. A comparative summary of methods is summarised in Table 29 and key patient characteristics in Table 30. Patient characteristics at baseline for studies considered for ITC (total trial population data)[35,50,51,58,59]

As can be seen from these data, there is observed heterogeneity across studies with regard to trial design and patient population. Key differences between studies included in the ITC are summarised in Table 28.[35,50,51,56,59,65,77-79]

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Table 28. Overview of key differences in studies included in the ITC[35,50,51,56,59,65,77-79]

	ARIEL3	SOLO2	Study 19	NOVA	NORA
Study design	Phase III	Phase III	Phase II		
Patient population	• High-grade serous or endometrioid OC • Somatic and germline BRCA mutated and non-BRCA mutated OC	• High-grade serous or endometroid OC • Germline BRCA mutated OC	• High-grade serous OC • Somatic and germline BRCA mutated and non-BRCA mutated OC	• High-grade serous OC • Germline BRCA mutated and non-germline BRCA mutated OC	• High-grade serous OC (or no histological restrictions for patients with germline BRCA mutation) • Germline BRCA mutated and non-germline BRCA mutated OC
Stratification	Used BRCA status as one stratification factor in the randomisation process	BRCA status was not stratified in randomisation because all patients had germline BRCA mutation	Used ancestry (Jewish vs. non-Jewish) as a proxy of BRCA status in the stratified randomisation	BRCA status was not stratified in randomisation because results were reported separately for the germline BRCA mutation cohort and the non-germline BRCA mutation cohort	Used germline BRCA status as one stratification factor in the randomisation process
Dosing	Rucaparib in tablet formulation was dosed at 1200mg/day	Olaparib in tablet formulation was dosed at 600mg/day	Olaparib in capsule formulation was dosed at 800mg/day	Niraparib in capsule formulation was dosed at 300mg/day	Niraparib in capsule formulation was dosed at 200mg/day or 300mg/day depending on weight and platelet count[b]
OS maturity	Mature with 77 months follow-up	Mature with 65.7 months follow-up with olaparib and 64.5 months with placebo	Mature with 78.0 month follow-up	Mature with median follow-up of >75 months	Immature data with no more than 15.8 months follow-up

BRCA, BReast CAncer gene; CR, complete response; OC, ovarian cancer; OS, overall survival

[a] The ARIEL3 and Study 19 BRCA mutated cohorts included patients with somatic and germline BRCA mutations, while the SOLO2, NOVA and NORA BRCA mutated cohorts included only patients with germline BRCA mutations

[b] The niraparib starting dose was 300mg/day for patients with bodyweight ≥77 kg and platelet count ≥150 x 10^3mcl; the niraparib starting dose was 200mg/day for patients with bodyweight <77 kg or platelet count <150 x 10^3mcl

Source: Coleman et al. 2017[35]; Ledermann et al. 2012[77]; Pujade-Lauraine et al. 2017[50]; Mirza et al. 2016[51]; Wu et al. 2021[59]; ARIEL3 CSR addendum[56]; Poveda et al. 2021[78]; Friedlander et al. 2018[65]; Matulonis, 2023[79]

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Table 29. Comparative summary of studies considered for ITCs[35,50,51,56,59,65,77-80]

	ARIEL3	SOLO2	Study 19	NOVA	NORA
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.	Randomised, double-blind, placebo-controlled, multicentre, phase III.	Randomised, double-blind, placebo-controlled, multicentre, phase III.
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.	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.	Adult patients with platinum-sensitive, relapsed, high-grade serous OC (or no histological restrictions for patients with germline BRCA mutation) 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)	Niraparib 300mg/day (n=138 with germline BRCA mutation; n=234 without germline BRCA mutation)	Niraparib 200mg/day or 300mg/day[a] (n=177)
Comparator	Placebo (n=189)	Placebo (n=99)	Placebo (n=129)	Placebo (n=65 with germline BRCA mutation; n=116 without germline BRCA mutation)	Placebo (n=88)
Primary endpoint	INV-PFS	INV-PFS	INV-PFS	IRC-assessed PFS	IRC-assessed PFS
Median follow-up duration	• PFS: Minimum follow-up duration ~9 months • OS and PFS2: 77 months	• PFS and PFS2: 22.1 months with olaparib; 22.2 with placebo • OS: 65.7 months with olaparib; 64.5 months with placebo	• PFS: Not reported • OS: 78 months	• PFS: 16.9 months • OS and PFS2: >75 months	• PFS and TFST: 15.8 months • OS: Not reported

BRCA, breast cancer gene; CR, complete response; INV-PFS, investigator-assessed progression-free survival; IRC, independent review committee; ITC, indirect treatment comparison; NR, not reported; OC, ovarian cancer; PFS, progression-free survival; PR partial response.

[a] The niraparib starting dose was 300mg/day for patients with bodyweight ≥77 kg and platelet count ≥150 x 10^3mcl; the niraparib starting dose was 200mg/day for patients with bodyweight <77 kg or platelet count <150 x 10^3mcl

Source: Coleman et al. 2017[35]; Ledermann et al. 2012[77]; Pujade-Lauraine et al. 2017[50]; Mirza et al. 2016[51]; Wu et al. 2021[59]; ARIEL3 CSR addendum[56]; Poveda et al. 2021[78]; Friedlander et al. 2018[65]; Matulonis, 2023[79]; Wu et al. 2021[59]; Wu et al. 2023[80]

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Table 30. Patient characteristics at baseline for studies considered for ITC (total trial population data)[35,50,51,58,59]

	ARIEL3		SOLO2		Study 19		NOVA (germline BRCA mutation)		NOVA (no germline BRCA mutation)		NORA	
	Rucaparib (n=375)	Placebo (n=189)	Olaparib (n=196)	Placebo (n=99)	Olaparib (n=136)	Placebo (n=129)	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)	Niraparib (n=177)	Placebo (n=88)
Age in years, median (range)	61 (53, 67)	62 (53, 68)	56 (51, 63)	56 (49, 63)	58 (21, 89)	59 (33, 84)	57 (36, 83)	58 (38, 73)	63 (33, 84)	61 (34, 82)	53 (35, 78)	55 (38, 72)
Race, white %	80.5	78.8	88.3	91.9	95.6	97.7	89.1	84.6	85.9	87.1	NR	NR
BMI, mean	27.9	26.6	NR	NR	NR	NR	NR	NR	NR	NR	24.4	24.2
ECOG PS ≥1, %	25.3	28.0	16.3	22.2	17.6	24.8	34.1	26.2	31.6	32.8	60.5	60.2
FIGO ≥III, %	88.0	86.8	NR	NR	88.2	89.1	83.3	84.6	90.1	94.8	84.2	80.7
Ovarian tumour site, %	83.2	84.1	83.7	86.9	87.5	84.5	88.4	81.5	82.1	82.8	NR	NR
Serous histology, %	95.2	94.7	100	100	100	100	100	100	100	100	98.3	97.7
BRCA mutation[a], %	34.7	34.9	100	100	54.4	48.1	100	100	0	0	36.7	39.8
Prior lines of platinum chemotherapy, median (range)	2 (2, 6)	2 (2, 5)	Lines, %: 2: 56.1 3: 30.6 4: 9.2 ≥5: 3.6	Lines, %: 2: 62.6 3: 20.2 4: 12.1 ≥5: 5.0	2 (0, 7)	2 (2, 7)	Lines, %: 1: 0.7 2: 50.7 ≥3: 48.6	Lines, %: 1: 0 2: 46.2 ≥3: 53.8	Lines, %: 1: 0 2: 66.2 ≥3: 33.8	Lines, %: 1: 0 2: 66.4 ≥3: 32.8	2 (2, 2)	2 (2, 2)
Platinum-free interval >12 months, %	59.2	64.0	59.7	59.6	61.0	58.1	≥12 months: 60.9	≥12 months: 60.0	≥12 months: 61.5	≥12 months: 62.1	≥12 months: 68.4	≥12 months: 68.2
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	CR: 51 PR: 49	CR: 51 PR: 49	CR: 50 PR: 50	CR: 52 PR: 48	CR: 51 PR: 49	CR: 52 PR: 48

BRCA, breast cancer gene; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; ITC, indirect treatment comparison; NR, not reported; PBO, placebo; PR, partial response.

[a] The ARIEL3 and Study 19 BRCA mutated cohorts included patients with somatic and germline BRCA mutations, while the SOLO2, NOVA and NORA BRCA mutated cohorts included only patients with germline BRCA mutations

Source: Coleman et al. 2017[35]; Ledermann et al. 2016[58]; Pujade-Lauraine et al. 2017[50]; Mirza et al. 2016[51]; Wu et al. 2021[59]

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B.3.9.1.2 Clinical study data

The raw data used to populate the ITC were sourced from published literature (described above) in addition to post-hoc analyses of the ARIEL3 clinical study (Table 31).[35,50,51,55,56,59,65,77-81]

Further information about efficacy outcomes from these trials, including data are presented in Appendix D.

Table 31. Summary of outcomes for the BRCA mutated and non-BRCA mutated cohorts[35,50,51,55,56,59,65,77-81]

HR (95% CI)	Rucaparib vs. placebo	Olaparib vs. placebo		Niraparib vs. placebo	
	ARIEL3	SOLO2	Study 19	NOVA	NORA
BRCA mutated cohort[a]					
INV-PFS	0.23 (0.16, 0.34)	0.30 (0.22, 0.41)	0.18 (0.10, 0.31)	Not reported	Not reported
OS	0.832 (0.581, 1.192)	0.74 (0.54, 1.00)	0.62 (0.42, 0.93)	0.85 (0.61, 1.20)	0.764 (0.398, 1.464)
PFS2	0.672 (0.48, 0.941)	0.5 (0.34, 0.72)	Not reported	0.7 (0.500, 0.968)	Not reported
Non-BRCA mutated cohort[a]					
INV-PFS	LOH^{high}: 0.44 (0.29, 0.66) LOH^{low}: 0.58 (0.40, 0.85) $LOH^{unknown}$: 0.25 (0.11, 0.56)	Not applicable	0.54 (0.34, 0.85)	Not reported	Not reported
OS	1.096 (0.852, 1.411)	Not applicable	0.84 (0.57, 1.25)	1.06 (0.81, 1.37)	0.855 (0.529, 1.381)
PFS2	0.713 (0.563, 0.903)	Not applicable	Not reported	0.8 (0.627, 1.022)	Not reported

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; OS, overall survival; PFS2, progression-free survival on a subsequent line of treatment
[a] The ARIEL3 and Study 19 BRCA mutated cohorts included patients with somatic and germline BRCA mutations, while the SOLO2, NOVA and NORA BRCA mutated cohorts included only patients with germline BRCA mutations
Source: Coleman et al. 2017[35]; Ledermann et al. 2012[77]; Ledermann et al. 2014[81]; Pujade-Lauraine et al. 2017[50]; Mirza et al. 2016[51]; Wu et al. 2021[59]; ARIEL3 CSR 2017[55]; ARIEL3 CSR addendum[56]; Poveda et al. 2021[78]; Friedlander et al. 2018[65]; Matulonis, 2023[79]; Wu et al. 2023[80]

B.3.9.1.3 Systemic Anti-Cancer Therapy (SACT) dataset

Following the original NICE appraisals for rucaparib and niraparib for relapsed OC, both PARP inhibitors were recommended for commissioning through the CDF to allow a period of managed access. During the managed access period, the real-world treatment effectiveness of rucaparib and niraparib were assessed by NHS England to address clinical uncertainty. SACT data for rucaparib were made available on request for this submission while the corresponding data for niraparib were identified from appraisal TA784.[82,83] Analyses

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comparing treatment outcomes described in the SACT dataset are presented in Section 3.9.4.

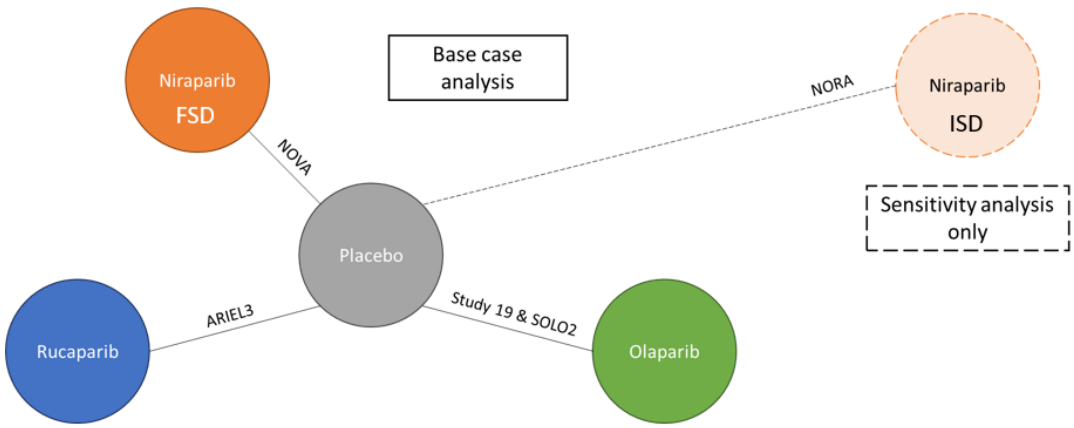
B.3.9.2 Network meta-analysis (NMA)

B.3.9.2.1 Methods

ARIEL3, SOLO2, Study 19 and NOVA share a common comparator in placebo and included patients with ≥2 prior lines of platinum-based chemotherapy. These studies could be linked in a network of evidence, as shown in Figure 23 and were used in the base case analysis.

However, although NORA could also have been linked to the network through its placebo arm, this study was excluded from the base case analysis for 2 reasons: 1) the number of prior lines of chemotherapy (i.e., exactly 2 prior lines), and 2) use of a 200 mg/day starting dose of niraparib for the majority of patients in the niraparib treatment arm. This 200 mg/day starting dose is lower than that used in the NOVA trial and also lower than the dose recommended in the Summary of Product Characteristics (SmPC) for niraparib (300 mg once daily); moreover, the SmPC noted a 200 mg dose appears to give a lower treatment effect than a 300 mg dose in newly diagnosed patients with homologous recombination proficient OC.[45] Details of the sensitivity analyses, which included NORA in the network of evidence, are included in Appendix D.

Figure 23. Network diagram



Note: ARIEL3, Study 19, SOLO2 and NOVA were included in the base case analysis; NORA was included in the sensitivity analysis.
FSD = fixed starting dose, ISD = individualized starting dose

Full details of the methods adopted for NMA are provided in Appendix D; methods followed those recommended by NICE.[84] Bayesian fixed effects NMAs were used for all outcomes

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given the limited evidence base, and a proportional hazards assumption test supported the use of HRs as a summary measure for outcomes of interest.

B.3.9.2.2 Results

Results of efficacy NMAs, conducted on the population of interest in this appraisal for comparison to niraparib (a relevant comparator in the BRCA mutated and non-BRCA mutated cohorts) and olaparib (a relevant comparator in the BRCA mutated cohort only), are summarised in Table 32. No statistically significant advantage or disadvantage was observed for rucaparib vs. either olaparib or niraparib for PFS, PFS2, TSST or OS. However, a substantially higher proportion of patients randomised to placebo in the ARIEL3 trial were treated with subsequent PARP inhibitors compared to SOLO2 and NOVA; this may have biased estimates in favour of niraparib and olaparib (Section B.3.6.2.3.1 and Section B.3.9.5).[40,41,56] It should also be noted that only immature PFS2 data were available in SOLO2 and mature PFS2 was not reported for that trial, which may have contributed to further bias in the NMA results.

Comparisons between rucaparib vs. olaparib for PFS and PFS2 in the non-BRCA mutated cohort could not be estimated because neither SOLO2 nor Study 19 reported data for this cohort.

Table 32. NMA outcomes, BRCA mutated and non-BRCA mutated cohorts (base case network)

	Rucaparib vs. olaparib[a]	Rucaparib vs. niraparib[b]
BRCA mutated cohort		
INV-PFS, HR (95% CI)	[redacted]	[redacted]
OS, HR (95% CI)	[redacted]	[redacted]
PFS2, HR (95% CI)	[redacted][c]	[redacted]
TSST, HR (95% CI)	[redacted]	[redacted]
Non-BRCA mutated cohort		
INV-PFS, HR (95% CI)	[redacted]	[redacted]
OS, HR (95% CI)	[redacted]	[redacted]
PFS2, HR (95% CI)	[redacted]	[redacted]
TSST, HR (95% CI)	[redacted]	[redacted]

CI, confidence interval; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; NMA, network meta-analysis; OS, overall survival; PFS2, progression-free survival on a subsequent line of treatment; TSST, time to start of second subsequent therapy
Note: ARIEL3, Study 19, SOLO2 and NOVA were included in the base case analysis
[a] Olaparib is a relevant comparator in the BRCA mutated cohort only
[b] Niraparib is a relevant comparator in both the BRCA mutated and non-BRCA mutated cohorts
[c] Only immature PFS2 data were available in SOLO2 and mature PFS2 was not reported for that trial.

Sensitivity analysis based on the extended version of the base case network that included NORA as an additional node (see Figure 23) did not impact the relative efficacy between rucaparib and olaparib and between rucaparib and niraparib (200 mg daily dose). Please

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see Appendix D for sensitivity analysis results including the NORA study of niraparib in the network.

B.3.9.3 Matching-adjusted indirect comparison (MAIC)

B.3.9.3.1 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 potentially important differences in the proportion of patients with BRCA mutation, as well as differences in treatment history. While these were minimised by conducting the NMA in a focused cohort of patients, this does have its own limitations (see Section B.3.9.5). The impact of other potential effect modifiers (for example, differences in response to latest platinum-based chemotherapy) could not be addressed through NMA.

Therefore, MAICs were conducted in addition to the NMA. More specifically, anchored MAICs for PFS, OS and PFS2 adjusting for clinically validated treatment effect modifiers (EMs) were conducted based on ARIEL3, SOLO2, and NOVA clinical studies in BRCA and non-BRCA mutated cohorts. Exploration of EMs based on published subgroup analyses of PARP inhibitors identified four key EMs (see Appendix D for additional details):

- Number of prior lines of platinum therapy
- Length of platinum-free interval
- Response to platinum therapy
- Body–mass index (BMI; reported only for NOVA arms)

The anchored MAICs attempted to adjust for all EMs. Further MAIC models with adjustments for all commonly available population characteristics were explored in a sensitivity analysis. In addition, to reduce potential bias due to difference in the proportion of patients 'switching' to PARP inhibitors in the placebo arms in ARIEL3 ([redacted]) and SOLO2 (38.4%), unanchored MAIC adjusting for all available factors was conducted for OS and PFS2.[40,41,56] The following population characteristics were used for adjustments in the sensitivity analysis of anchored MAIC against NOVA and SOLO2 and in the unanchored MAIC against SOLO2:

- ECOG PS
- Number of prior lines of chemotherapy
- Location of primary tumour
- Histological class
- FIGO stage (reported only for NOVA arms)

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- Prior use of bevacizumab
- Age
- Race
- BRCA mutation type (reported only for SOLO2 arms)
- Tumour lesion(s) at baseline (reported only for SOLO2 arms)
- Time since last platinum therapy (reported only for SOLO2 arms)
- Time since diagnosis (reported only for NOVA arms)
- Number of metastatic sites (reported only for NOVA arms)

Full details of the methods adopted for MAIC are provided in Appendix D and followed NICE technical guidance.[85] In summary, patient-level data from ARIEL3 were matched to aggregate data from NOVA and SOLO2 in the BRCA and non-BRCA mutated cohorts (wherever applicable). The indirect relative effect of rucaparib versus the comparator was calculated based on the HR obtained from ARIEL3 by using re-weighted Cox regression analysis.

B.3.9.3.2 Results

The key EMs were reported for NOVA and SOLO2 studies, with the exception of BMI, which was not reported in SOLO2. Matching on all available EMs was successful in each arm of BRCA and non-BRCA mutated cohorts for each comparator. The effective sample size (ESS) was found to be sufficient for MAIC analysis for all matching. When matching against NOVA study arms the ESS was 152 in the BRCA mutated cohort (78% of the cohort population, N=196) and 306 in the non-BRCA mutated cohort (83% of the cohort population, N=368). When matching against SOLO2 study arms in the BRCA mutated cohort the ESS was 185 (94% of the cohort population, N=196). Baseline characteristics of the rucaparib and placebo populations of the ARIEL3 trial before and after matching for the base case analysis comparing with niraparib are provided in Table 33 and Table 34; weighting for the base case analysis comparing with olaparib is provided in Table 35.

Table 33. Baseline characteristics before and after matching: BRCA mutated; NOVA; anchored MAIC

Variable	Original index data mean		Weighted index data mean		Comparator data mean	
	Rucaparib (N=130)	Placebo (N=66)	Rucaparib (ESS=95)	Placebo (ESS=57)	Niraparib (N=138)	Placebo (N=65)
Prior lines of platinum therapy, ≥3 (vs. 2), %	40.8	37.9	42.0	43.1	42.0	43.1
PFI, >12 months (vs. <12 months), %	56.9	60.6	60.9	60	60.9	60.0

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Variable	Original index data mean		Weighted index data mean		Comparator data mean	
	Rucaparib (N=130)	Placebo (N=66)	Rucaparib (ESS=95)	Placebo (ESS=57)	Niraparib (N=138)	Placebo (N=65)
Response to prior platinum therapy, CR (vs. other), %	35.4	36.4	51.4	50.8	51.4	50.8
BMI, mean	27.896	26.918	26.06	26.78	26.06	26.78
Prior lines of chemotherapy ≥3 (vs. 2), %	43.8	39.4	44.7	45.4	48.6	53.8
BRCA type, 2 (vs. 1), %	38.5	43.9	34.5	45.5	37.0	27.7
ECOG PS, ≥1 (vs. 0), %	22.3	36.4	20.0	33.7	34.1	26.2
Tumour site, ovarian (vs. other), %	80.8	84.8	81.9	84.8	88.4	81.5
Histology type, serous (vs other), %	97.7	90.9	97.8	90.7	84.8	90.8
FIGO stage, ≥3 (v. <3), %	92.2	83.1	94.8	84.5	83.3	84.6
Prior use of bevacizumab, yes (vs. no), %	21.5	16.7	20.5	16.2	23.9	26.2
Age, median (≤57 y)*, %	44.6	48.5	46.6	47.3	50.0	50.0
Race, white (vs. other), %	88.3	84.2	87.0	87.9	89.1	84.6
Time since diagnosis (years), mean	3.986	4.064	4.04	4.137	4.37	4.07
Number of metastatic sites, <3 (vs ≤3), %	84.6	78.8	87.7	84.6	64.5	61.5

*Age, median (≤58 y) for placebo
BMI, body-mass index; BRCA, breast cancer gene; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, estimated sample size; FIGO, International Federation of Gynecology; MAIC, matching adjusted indirect comparison; PFI, platinum-free interval

Table 34. Baseline characteristics before and after matching: non-BRCA; NOVA; anchored MAIC

Variable	Original index data mean		Weighted index data mean		Comparator data mean	
	Rucaparib (N=245)	Placebo (N=123)	Rucaparib (ESS=191)	Placebo (ESS=115)	Niraparib (N=138)	Placebo (N=116)
Prior lines of platinum therapy, ≥3 (vs. 2), %	35.1	30.9	25.6	24.1	25.6	24.1
PFI, >12 months (vs. <12 months), %	60.4	65.9	61.5	62.1	61.5	62.1
Response to prior platinum therapy, CR (vs. other), %	31.4	29.3	50.0	25.6	50.0	25.6
BMI, mean	27.862	26.354	26.29	26.31	26.29	26.31
Prior lines of chemotherapy ≥3 (vs. 2), %	35.5	31.7	26.0	25.2	33.8	32.8
ECOG PS, ≥1 (vs. 0), %	26.9	23.6	26.0	24.8	31.6	32.8
Tumour site, ovarian (vs. other), %	84.5	84.6	83.7	83.3	82.1	82.8
Histology type, serous (vs other), %	94.3	96.7	94.6	97.6	91.9	94.8
FIGO stage, ≥3 (v. <3), %	86.8	90.9	86.8	90.6	90.2	94.8

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Variable	Original index data mean		Weighted index data mean		Comparator data mean	
	Rucaparib (N=245)	Placebo (N=123)	Rucaparib (ESS=191)	Placebo (ESS=115)	Niraparib (N=138)	Placebo (N=116)
Prior use of bevacizumab, yes (vs. no), %	22.4	26.0	22.9	23.5	26.5	25.9
Age, median (≤63 y)*, %	55.1	41.5	57.8	39.7	50.0	50.0
Race, white (vs. other), %	89.9	91.4	89.4	91.7	85.9	87.1
Time since diagnosis (years), mean	4+.053	3.756	3.626	3.544	3.33	3.59
Number of metastatic sites, <3 (vs ≤3), %	73.5	77.2	79.8	76	67.1	68.1

*Age, median (≤61 y) for placebo
BMI, body-mass index; BRCA, breast cancer gene; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, estimated sample size; FIGO, International Federation of Gynecology; MAIC, matching adjusted indirect comparison; PFI, platinum-free interval

Table 35. Baseline characteristics before and after matching, BRCA; SOLO2; anchored MAIC

Variable	Original index data mean		Weighted index data mean		Comparator data mean	
	Rucaparib (N=130)	Placebo (N=66)	Rucaparib (ESS=123)	Placebo (ESS=62)	Olaparib (N=196)	Placebo (N=99)
Prior lines of platinum therapy, ≥3 (vs. 2), %	40.8	37.9	43.4	37.4	43.4	37.4
PFI, >12 months (vs. <12 months), %	56.9	60.6	59.7	59.6	59.7	59.6
Response to prior platinum therapy, CR (vs. other), %	35.4	36.4	46.4	47.5	46.4	47.5
BRCA type, 2 (vs. 1), %	38.5	43.9	36.3	44.1	29.6	35.4
ECOG PS, ≥1 (vs. 0), %	22.3	36.4	21.4	33.6	16.3	22.2
Tumour site, ovarian (vs. other), %	80.8	84.8	81.6	84.3	83.7	86.9
Tumour lesion(s) at baseline (mm), >20 (vs. ≤20), %	16.2	15.2	14.8	12.0	15.3	18.2
Histology type, serous (vs other), %	97.7	90.	97.6	91.4	93.4	86.9
Prior use of bevacizumab, yes (vs. no), %	21.5	16.7	22.3	15.7	16.9	20.2
Time since last platinum therapy (weeks), >8 (vs. ≤8), %	6.9	3.0	6.8	3.2	4.1	2.0
Age, median (≤56 y), %	41.5	40.9	44.0	41.6	50.0	50.0
Race, white (vs. other), %	88.3	84.2	89.0	86.4	88.3	91.9

BRCA, breast cancer gene; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, estimated sample size; MAIC, matching adjusted indirect comparison; PFI, platinum-free interval

The proportional hazard (PH) assumption was investigated by the visual inspection of log cumulative hazard plots and Schoenfeld residuals plots in ARIEL3, NOVA and SOLO2 for each cohort and outcome of interest. However, some signals were identified for potential violation of proportionality, no conclusive evidence against the proportional hazard

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assumption was found for INV-PFS, OS and PFS2 in either BRCA or non-BRCA mutated cohorts (see Appendix D). These findings were further supported by testing an interaction term between treatment and time or log-time in Cox regression models indicating no evidence against constant relative effect over time between the treatment arms. Therefore, conducting anchored MAICs for PFS-INV, OS, and PFS2 for rucaparib versus niraparib or olaparib in BRCA and non-BRCA mutated cohorts were found appropriate.

As an illustration, Kaplan-Meier survival plots for PFS, OS, and PFS2 before and after MAIC adjustment are presented in Figure 24 to Figure 32. Relative efficacy estimates for PFS, OS and PFS2 along with 95% confidence intervals and p values from the anchored MAIC adjusting for all available EMs in the BRCA mutated cohort and in the non-BRCA mutated cohort are summarised in Table 36. Results across MAIC analyses were generally similar to those in the NMA, suggesting that studies were generally well balanced on any strong effect modifiers. No consistent trends in favour of one treatment or another were observed when comparing across the PARP inhibitor maintenance treatments. Importantly, a substantially higher proportion of patients randomised to placebo in the ARIEL3 trial were treated with subsequent PARP inhibitors compared to SOLO2 and NOVA; this may have biased estimates in favour of niraparib and olaparib (Section B.3.6.2.3.1 and Section B.3.9.5).[40,41,56] It should also be noted that the PFS2 data in SOLO2 were immature, which may have contributed to further bias in the MAIC results.

The sensitivity analysis for anchored MAIC adjusting for all commonly available population characteristics resulted in low ESS against NOVA in each mutated cohorts (20% of the cohort population in BRCA and 24% of the cohort population in non-BRCA). Therefore, results in these cases should be treated with caution. In spite of some numerical differences in the relative efficacy estimates, findings of the sensitivity analyses supported the results of base case analysis and provided no indication of statistically significant differences in efficacy across PARP inhibitors. Additional details of the sensitivity analysis are presented in Appendix D.

Comparing with the anchored MAIC, the unanchored MAIC of long-term outcomes against SOLO2 (see Table 37) provided similar HRs for OS ([redacted]) and [redacted] and reduced the numerical difference in PFS2 from [redacted] to [redacted]. The differences were not statistically significant in either case (see Appendix D).

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Table 36. Anchored MAIC for INV-PFS, OS, and PFS2

Outcome	Cohort	Comparator Trial	Index Treatment	Comparator Treatment	Naïve comparison, HR (95% CI)	Naïve p-value	MAIC, HR (95% CI)	MAIC p-value
INV-PFS	BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	NON-BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	BRCA	SOLO2	Rucaparib	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
OS	BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	NON-BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	BRCA	SOLO2	Rucaparib	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
PFS2	BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	NON-BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	BRCA	SOLO2[a]	Rucaparib	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]

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; PFS2, time to second progression event; OS, overall survival.
[a] Only immature PFS2 data were available in SOLO2; mature PFS2 was not published.

Table 37. Unanchored MAIC for OS, and PFS2 against SOLO2

Outcome	Cohort	Comparator Trial	Index Treatment	Comparator Treatment	Naïve comparison, HR (95% CI)	Naïve p-value	MAIC, HR (95% CI)	MAIC p-value
OS	BRCA	SOLO2	Rucaparib	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
PFS2	BRCA	SOLO2[a]	Rucaparib	Olaparib	[redacted]	[redacted]	[redacted][a]	[redacted]

CI, confidence interval; HR, hazard ratio; MAIC, matching adjusted indirect comparison; OS, overall survival; PFS2, progression-free survival 2
[a] Only immature PFS2 data were available in SOLO2 and mature PFS2 was not published.

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Figure 24. Observed and adjusted INV-PFS for rucaparib and placebo (in ARIEL3) in the BRCA mutated cohort[a]

BRCA, breast cancer gene; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival
[a] INV-PFS KM curves for niraparib and placebo in NOVA BRCA cohort are not available, only HRs are available

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Figure 25. Observed and adjusted OS for rucaparib (index active in ARIEL3) and placebo (index anchor in ARIEL3) and observed OS for niraparib (comparator active in NOVA) and placebo (comparator anchor in NOVA) in the BRCA mutated cohort

BRCA, breast cancer gene; OS, overall survival; P, probability

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Figure 26. Observed and adjusted PFS2 for rucaparib (index active in ARIEL3) and placebo (index anchor in ARIEL3) and observed PFS2[a] for niraparib (comparator active in NOVA) and placebo (comparator anchor in NOVA) in the BRCA mutated cohort

BRCA, breast cancer gene; HR, hazard ratio; KM = Kaplan-Meier; P, probability; PFS2, progression-free survival 2
Since PFS2 KM curves in NOVA were not reported in Matulonis et. al., 2023[79] reporting the most recent HR estimates, PFS2 KM curves from Matulonis et. al., 2021[71] were used for diagnostics

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Figure 27. Observed and adjusted INV-PFS for rucaparib and placebo (in ARIEL3) in the non-BRCA mutated cohort[a]

BRCA, breast cancer gene; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; KM, Kaplan-Meier
INV-PFS KM curves for niraparib and placebo in NOVA non-BRCA cohort are not available, only HRs are available

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Figure 28. Observed and adjusted OS for rucaparib (index active in ARIEL3) and placebo (index anchor in ARIEL3) and observed OS for niraparib (comparator active in NOVA) and placebo (comparator anchor in NOVA) in the non-BRCA mutated cohort

BRCA, breast cancer gene; OS, overall survival; P, probability

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Figure 29. Observed and adjusted PFS2 for rucaparib (index active in ARIEL3) and placebo (index anchor in ARIEL3) and observed PFS2[a] for niraparib (comparator active in NOVA) and placebo (comparator anchor in NOVA) in the non-BRCA mutated cohort

BRCA, breast cancer gene; HR, hazard ratio; KM, Kaplan-Meier; P, probability; PFS2, progression-free survival 2
Since PFS2 KM curves in NOVA were not reported in Matulonis et. al., 2023[79] reporting the most recent HR estimates, PFS2 KM curves from Matulonis et. al., 2021[71] were used for diagnostics

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Figure 30. Observed and adjusted INV-PFS for rucaparib and placebo (in ARIEL3) and olaparib and placebo (in SOLO2) in the BRCA mutated cohort

BRCA, breast cancer gene; INV-PFS, investigator-assessed progression-free survival

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Figure 31. Observed and adjusted OS for rucaparib (index active in ARIEL3) and placebo (index anchor in ARIEL3) and observed OS for olaparib (comparator active in SOLO2) and placebo (comparator anchor in SOLO2) in the BRCA mutated cohort

BRCA, breast cancer; OS, overall survival; P, probability

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Figure 32. Observed and adjusted PFS2 for rucaparib (index active in ARIEL3) and placebo (index anchor in ARIEL3) and observed PFS2 for olaparib (comparator active in SOLO2) and placebo (comparator anchor in SOLO2) in the BRCA mutated cohort

BRCA, breast cancer gene; P, probability; PFS2, progression-free survival 2

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B.3.9.4 Comparisons using SACT data

B.3.9.4.1 Patient characteristics

Between 11 October 2019 and 31 July 2022, 887 patients received treatment with rucaparib through the CDF and were included in the SACT analysis.[82] Similarly, between 1 June 2018 and 30 November 2019, 1,016 patients received treatment with niraparib through the CDF and were included in the SACT analysis.[83]

The majority of patients in both the rucaparib and niraparib SACT data sets did not have a BRCA mutation, indicating that the BRCA population in UK clinical practice is small.[82,83] Characteristics of patients treated with rucaparib and niraparib, separated into BRCA mutated and non-BRCA mutated cohorts, are presented in Table 38.[82,83] Key Blueteq data items in patients treated with rucaparib are presented in Table 39. There were a number of key differences between the rucaparib and niraparib SACT data sets:

- A significantly higher proportion of patients in the rucaparib SACT dataset were aged ≥80 years compared to the niraparib SACT data (12% vs. 6%; p<0.001) in the non-BRCA cohort.
- The proportion of patients with ECOG PS 1 was higher in the rucaparib dataset (53% to 62%) than in the niraparib data (42% to 52%); however, the rate of missing observation was higher for rucaparib (24% to 25%) than for niraparib (15% to 16%), which limits the comparability of ECOG PS between data sets. The imbalance in ECOG PS could not be adjusted for in the comparative analysis due to the lack of individual participant data.[82,83]
- While all patients included in the BRCA mutant cohort of the niraparib SACT data had germline mutations, 13% of patients in the rucaparib BRCA mutant cohort had mutations in the somatic tissue only.[82,83]
- Patients included in the niraparib SACT had not been previously treated with any PARP inhibitors. However, 18% of patients who received rucaparib in the BRCA mutant cohort and 6% of patients in the non-BRCA mutant cohort had prior maintenance therapy with a PARP inhibitor, which had to be stopped due to dose-limiting toxicity. Therefore, OS outcomes for patients treated with rucaparib are likely an underestimate due to lead time bias caused by prior treatment with PARP inhibitors.[82,83]

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There were also a number of uncertainties associated with the niraparib SACT data. It is unclear whether patients with somatic BRCA mutation were included in the non-BRCA mutant cohort of the SACT data, which was the case in the NOVA trial.[51,83] Moreover, the dose of niraparib administered to patients through the CDF was not stated in the SACT report.[83]

Table 38. Patient characteristics in the rucaparib and niraparib SACT data sets[82,83]

Patient characteristics	BRCA mutated cohort[a]		Non-BRCA mutated cohort	
	Rucaparib, n (%)	Niraparib, n (%)	Rucaparib, n (%)	Niraparib, n (%)
Sex				
Female	70 (100%)	157(100%)	817 (100%)	859 (100%)
Age				
Median age	61	60	69	68
<40	0 (0%)	3 (2%)	0 (0%)	4 (< 1%)
40 to 49	10 (14%)	21 (13%)	22 (3%)	27 (3%)
50 to 59	24 (34%)	52 (33%)	152 (19%)	169 (20%)
60 to 69	22 (31%)	46 (29%)	235 (29%)	283 (33%)
70 to 79	11 (16%)	29 (18%)	311 (38%)	324 (38%)
80+	3 (4%)	6 (4%)	97 (12%)	52 (6%)
ECOG PS				
Missing/unknown	17 (24%)	25 (16%)	207 (25%)	132 (15%)
0	23 (43%)	76 (58%)	231 (38%)	339 (47%)
1	28 (53%)	56 (42%)	376 (62%)	378 (52%)
2	2 (4%)	0 (0%)	3 (0%)	10 (1%)
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)

BRCA, breast cancer gene; ECOG PS, Eastern Cooperative Oncology Group performance status; SACT, Systemic Anti-Cancer Therapy
[a] The rucaparib BRCA mutated cohort included patients with somatic and germline BRCA mutations, while the niraparib BRCA mutated cohort included only patients with germline BRCA mutations
Source: National Disease Registration Service 2023 (rucaparib SACT data)[82]; NICE Committee Papers - ID1644[83]

Table 39. Distribution of key Blueteq data items in the rucaparib and niraparib SACT data sets[82,83]

Blueteq data items[a]	Rucaparib: BRCA mutated cohort (n=70), n (%)	Rucaparib: Non-BRCA mutated cohort (n=817), n (%)	Niraparib: BRCA mutated cohort (n=157), n (%)	Niraparib: Non-BRCA mutated cohort (n=859), n (%)
Germline or tumour detection of BRCA mutation				
Germline only	52 (74%)	Not applicable	100%	Not applicable
Tumour only	9 (13%)	Not applicable	0%	Not applicable
Both	5 (7%)	Not applicable	0%	Not applicable
Not captured	4 (6%)	Not applicable	0%	Not applicable
BRCA1 or BRCA2 mutation				
BRCA1	46 (66%)	Not applicable	Not reported	Not applicable
BRCA2	20 (29%)	Not applicable	Not reported	Not applicable
Both	0 (%)	Not applicable	Not reported	Not applicable
Not captured	4 (6%)	Not applicable	100%	Not applicable
Line of platinum-based treatment				

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Blueteq data items[a]	Rucaparib: BRCA mutated cohort (n=70), n (%)	Rucaparib: Non-BRCA mutated cohort (n=817), n (%)	Niraparib: BRCA mutated cohort (n=157), n (%)	Niraparib: Non-BRCA mutated cohort (n=859), n (%)
2L	57 (81%)	702 (86%)	Not reported	Not reported
3L	9 (13%)	92 (11%)	Not reported	Not reported
≥4L	0 (0%)	23 (3%)	Not reported	Not reported
Not captured	4 (6%)	0 (0%)	100%	Not reported
PARP inhibitor				
No previous PARP inhibitor	51 (73%)	765 (94%)	100%	100%
Prior niraparib (CDF)[b]	8 (11%)	48 (6%)	0 (0%)	0 (0%)
Prior olaparib (CDF)[b]	5 (7%)	0 (0%)	0 (0%)	0 (0%)
Prior rucaparib (early access)	2 (3%)	4 (<1%)	0 (0%)	0 (0%)
Not captured	4 (6%)	0 (0%)	0 (0%)	0 (0%)
Response assessment after most recent platinum-base chemotherapy				
PR	35 (50%)	606 (74%)	Not reported	Not reported
CR	22 (31%)	156 (19%)	Not reported	Not reported
Not captured	13 (19%)	55 (7%)	100%	100%

BRCA, breast cancer gene; CDF, Cancer Drugs Fund; CR, complete response; CT, computer tomography; PARP, Poly (ADP-ribose) polymerase; PR, partial response

[a] Figures may not add up to 100% due to rounding
[b] Which had to be stopped within 3 months solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression
Source: National Disease Registration Service 2023 (rucaparib SACT data)[82]; CDF review TA528 (niraparib SACT data)[83]

B.3.9.4.2 Results

The SACT datasets provide strong evidence to support the equivalent effectiveness of PARP inhibitors in UK clinical practice, particularly in the non-BRCA mutated cohort which included over 800 patients in both the rucaparib and niraparib groups. While the BRCA mutated cohorts were substantially smaller (n=70 in the rucaparib data set; n=157 in the niraparib data set), and the follow-up duration was substantially shorter for the niraparib dataset, naïve comparison of OS and TTD outcomes suggests rucaparib and niraparib are similar regardless of BRCA mutation status (Table 40).[82,83]

Median OS follow-up for niraparib in the BRCA mutated cohort was substantially shorter than for rucaparib (13.7 months vs. 19.5 months); therefore, OS outcomes were more mature in the rucaparib SACT data set than in the niraparib SACT data set. In the BRCA mutated cohort, median OS was 30.8 months with rucaparib and not reached with niraparib. The estimated HR, calculated by Cox proportional hazard model, suggests rucaparib and niraparib are similar (HR: 1.04 [95% CI: 0.64, 1.69]).

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In the non-BRCA mutated cohort, median OS was 3 months longer in the rucaparib SACT data set than in the niraparib SACT data set (25.7 months vs. 22.6 months). The estimated HR supports a numerical advantage with rucaparib though statistical significance was not reached (HR: 0.88 [95% CI: 0.76, 1.02]). It should be noted that 18% and 6% of patients who received rucaparib in the BRCA mutant and non-BRCA mutant cohorts, respectively, had prior treatment with PARP inhibitors in the same line, while no patients treated with niraparib had previously received any PARP inhibitors. The OS observed in SACT for rucaparib may therefore be reduced by the time rucaparib patients spent on prior PARP inhibitor treatments before switching to rucaparib. Therefore, in comparison with niraparib the OS in SACT may be biased against rucaparib due to lead time bias caused by prior PARP inhibitors.[82,83]

Estimated HRs for TTD in both the BRCA mutated and non-BRCA mutated cohorts also suggest the effectiveness of rucaparib and niraparib are comparable. Overall, results from the naïve comparison of rucaparib and niraparib based on SACT data are in line with outcomes from the NMA (Section B.3.9.2.2) and MAIC (Section B.3.9.3.2).[82,83]

Table 40. Naïve comparison of OS and TTD outcomes from the rucaparib and niraparib SACT data sets[82,83]

Outcome	BRCA mutated cohort[a]		Non-BRCA mutated cohort	
	Rucaparib (n=70)	Niraparib (n=157)	Rucaparib (n=817)	Niraparib (n=859)
OS outcomes				
Median follow-up (months)	19.5	13.7	14.7	12.0
Maximum follow-up (months)	37.7	32	37.7	32
Median (months)	30.8	Not reached	25.7	22.6
HR (95% CI)[a]	1.04 (0.64, 1.69)		0.88 (0.76, 1.02)	
TTD outcomes				
Median follow-up (months)	9.7	6.8	5.5	4.6
Maximum follow-up (months)	33.6	19	33.6	19
Median (months)	12.4	12.2	6.5	6.4
HR (95% CI)[a]	1.11 (0.75, 1.63)		1.032 (0.91, 1.16)	

BRCA, breast cancer gene; OS, overall survival; TTD, time to treatment discontinuation
[a] Hazard ratio was calculated by Cox proportional hazard model based on re-constructed patient level data from digitized curves following the algorithm described in Guyot et al. 2012.[86]
Source: National Disease Registration Service 2023 (rucaparib SACT data)[82]; NICE Committee Papers - ID1644[83]

KM curves of OS and TTD for rucaparib and niraparib in BRCA and non-BRCA mutated cohorts were digitised and the digitised coordinates were used to re-construct patient level data (PLD) for each curve using methods described by Guyot et al. 2012.[86] As a naïve comparison between rucaparib and niraparib in SACT data, KM curves were overlayed in BRCA and non-BRCA mutated cohorts, and comparative efficacy was calculated by Cox-proportional hazard model with treatment as a predictor.

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As shown in Figure 33 to Figure 36, rucaparib and niraparib were comparable in terms of OS and TTD outcomes regardless of BRCA mutation status. This is in line with results presented in Table 40, where HRs for rucaparib vs. niraparib were close to 1. It is important to note that comparisons of the SACT data are naïve because population adjustments are not possible. Moreover, the comparison should be interpreted with caution given 18% of patients in the rucaparib BRCA mutant cohort and 6% of patients in the rucaparib non-BRCA mutant cohort had received prior PARP inhibitor treatment compared to no patients in the niraparib SACT.

Figure 33. KM analysis, OS for patients treated with rucaparib or niraparib in the BRCA mutated cohort[a]

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival
[a] The rucaparib BRCA mutated cohort included patients with somatic and germline BRCA mutations, while the niraparib BRCA mutated cohort included only patients with germline BRCA mutations

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Figure 34. KM analysis, OS for patients treated with rucaparib or niraparib in the non-BRCA mutated cohort

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival

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Figure 35. KM analysis, TTD for patients treated with rucaparib or niraparib in the BRCA mutated cohort

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; TTD, time to treatment discontinuation
[a] The rucaparib BRCA mutated cohort included patients with somatic and germline BRCA mutations, while the niraparib BRCA mutated cohort included only patients with germline BRCA mutations

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Figure 36. KM analysis, TTD for patients treated with rucaparib or niraparib in the non-BRCA mutated cohort

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; TTD, time to treatment discontinuation

B.3.9.5 Limitations and conclusions of indirect and mixed treatment comparisons

There was marked heterogeneity across clinical trials investigating rucaparib and those investigating olaparib and niraparib with regards to trial design, patient population, and subsequent anti-cancer regimens (including subsequent treatment with PARP inhibitors). These differences may lead to bias. For example, the higher proportion of patients with post-progression PARP inhibitor treatment in the placebo arm of the ARIEL3 trial ( ) vs. that in NOVA (49.2%) and SOLO 2 (38.4%) could lead to lower relative efficacy estimates in ARIEL3 for long-term outcomes such as OS and PFS2.[40,41,56] Similarly, 6% (non-BRCA mutant cohort) to 18% (BRCA mutant cohort) patients included in the rucaparib SACT data set had received prior PARP inhibitor treatment compared to no patients in the niraparib data set, leading to potential bias in comparative OS outcomes, likely in favour of niraparib.[82,83]

An additional limitation associated with clinical trial data is the small sample sizes. Most analyses were conducted in patient subgroups within clinical trials to ensure results were

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relevant to the population for this appraisal. However, data for patients with BRCA1 or BRCA2 mutations and who have responded to the second or subsequent course of platinum-based chemotherapy are limited, both in terms of availability and patient numbers. Thus, results from the NMA and MAIC are uncertain, as demonstrated by the wide 95% CIs (Section B.3.9.2.2 and Section B.3.9.3.2). The SACT data addresses this limitation by providing real-world evidence on the effectiveness of PARP inhibitors in patients with OC in the UK (N=887 in the rucaparib data set; N=1,016 in the niraparib data set), particularly in the non-BRCA mutated cohort (n=817 in the rucaparib data set; n=859 in the niraparib data set).[82,83]

One strength of the ITC findings is the consistency of comparative efficacy/effectiveness outcomes across the NMA, anchored MAIC and naïve comparison of SACT data sets. There were no statistically significant differences between rucaparib and olaparib or niraparib regardless of BRCA mutation status in any of the comparisons, supporting the equivalent efficacy/effectiveness of this group of PARP inhibitors both in clinical trials and in clinical practice.

B.3.10 Adverse reactions

The target number of progression events in the BRCA mutated cohort was achieved as of 15 April 2017, at which point the database lock was triggered and safety data were collected. Additional safety data analyses occurred at database locks for updated safety data analysis (31 December 2017) and for the final analysis (4 April 2022).[55,56]

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).[56] Data presented in this section pertain to the safety population, unless otherwise specified.

B.3.10.1 Treatment exposure and subsequent treatment

The median number of treatment cycles initiated at final analysis (4 April 2022) was [redacted] in the rucaparib group and [redacted] in the placebo group.[56] The median duration of treatment was 8.3 months (range: 0, 89) for the rucaparib group and 5.5 months (range: 0, 91) for the placebo group.[68]

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] of patients in the rucaparib group had dose reduction compared with [redacted] in the placebo group. Of those

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patients with a dose reduction in the rucaparib group, [redacted] required only one dose reduction. Of the patients with a dose reduction, the majority were reduced to 480 mg twice daily, which was the next dose level permitted.[56]

At the final analysis (4 April 2022), 78.1% of patients in the rucaparib group and 88.9% of the placebo group had received at least one subsequent anti-cancer treatment (ITT population). The median number of subsequent treatments was 3 in both the rucaparib (range: 1, 10) and placebo (range: 1, 8) treatment groups.[68] The most common subsequent treatments were platinum-based chemotherapy (rucaparib: [redacted]; placebo: [redacted]), non-platinum chemotherapy (rucaparib: [redacted]; placebo: [redacted]) and PARP inhibitors (rucaparib: [redacted]; placebo: [redacted]).[56]

B.3.10.2 AEs

The safety profile of rucaparib was consistent across all patient efficacy cohorts at primary analysis (15 April 2017) and updated safety analysis (31 December 2017). Data on AEs was reported only for the overall safety population at final analysis (4 April 2022).[56,68] Treatment-emergent adverse events (TEAEs) for the overall safety population are summarised in Table 41.[35,36,55,56,68,87]

As of the final analysis (4 April 2022), the majority of patients in the safety population experienced at least one TEAE (rucaparib: 100%; placebo: 96.3%), with treatment-related TEAEs reported for [redacted] and [redacted] of rucaparib and placebo patients, respectively. Nine patients (2.4%) who received rucaparib and two patients (1.1%) who received placebo had a fatal TEAE; of which, [redacted] deaths ([redacted]) in the rucaparib group were considered by an investigator to be related to study treatment.[56,68]

The results observed in the final analysis (4 April 2022) are comparable to those observed at the updated safety analysis (31 December 2017) and the 15 April 2017 data cut (Table 41).[35,36,55,56,68,87] 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.

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Table 41. Overall summary of TEAEs (safety population)[35,36,55,56,68,87]

TEAE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)		Final analysis (4 April 2022)	
	Rucaparib (n=372)	Placebo (n=189)	Rucaparib (n=372)	Placebo (n=189)	Rucaparib (n=372)	Placebo (n=189)
One or more TEAEs	372 (100.0)	182 (96.3)	372 (100.0)	182 (96.3)	372 (100.0)	182 (96.3)
One or more treatment-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One or more serious TEAEs	78 (21.0)	20 (10.6)	[redacted]	[redacted]	[redacted]	[redacted]
One or more serious treatment-related TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs of Grade 3 or higher	209 (56.2)	28 (14.8)	222 (59.7)	30 (15.9)	233 (62.6)	31 (16.4)
One or more treatment-related TEAEs of Grade 3 or higher	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs leading to death	6 (1.6)	2 (1.1)	[redacted]	[redacted]	9 (2.4)	2 (1.1)
One or more treatment-related TEAEs leading to death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs leading to study drug discontinuation	50 (13.4)	3 (1.6)	57 (15.3)	4 (2.1)	75 (20.2)	4 (2.1)
One or more treatment-related TEAEs leading to study drug discontinuation	[redacted]	[redacted]	49 (13.2)	1 (0.5)	[redacted]	[redacted]
One or more TEAEs leading to study drug interruption	237 (63.7)	19 (10.1)	243 (65.3)	19 (10.1)	251 (67.5)	19 (10.1)
One or more treatment-related TEAEs leading to study drug interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs leading to study drug dose reduction	203 (54.6)	8 (4.2)	206 (55.4)	8 (4.2)	209 (56.2)	8 (4.2)
One or more treatment-related TEAEs leading to study drug dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One or more TEAEs leading to dose reduction or interruption	263 (70.7)	20 (10.6)	[redacted]	[redacted]	[redacted]	[redacted]
One or more treatment-related TEAEs leading to dose reduction or interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TEAE, treatment emergent adverse event.
Source: Coleman et al. 2017[35]; ARIEL3 CSR[55]; Summary of clinical safety - May 2018[87]; Ledermann 2020[36]; ARIEL3 CSR addendum[56]; Coleman et al. 2022 (ICGS oral presentation)[68]

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B.3.10.2.1 Common TEAEs

All patients (100%) in the rucaparib group and 96.3% of patients in the placebo group experienced at least one TEAE at the primary analysis (15 April 2017), the updated safety analysis (31 December 2017) and the final analysis (4 April 2022). The TEAEs that occurred in ≥20% of patients in either treatment arm at all three data cut off dates are summarised in Table 42.

As of the final analysis (4 April 2022), the most common TEAEs that occurred in the rucaparib group were nausea ([redacted]), combined asthenia/fatigue ([redacted]) and abdominal pain ([redacted]). 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 combined asthenia/fatigue ([redacted]), abdominal pain ([redacted]) and nausea ([redacted]).[56]

The incidence of TEAEs in rucaparib and placebo patients observed in the final data analysis (4 April 2022), the updated safety data analysis (31 December 2017) and the primary analysis database lock (15 April 2017) are comparable (Table 42).[35,36,56,87]

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Table 42. TEAEs reported in ≥ 20% of patients in any treatment group (safety population)[35,36,56,87]

AE, n (%)	15 April 2017 data cut		31 December 2017 data cut		4 April 2022 data cut	
	Rucaparib (n=372)	**Placebo (n=189)**	**Rucaparib (n=372)**	**Placebo (n=189)**	Rucaparib (n=372)	Placebo (n=189)
Number of Patients With at Least One TEAE	372 (100)	182 (96.3)	372 (100)	182 (96.3)	[redacted]	[redacted]
Nausea	280 (75.3)	69 (36.5)	282 (75.8)	69 (36.5)	[redacted]	[redacted]
Asthenia/fatigue	258 (69.4)	83 (43.9)	263 (70.7)	84 (44.4)	[redacted]	[redacted]
Abdominal pain	111 (29.8)	49 (25.9)	112 (30.1)	49 (25.9)	[redacted]	[redacted]
Rash	46 (12.4)	17 (9.0)	50 (13.4)	17 (9.0)	[redacted]	[redacted]
Anaemia/haemoglobin decreased	139 (37.4)	11 (5.8)	145 (39.0)	10 (5.3)	[redacted]	[redacted]
Constipation	136 (36.6)	45 (23.8)	141 (37.9)	46 (24.3)	[redacted]	[redacted]
Vomiting	136 (36.6)	28 (14.8)	138 (37.1)	29 (15.3)	[redacted]	[redacted]
ALT/AST increased	126 (33.9)	7 (3.7)	129 (34.7)	8 (4.2)	[redacted]	[redacted]
Diarrhoea	118 (31.7)	41 (21.7)	121 (32.5)	41 (21.7)	[redacted]	[redacted]
Nasopharyngitis/URTI*	NR	NR	NR	NR	[redacted]	[redacted]
Dysgeusia	146 (39.2)	13 (6.9)	148 (39.8)	13 (6.9)	[redacted]	[redacted]
Thrombocytopenia/platelet count decreased	104 (28.0)	5 (2.6)	109 (29.3)	5 (2.6)	[redacted]	[redacted]
Combined stomatitis*	NR	NR	NR	NR	[redacted]	[redacted]
Decreased appetite	87 (23.4)	26 (13.8)	88 (23.7)	26 (13.8)	[redacted]	[redacted]
Arthralgia	57 (15.3)	24 (12.7)	59 (15.8)	24 (12.7)	[redacted]	[redacted]
Neutropenia/neutrophil count decreased	67 (18.0)	9 (4.8)	72 (19.4)	9 (4.8)	[redacted]	[redacted]

AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment emergent adverse event; URTI = upper respiratory tract infection
* Combined nasopharyngitis/URTI and combined stomatitis were not reported during the 15 April 2017 data cut and 31 December 2017 safety data cut
Source: Coleman et al. 2017[35]; Summary of clinical safety – May 2018[87]; Ledermann 2020[36]; ARIEL3 CSR addendum[56]

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B.3.10.2.2 Grade 3 or higher TEAEs

Table 43 summarises the Grade ≥3 TEAEs, regardless of causality, with incidence ≥5% in either treatment group at the primary analysis (15 April 2017), the updated safety analysis (31 December 2017) and the final analysis (4 April 2022).

As of the final analysis (4 April 2022), 62.6% of patients in the rucaparib-treated group experienced a Grade ≥3 TEAE compared with 16.4% of placebo patients.[68] The most common Grade ≥3 TEAEs in the rucaparib group were anaemia/haemoglobin decreased ([redacted]), increased alanine aminotransferase (ALT)/aspartate transaminase (AST) increased ([redacted]) and neutropenia/neutrophil count decreased ([redacted]).[56]

The incidence of Grade ≥3 TEAEs in rucaparib and placebo patients observed in the final analysis (4 April 2022) were comparable with those observed at the updated safety analysis (31 December 2017) and the primary analysis (15 April 2017; Table 43).[35,55,56,68,87]

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.[55] Despite the greater incidence of Grade ≥3 ALT/AST increase with rucaparib treatment, only two patients (0.5%) discontinued treatment due to this event.[56]

Table 43. Grade 3 or higher TEAEs reported in ≥5% of patients in any treatment group (safety population)[35,55,56,68,87]

AE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)		Final analysis (4 April 2022)	
	Rucaparib (n=372)	Placebo (n=189)	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)	233 (62.6)	31 (16.4)
Combined preferred terms						
Combined ALT/AST increased	39 (10.5)	0 (0.0)	38 (10.2)	0 (0.0)	[redacted]	[redacted]
Combined anaemia and/or low/decreased haemoglobin	70 (18.8)	1 (0.5)	80 (21.5)	1 (0.5)	[redacted]	[redacted]
Combined asthenia/fatigue	25 (6.7)	5 (2.6)	26 (7.0)	5 (2.6)	[redacted]	[redacted]
Combined neutropenia and/or low/decreased ANC	25 (6.7)	2 (1.1)	29 (7.8)	2 (1.1)	[redacted]	[redacted]
Combined Thrombocytopenia	19 (5.1)	0 (0.0)	20 (5.4)	0 (0.0)	[redacted]	[redacted]

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AE, n (%)	Primary analysis data cut (15 April 2017)		Updated data cut (31 December 2017)		Final analysis (4 April 2022)	
	Rucaparib (n=372)	Placebo (n=189)	Rucaparib (n=372)	Placebo (n=189)	Rucaparib (n=372)	Placebo (n=189)
and/or low/decreased platelets						
System organ class Preferred term						
Blood and lymphatic system disorders	87 (23.4)	2 (1.1)	95 (25.5)	3 (1.6)	[redacted]	[redacted]
Anaemia	65 (17.5)	1 (0.5)	73 (19.6)	1 (0.5)	[redacted]	[redacted]
Neutropenia	18 (4.8)	1 (0.5)	19 (5.1)	1 (0.5)	[redacted]	[redacted]
Gastrointestinal disorders	47 (12.6)	12 (6.3)	49 (13.2)	12 (6.3)	[redacted]	[redacted]
General disorders and administration site conditions	29 (7.8)	6 (3.2)	31 (8.3)	6 (3.2)	[redacted]	[redacted]
Investigations	72 (19.4)	1 (0.5)	77 (20.7)	1 (0.5)	[redacted]	[redacted]
ALT increased	38 (10.2)	0 (0.0)	37 (9.9)	0 (0.0)	[redacted]	[redacted]
Metabolism and nutrition disorders	15 (4.0)	1 (0.5)	19 (5.1)	1 (0.5)	[redacted]	[redacted]

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; ARIEL3 CSR[55]; Summary of clinical safety - May 2018[87]; ARIEL3 CSR addendum[56]; Coleman et al. 2022 (ICGS oral presentation)[68]

B.3.10.2.3 Treatment-related TEAEs

As of the final analysis (4 April 2022), treatment-related TEAEs were reported for [redacted] and [redacted] of rucaparib and placebo patients, respectively. The most common treatment-related TEAEs in the rucaparib group were nausea ([redacted]), asthenia/fatigue ([redacted]) and anaemia/decreased haemoglobin ([redacted]).[56]

Grade ≥3 treatment-related TEAEs were reported in [redacted] of patients in the rucaparib compared with [redacted] of patients in the placebo group. The most common Grade ≥3 treatment-related TEAEs in the rucaparib group were anaemia/decreased haemoglobin ([redacted]), combined increased ALT/AST ([redacted]), asthenia/fatigue ([redacted]) and neutropenia/neutrophil count decreased ([redacted]).[56]

The incidence of treatment-related TEAEs and treatment-related Grade ≥3 TEAEs observed in the final analysis (4 April 2022) was comparable to those observed at the updated safety analysis (31 December 2017) and the primary analysis (15 April 2017).

B.3.10.2.4 Serious TEAEs and serious treatment-related TEAEs

At the final analysis (4 April 2022), [redacted] of patients in the rucaparib group and [redacted] of patients who were treated with placebo had at least one serious TEAE. The most common serious TEAEs in the rucaparib group were anaemia/haemoglobin decreased ([redacted]),

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vomiting ([redacted]) and combined abdominal pain ([redacted]). Serious TEAEs assessed as related to study drug were observed among [redacted] of patients treated with rucaparib and [redacted] of those treated with placebo. The most common serious TEAEs assessed as related to study drug were anaemia ([redacted]), investigations ([redacted]) and neoplasms (benign, malignant and unspecified; [redacted])[56]

B.3.10.2.5 Deaths

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 15 April 2017 data cut. TEAEs with an outcome of death in the rucaparib group were progressive disease (n=2), histiocytosis haematophagic (n=1), cardiac arrest (n=1), acute myeloid leukaemia (AML; n=1) and myelodysplastic syndrome (MDS; n=1). TEAEs with an outcome of death in the placebo group were PD and pulmonary embolism (n=1 for both).[35]

By the time of the final analysis (4 April 2022), three additional patients experienced TEAE with a fatal outcome ([redacted]). Of the nine patients in the rucaparib group with a TEAE that lead to death, [redacted] developed AML or MDS, which was considered to be related to rucaparib by the investigator. However, there are many confounding risk factors in assessing drug relationships in the cases of MDS/AML.[56,68]

B.3.10.2.6 TEAEs leading to treatment discontinuation

As of the final analysis (4 April 2022), in the rucaparib group, 20.2% of patients had a TEAE the led to study drug discontinuation, compared with 2.1% in the placebo group.[68] These data do not include treatment emergent disease progressions. TEAEs leading to treatment discontinuation in the rucaparib group included anaemia/haemoglobin decreased ([redacted]), nausea ([redacted]), thrombocytopenia/platelet count decreased ([redacted]), asthenia/fatigue ([redacted]) and vomiting ([redacted]).Most of the events leading to study drug discontinuation were assessed as related to study treatment.[56]

B.3.10.2.7 TEAEs resulting in dose reduction or interruption

At the final analysis (4 April 2022), the incidence of TEAEs leading to dose reduction was greater for the rucaparib group (56.2%) than the placebo group (4.2%).[68] The most commonly reported TEAEs leading to rucaparib dose reduction were combined anaemia/haemoglobin decreased ([redacted]), ALT/AST increased ([redacted]) and thrombocytopenia/platelet count decreased ([redacted]). No TEAEs leading to dose reduction

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were reported in more than [redacted] of patients treated with placebo. Mostly, the TEAEs leading to dose reduction were considered by the investigator to be treatment related.[56]

The incidence of TEAEs leading to treatment interruption was 67.5% in the rucaparib group and 10.1% in the placebo group.[68] The most commonly reported TEAEs leading to rucaparib treatment interruption were thrombocytopenia/platelet count decreased ([redacted]), anaemia/haemoglobin decreased ([redacted]) and nausea ([redacted]). No TEAEs leading to treatment interruption were reported in more than [redacted] of patients treated with placebo. Mostly, the TEAEs leading to treatment interruption were considered by the investigator to be treatment related.[56]

B.3.10.3 Safety profile summary

Overall, rucaparib was generally well tolerated with AEs observed in the trial consistent with the known safety profile of rucaparib.[35,36,55,56,68,87] There was no meaningful increase in mortality or morbidity in the rucaparib group compared with the placebo group.[56] During the ARIEL3 study, the rucaparib treatment discontinuation rate due to TEAEs was low at primary analysis (13.4%; 15 April 2017), the updated safety data analysis (15.3%; 31 December 2017) and the final analysis (4 April 2022; 20.2%), with TEAEs generally managed through dose modifications and supportive care.[35,36,68] [redacted] deaths in the rucaparib group were considered to be related to treatment ([redacted]).[56]

The side effect profile observed for rucaparib was generally in line with that observed in previous studies of maintenance treatment with PARP inhibitors, that is, gastrointestinal side effects, fatigue, asthenia, and myelosuppression. Observations from early PARP inhibitor studies raised some concerns about a potential risk of MDS/AML with this class of treatment, but only [redacted] of patients treated with rucaparib in ARIEL3 developed treatment-emergent MDS/AML.[56]

Some differences in PARP inhibitor safety profiles have been noted and are reflected in the Summary of Product Characteristics with special warnings of photosensitivity with rucaparib, pneumonitis with olaparib, and hypertension, including hypertensive crisis with niraparib. Differences in thrombocytopenia rates are also observed.[1,45,46] Overall, rucaparib has a consistent and manageable safety profile, with no requirement to reduce rucaparib starting dose in patients with mild or moderate hepatic or renal impairment, in elderly patients (≥65 years), nor in patients receiving treatment with strong or moderate cytochrome P450 3A4 inhibitors.[88]

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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.3.11 Conclusions about comparable health benefits and safety

B.3.11.1 Principal findings from the available clinical evidence to support rucaparib

As shown in both a robust randomised, placebo controlled clinical study (ARIEL3) and in a large cohort of UK patients in real-world clinical practice (i.e., SACT data), 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 CFI and time to subsequent first and second anti-cancer treatments.[29,30,82] Moreover, the comparative analyses described above demonstrate the equivalent efficacy/effectiveness of rucaparib with other PARP inhibitors, niraparib and olaparib.

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 vs. 5.4 months; p<0.0001), CFI ([redacted] months vs. [redacted] months; [redacted]), TFST ([redacted] months vs. [redacted] months; [redacted]), PFS2 (20.6 months vs. 16.3 months; [redacted]) and TSST ([redacted] months vs. [redacted] months; [redacted]) compared with placebo.[35,53,56,68]

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, the rate of discontinuations due to TEAEs was low (20.2%) and only [redacted] of deaths were considered to be related to rucaparib treatment.[35,53,56,68] While common TEAEs align across the drug class, differences in the safety profiles of PARP inhibitor maintenance treatments are noted.[1,45,46]

Maintenance of HRQoL 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 of itself negatively impact HRQoL. In the real world setting, postponing subsequent platinum-based chemotherapy would generally be expected 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.[74]

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The real-world effectiveness of rucaparib has also been demonstrated in UK clinical practice.[82] Median OS for patients treated with rucaparib ranged from 25.7 months (non-BRCA mutated cohort) to 30.8 months (BRCA mutated cohort) in the SACT data set. Median TTD ranged from 6.5 months (non-BRCA mutated cohort) to 12.4 months (BRCA mutated cohort).[82]

No meaningful differences were observed across the NMA, anchored MAIC and naïve comparison in SACT data sets comparing rucaparib to olaparib and niraparib both in clinical trials and in clinical practice.[82,83] This clinical equivalency was evident despite heterogeneity (e.g., subsequent anti-cancer therapy including with PARP inhibitors) across clinical trials and real world use that may have introduced bias in favour of niraparib. This suggests that rucaparib provides at least similar clinical benefits to current PARP inhibitor maintenance treatment but in a broader patient group. Additionally, rucaparib offers patients and physicians a reduced administration burden and a safety profile that differs from the safety profile of other PARP inhibitor maintenance treatments.[1,45,46] Therefore, in demonstrably achieving the goals of maintenance therapy in OC,[30] rucaparib is expected to help further advance the incorporation of PARP inhibitor maintenance treatment within the standard of care for people with platinum-sensitive relapsed OC.

B.3.11.2 Internal validity

ARIEL3 was a well-designed, multicentre, randomised, double-blind, placebo-controlled, phase III study providing comparative evidence of rucaparib vs. placebo (representative of routine surveillance). The ARIEL3 study was conducted in line with Good Clinical Practice Guidelines of the International Council for Harmonisation,[63] 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. During the previous assessment of TA611, the ERG considered the overall risk of bias for ARIEL3 in the ITT population to be low.[62]

One potential source of bias against rucaparib in the ARIEL3 trial is the use of subsequent PARP inhibitor treatment in patients randomised to placebo following progression. Use of post-progression PARP inhibitor treatment may mask the true OS difference between treatment with rucaparib vs. placebo.[56] The frequency of subsequent PARP inhibitor use in ARIEL3 was higher than in SOLO2 and NOVA,[56,64-66] likely due the availability of olaparib and niraparib as maintenance therapies for relapsed platinum-sensitive OC at the time ARIEL3 participants were candidates for subsequent treatment lines.[40,41] Exploratory analyses found that adjusting for subsequent treatment with PARP inhibitors in ARIEL3 and

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NOVA did not substantially alter OS outcomes, likely due to small patient numbers and a high proportion of subsequent PARP inhibitor treatment (see Section B.3.6.2.3.1).[56]

Following analysis of INV-PFS and IRR-PFS at the 15 April 2017 data cut, which demonstrated a highly significant clinical benefit of rucaparib over placebo, significant improvements were observed in CFI, TFST, PFS2 and TSST at the final analysis. Results from the final analysis confirm the long-term benefit of rucaparib in patients with relapsed platinum-sensitive OC. OS was not significantly different between patients treated with rucaparib and patients treated with placebo, but the high proportion of patients randomised to placebo who received subsequent PARP inhibitors in the post-progression phase may have biased estimates in favour of placebo.[56]

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 PARP inhibitor treatments were being developed in parallel).[35,77] Similarly, Study 19, SOLO2, NOVA and NORA trials also compared active treatment with placebo.[50,51,59 #110,65,78-80] In the absence of head-to-head trial data, ITC analyses with varying methodologies, in accordance with NICE technical support guidance, have been conducted to provide estimates of rucaparib compared with olaparib and niraparib in the relevant patient population (people who have BRCA mutations and who have responded to two or more courses of platinum-based chemotherapy). Comparison of SACT data for rucaparib and niraparib also suggest the two PARP inhibitors have similar effectiveness in UK clinical practice.[82,83] As described above, these analyses consistently demonstrated that there were no statistically significant differences between rucaparib and olaparib or niraparib regardless of BRCA mutation status. The ITC findings presented here support the equivalency across PARP inhibitors in this setting.

B.3.11.3 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.[55]

ARIEL3 was an inclusive PARP inhibitor maintenance treatment trial that robustly demonstrated the efficacy of rucaparib 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.[35,53,55,56,68]

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Overall, the ARIEL3 study population is 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,[35] which is similar to the median age of observed for patients in UK clinical practice (60 to 69 years)[82,83] and the majority of patients had EOC (83.5%), similar to the observed UK population (90%).[4]

The primary efficacy endpoint of the ARIEL3 study was INV-PFS.[35] 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 and demonstrated 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 HRQoL data collected during the ARIEL3 study, prolonged response to platinum-based chemotherapy (as demonstrated by a statistically significant extension in PFS) is expected to have a positive impact in the real-world setting. An extended period of symptom-free disease may allow patients to return to some sort of normal living. Furthermore, multiple ARIEL3 study outcomes indicate that rucaparib is able to provide an extended period of chemotherapy-free living. These include improvements in CFI, TSFT, TSST and PFS2. In turn, these outcomes are likely to reduce further exposure to the potentially deleterious side effects of more toxic OC treatments. Improvements in these results also allow patients to be considered for re-treatment with platinum-based chemotherapy at relapse, thus facilitating more effective subsequent treatment lines.

B.3.12 Ongoing studies

Not applicable.

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B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Rucaparib is not anticipated to require any changes to the current service provision and management. Rucaparib is orally administered twice daily with or without food.[1] The comparators included within the NICE scope are also orally administered once daily therefore there are minimal differences in dosing and administration.[45,46]

Similar to other PARP inhibitors, rucaparib requires monthly monitoring of complete blood counts.[1,45,46] Niraparib requires monitoring of complete blood counts weekly during the first month of treatment and blood pressure monitored weekly for the first two months.[45] Therefore, rucaparib has lower blood count and blood pressure monitoring requirements in the first month, in comparison to niraparib.[1,45] No starting dose adjustment is required in patients with mild or moderate hepatic impairment.[1]

B.4.2 Cost-comparison analysis inputs and assumptions

Based on findings of indirect treatment comparisons of RCT data (NMA and MAIC) and the comparison of the SACT data, there is robust evidence for both BRCA and non-BRCA patient populations that the underlying criterion for a cost comparison analysis, that rucaparib is very likely to provide similar or greater health benefits than the comparator technology in routine commissioning, were met. Based on advice from NICE at the Decision Problem meeting on 2 October, 2023, whilst the indirect comparisons considered both olaparib and niraparib, the cost comparison analyses were only carried out against niraparib. Niraparib is not under an ongoing assessment, and it is used among both BRCA and non-BRCA patient population. It also has extensive SACT data in the public domain.

B.4.2.1 Features of the cost-comparison analysis

The cost-comparison analysis was conducted to evaluate the cost and resource use associated with 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. The analysis includes two populations, BRCA and non-BRCA subgroups, based on the current clinical pathway for maintenance treatment of ovarian cancer. The cost-comparison model compared rucaparib versus niraparib for both subgroups.

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

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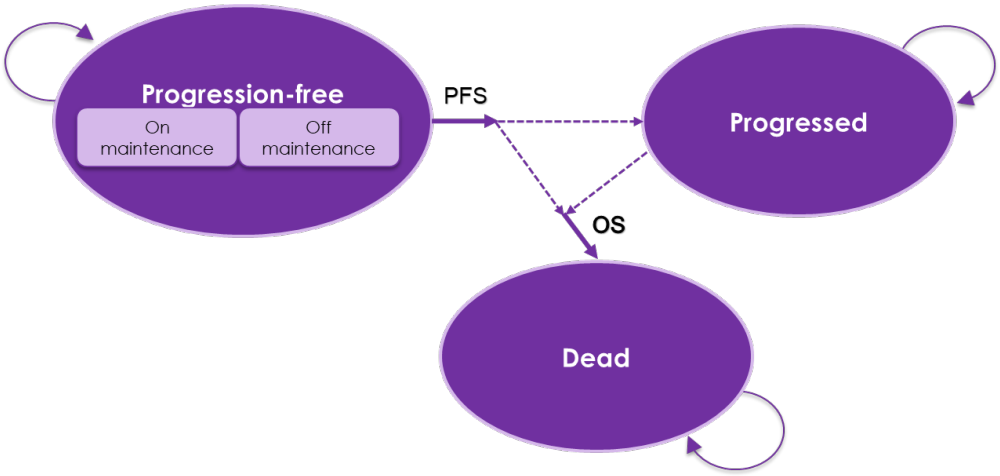
population in the ARIEL3 trial was 61 years.[55] Therefore, 30 years was assumed to be long enough to capture the long-term clinical and economic impacts of maintenance therapy over the entire patient lifetime.

A cycle length of 1 month corresponding to the treatment cycle length in the ARIEL3 trial was used. 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 niraparib were assumed to be incurred at the beginning of each cycle, therefore half-cycle correction was not applied in these cost categories.

Costs were discounted at 3.5% consistent with the NICE reference case.

An economic model, constructed in Microsoft Excel® with the structure and possible transitions represented in Figure 37 was submitted as part of TA611 in 2019. The model was adapted for the cost comparison analyses.

Figure 37. Structure of the cost-effectiveness model



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

The original model used a partitioned survival analysis structure as this is a late stage metastatic cancer with patients not surviving for a long time so it does not require details of sequencing.[89] Also, the model structure had been used in previous relevant health technology assessments and is a widely accepted approach in oncology indications.

The original model's three main health states were retained: 'Progression-free' (where all patients enter the model), 'Progressed' and 'Dead'. The Progression-free health state is divided into 'On maintenance' and 'Off maintenance'. However, as this is a cost-comparison analysis, PFS and OS are assumed to be the same for rucaparib and niraparib as supported by the NMA and MAIC results (shown in Section B.3.9) which demonstrate the comparability

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of these PARP treatments and thus supports the assumption of clinical equivalence. TTD, however, is allowed to differ for rucaparib and niraparib.

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 is populated based on two sets of data sources: RCT data and, as an alternative source, both rucaparib and niraparib SACT data (as described in section B.3.9.1.3) were also used to inform TTD and OS.[82,83]

In line with previous appraisals, it was deemed inappropriate to mix SACT vs trial-based data given the differences in the data generating process in an RCT compared to RWD collection, and likely the patients.[41]

Therefore, model allows the use of either extrapolations assuming equivalence between rucaparib and niraparib based on the ARIEL3 trial for PFS and OS, or based entirely on rucaparib or entirely on niraparib SACT data for TTD and OS. PFS is not reported in SACT data therefore, in scenarios investigating SACT data, we modelled PFS through a HR relative to TTD, as observed in ARIEL3. For all scenarios, the assumption of PFS and OS equivalence is maintained.

B.4.2.2 Clinical parameters used in the model

The pivotal study used to inform the cost-effectiveness analysis was ARIEL3[35,56], as described in detail in Section B.3.9.1.3 To supplement ARIEL3 data, SACT data for both rucaparib and niraparib are utilized in scenario analysis.[82,83]

The following clinical outcomes were assessed:

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- Investigator-assessed PFS
- OS
- Time to discontinuation (TTD)

The data for most of these outcomes, although relatively mature, are still limited. 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.

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.[85,90] 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.[35]

As described in Section B.3.9, an NMA and MAIC were performed to compare rucaparib and niraparib in the BRCA and non-BRCA 2L+ population, as no head-to-head trials of the two treatments exist. As the comparisons showed no conclusive evidence of differences in efficacy between rucaparib and niraparib, the model base case assumes equivalence of PFS and OS for the two treatments.

Parametric survival curves were fitted to PFS, OS and TTD data available from ARIEL3, TTD from NOVA. All analyses separated BRCA and non-BRCA patients. As described in Section B.3.9.4 Comparisons using SACT data, the SACT KM curves of OS and TTD for rucaparib and niraparib in BRCA and non-BRCA mutated cohorts were digitised, and the digitised coordinates were used to re-construct patient level data for each curve using methods described by Guyot et al. 2012.[86] Parametric fits were conducted using R (version 4.3.1) and 'flexsurv' package (version 2.2.2).

For all endpoints and data sources, distributions fitted included exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma in line with the NICE reference case.[91]

B.4.2.1.1 Extrapolation of PFS data

B.4.2.1.1.1 PFS for patients with BRCA mutation

Figure 5 above shows the KM curve for investigator-assessed PFS (INV-PFS) in the ARIEL3 trial, displaying both active treatment and placebo arms in the BRCA population. An

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overview of all curve fits for rucaparib INV-PFS data in the BRCA population is presented in Figure 38.

Table 44 presents the observed median and mean INV-PFS in weeks from ARIEL3, in addition to the median and mean as predicted by each fitted parametric survival model. Table 45 presents the Akaike information criterion (AIC) and Bayesian information criterion (BIC). Based on the goodness-of-fit statistics and visual inspection of long-term extrapolations the log-normal distribution was selected for the base case.

Figure 38. Overview of all parametric curve fits to the rucaparib INV-PFS KM data from the ARIEL3 in BRCA population

BRCA, breast cancer gene; INV-PFS, investigator-assessed progression-free survival; KM, Kaplan-Meier

Table 44. Predicted mean and median of INV-PFS in ARIEL3 in the BRCA population – rucaparib

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean (weeks)
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted]

BRCA, breast cancer gene; INV-PFS, investigator-assessed progression-free survival
Bold indicates base case.

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Table 45. Statistical fit of all INV-PFS parametric curve fits within BRCA population – rucaparib

	AIC	BIC
Exponential	280.76	283.63
Weibull	275.51	281.24
Gompertz	280.61	286.34
Log-logistic	271.73	277.46
Log-normal	**268.54**	**274.27**
Generalised gamma	269.48	278.09

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; INV-PFS, investigator-assessed progression-free survival
Bold indicates base case.

B.4.2.1.2 PFS for non-BRCA patients

Figure 17 shows the KM curve for INV-PFS in the ARIEL3 trial, displaying both active treatment and placebo arms in the non-BRCA population. An overview of all curve fits is presented in Figure 39.

Table 46 presents the observed median INV-PFS in weeks from ARIEL3, in addition to the median and mean as predicted by each fitted parametric survival model. Table 47 presents the AIC and BIC. For long-term extrapolations the log-normal distribution was selected for the base case. The generalized gamma has the lowest AIC/BIC however the mean is inestimable, and the curve has an unrealistic plateau, therefore the fit with the second lowest AIC/BIC is selected.

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Figure 39. Overview of all parametric curve fits to the rucaparib INV-PFS KM data from the ARIEL3 in non-BRCA population

BRCA, breast cancer gene; KM, Kaplan-Meier; INV-PFS, investigator-assessed progression-free survival

Table 46. Predicted mean and median of INV-PFS in ARIEL3 in the non-BRCA population – rucaparib

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean (weeks)
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted]

BRCA, breast cancer gene; INV-PFS, investigator-assessed progression-free survival
Bold indicates base case.

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Table 47. Statistical fit of all INV-PFS parametric curve fits within non-BRCA population – rucaparib

	AIC	BIC
Exponential	602.47	605.97
Weibull	592.05	599.05
Gompertz	603.76	610.76
Log-logistic	569.39	576.39
Log-normal	**559.85**	**566.86**
Generalised gamma	548.28	558.79

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; INV-PFS, investigator-assessed progression-free survival
Bold indicates base case.

PFS outcomes were not collected in SACT databases. Comparison of KM data in ARIEL3 BRCA and non-BRCA mutated cohorts showed strong association between TTDD and INV-PFS, and the KM curves were found to be similar in shape as well, with some lag identified between them. To capture the relationship Cox HRs were estimated between TTDD and INV-PFS. The Cox HR estimates were 0.868 (95% CI: 0.707-1.066) and 0.823 (95% CI: 0.597-1.134) for BRCA and non-BRCA mutated cohorts, respectively. Assuming the same relationship between TTD and PFS in SACT as observed in ARIEL3, the HR estimates from ARIEL3 were applied to the TTD in SACT to derive a SACT-specific PFS. The estimated HRs were applied to either rucaparib or niraparib TTD in SACT and the same curve was then used as the SACT-specific PFS of both therapies.

B.4.2.1.2 Time to treatment discontinuation

Four approaches for modelling time on maintenance treatment were incorporated in the cost-comparison model, based on the availability of data for rucaparib and niraparib. Information about time on maintenance with rucaparib was available directly from ARIEL3 and is available in the model as a time to discontinuation or death (TTDD) KM curve with parametric models fitted. This is used as the base case approach for rucaparib. TTDD data for niraparib in the form of a KM curve and/or parametric models were available from NOVA with parametric models fitted, this is used as the base case for niraparib. The proportion of patients discontinuing treatment due to AEs was available to derive constant discontinuation rates for niraparib and rucaparib. Additionally, an option tested in scenario analysis only assumes that patients receive maintenance treatment until progression, upon which treatment is discontinued. The options for modelling discontinuation are summarised in Table 48.

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Table 48. Options for modelling TTDD within the model

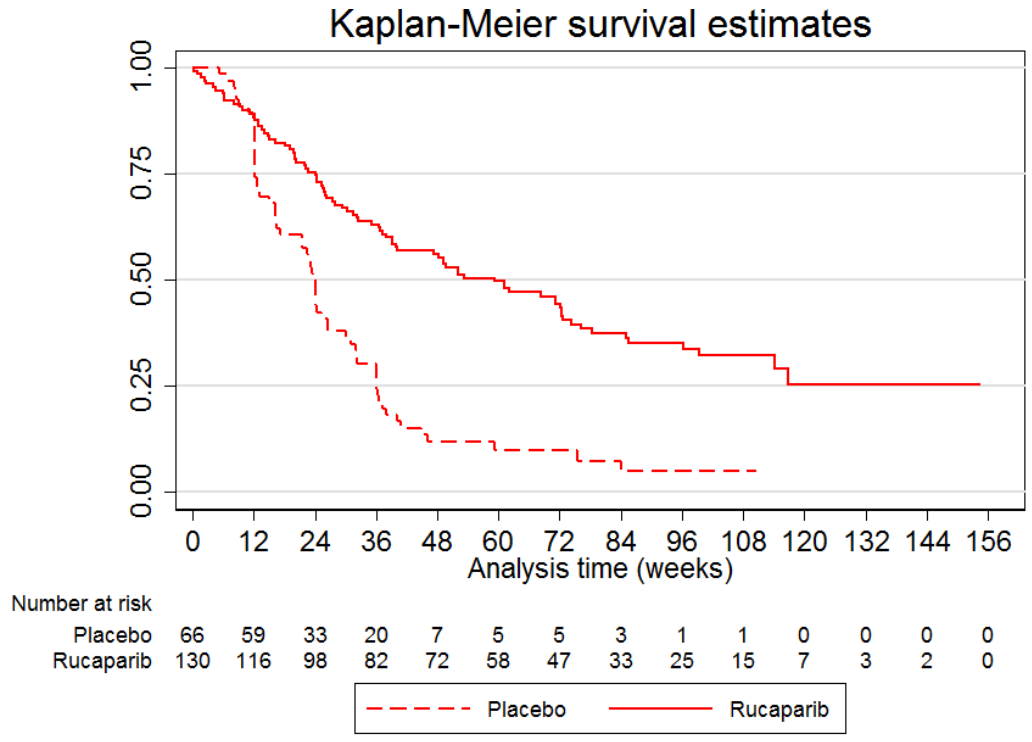
	Intervention(s) for which approach is an option	Source(s)
TTDD curve	Rucaparib	ARIEL3 – Base case
	Rucaparib	SACT
	Niraparib	NOVA – Base case
	Niraparib	SACT
Constant rate based on discontinuation due to AEs	Niraparib	NOVA
Treatment until progression	Niraparib	NOVA

AE, adverse event; BRCA, breast cancer gene; SACT, Systemic Anti-Cancer Therapy dataset; TTDD, Time to discontinuation or death
Sources: NICE ID1485;[62] NICE TA784;[41] SACT (niraparib);[83] SACT (rucaparib)[82]

B.4.2.1.2.1 TTD for BRCA patients based on ARIEL3 and NOVA

Figure 40 shows the KM curve for TTDD in the ARIEL3 trial, displaying both active treatment and placebo arms in the BRCA population. An overview of all curve fits is presented in Figure 41. Table 49 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 50 presents the AIC and BIC. Exponential is selected as the base case distribution based on fit statistics and visual inspection of the curves.

Figure 40. KM estimates of TTD in the BRCA mutated cohort of ARIEL3 (post-hoc analysis; 15 April 2017 data cut)



BRCA, breast cancer gene; TTD, time to treatment discontinuation

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Figure 41. Overview of all parametric curve fits to the rucaparib TTDD KM data from the ARIEL3 BRCA population

BRCA, breast cancer gene; KM, Kaplan-Meier; TTDD, time to discontinuation or death

Table 49. Predicted mean and median of TTDD in ARIEL3 in the BRCA population – rucaparib

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean (weeks)
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted]

BRCA, breast cancer gene; TTDD, time to discontinuation or death
Bold indicates base case.

Table 50. Statistical fit of all TTDD parametric curve fits from ARIEL3 within BRCA population – rucaparib

Model	AIC	BIC
Exponential	**381.89**	**384.76**
Weibull	383.60	389.34
Gompertz	382.69	388.42
Log-logistic	382.45	388.19
Log-normal	388.41	394.14
Generalised gamma	384.95	393.55

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; TTDD, time to discontinuation or death
Bold indicates base case.

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TTDD data were also available from the NOVA trial for niraparib for the BRCA population. An overview of all curve fits is presented in Figure 42.

Table 51 shows the observed and predicted mean and median of all the extrapolations and Table 52 shows the AIC and BIC. Exponential is selected based on fit statistics and visual inspection of the curves.

Figure 42. Overview of all parametric curve fits to niraparib TTDD KM data from the NOVA BRCA population

BRCA, breast cancer gene; KM, Kaplan-Meier; TTDD, time to discontinuation or death

Table 51. Predicted mean and median number of weeks of TTDD parametric curve fits from NOVA within BRCA population - niraparib

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean(weeks)
Rucaparib	Exponential	104.50	**84.78**	**122.31**
	Weibull		85.80	118.80
	Gompertz		87.58	111.22
	Log-logistic		82.42	304.58
	Log-normal		79.32	203.31
	Generalised gamma		87.58	113.21

BRCA, breast cancer gene; TTDD, time to discontinuation or death
Bold indicates base case.

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Table 52. Statistical fit of all TTDD parametric curve fits from NOVA within BRCA population – niraparib

Model	AIC	BIC
Exponential	**230.82**	**233.19**
Weibull	232.61	237.35
Gompertz	232.41	237.14
Log-logistic	234.84	239.58
Log-normal	236.07	240.81
Generalised gamma	234.56	241.67

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; TTDD, time to discontinuation or death
Bold indicates base case.

B.4.2.1.2.2 TTD for BRCA patients based on SACT Database

In addition to ARIEL3 data SACT data were also available for TTD for the BRCA population for both niraparib (n=157) and rucaparib (n=70). For details on the SACT data see Section B.3.9.4 Comparisons using SACT data. An overview of all curve fits is presented in Figure 43.

Table 53 presents the observed and predicted mean and medians for all extrapolations and Table 54 presents the AIC and BIC values. Based on fit statistics and visual inspection of the curves, the Weibull distribution was selected as the preferred fit for extrapolating TTD for rucaparib and the exponential distribution was selected as an alternative. Exponential is selected for niraparib, despite not being the best fitting curve, as other distributions with lower AIC/BIC generate implausibly long tail caused by the plateau in the observed data after the first 1 year. Assumedly, this plateau is due to immature data and would not appear in case of a longer follow for niraparib patients. The selected distributions are conservative in that they avoid overestimation of the drug cost for niraparib. The Weibull distribution was selected for sensitivity analysis for niraparib, to test a similar type of parametric model for both therapies.

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Figure 43. All parametric curve fits to rucaparib and niraparib TTD KM data from SACT - BRCA population

BRCA, breast cancer gene; KM, Kaplan Meier; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to discontinuation

Table 53. Predicted mean and median number of weeks of TTD in SACT in the BRCA population

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean (weeks)
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted]
Niraparib	Exponential		[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to discontinuation; NE, not estimable
Bold indicates base case.

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Table 54. Statistical fit of all TTDD parametric curve fits from SACT within BRCA population

	Rucaparib		Niraparib	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	352.68	354.93	**517.081**	**520.137**
Weibull	**351.66**	**356.16**	518.736	524.849
Gompertz	353.37	357.87	518.441	524.553
Log-logistic	352.22	356.72	514.800	520.912
Log-normal	351.97	356.47	511.261	517.373
Generalised gamma	353.00	359.75	511.109	520.278

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; SACT, Systemic Anti-Cancer Therapy dataset; TTDD, time to discontinuation or death
Bold indicates base case.

B.4.2.1.2.3 TTDD for Non-BRCA based on ARIEL3 and NOVA

Figure 18 shows the KM curve for TTDD in the ARIEL3 trial, displaying both active treatment and placebo arms in the non-BRCA population. An overview of all curve fits is presented in Figure 44.

Table 55 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 56 presents the AIC and BIC. Log-logistic was selected as the base case distribution based on fit statistics and visual inspection of the curves.

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Figure 44. Overview of all parametric curve fits to the rucaparib TTDD KM data from the ARIEL3 non-BRCA population

BRCA, breast cancer gene; KM, Kaplan-Meier; TTDD, time to discontinuation or death

Table 55. Predicted mean and median number of weeks of TTDD in ARIEL3 in the non-BRCA population – rucaparib

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean(weeks)
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted]

BRCA, breast cancer gene; TTDD, time to discontinuation or death
Bold indicates base case.

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Table 56. Statistical fit of all TTDD parametric curve fits for ARIEL3 within non-BRCA population – rucaparib

Model	AIC	BIC
Exponential	703.32	706.83
Weibull	700.70	707.70
Gompertz	705.20	712.21
Log-logistic	**677.64**	**684.65**
Log-normal	684.87	691.87
Generalised gamma	684.48	694.98

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; TTDD, time to discontinuation or death.
Bold indicates base case.

TTD data for niraparib were available from the NOVA trial for the non-BRCA population. An overview of all curve fits is presented in Figure 45.

Table 57 presents the predicted median and mean by each fitted parametric survival model and Table 58 presents the AIC and BIC. Exponential is selected based on fit statistics and visual inspection of the curves.

Figure 45. Overview of all parametric curve fits to niraparib TTDD KM data from the NOVA non-BRCA population

BRCA, breast cancer gene; KM, Kaplan-Meier; TTDD, time to discontinuation or death

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Table 57. Predicted mean and median of TTDD parametric curve fits from NOVA within non-BRCA population – niraparib

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean(weeks)
Niraparib	Exponential	39.25	**43.53**	**62.80**
	Weibull		42.53	63.77
	Gompertz		40.90	Not estimable
	Log-logistic		38.73	138.88
	Log-normal		36.72	96.63
	Generalised gamma		40.96	66.38

BRCA, breast cancer gene; TTDD, time to discontinuation or death

Table 58. Statistical fit of all TTDD parametric curve fits from NOVA within non-BRCA population – niraparib

Model	AIC	BIC
Exponential	**719.53**	**722.98**
Weibull	720.92	727.81
Gompertz	719.61	726.50
Log-logistic	723.17	730.05
Log-normal	732.23	739.12
Generalised gamma	721.60	731.93

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; TTDD, time to discontinuation or death
Bold indicates base case.

B.4.2.1.2.4 TTD for non-BRCA patients based on SACT Database

A large set of data were available from SACT for niraparib (n=859) and rucaparib (n=817) to inform TTD for non-BRCA patients. For details on the SACT data see Section B.3.9.4 Comparisons using SACT data. An overview of all curve fits is presented in Figure 46.

Table 59 presents the predicted median and mean by each fitted parametric survival model and Table 60 presents the AIC and BIC for each extrapolation. Log-normal is selected as the base case distribution for rucaparib, and exponential is selected for niraparib based on fit statistics and visual inspection. Note that although the distributions selected are from a different family, the calculations are conservative in avoids overestimation of niraparib TTD.

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Figure 46. Overview of all parametric curve fits to the rucaparib and niraparib TTD KM data from the SACT non-BRCA population

BRCA, breast cancer gene; KM, Kaplan-Meier; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to discontinuation

Table 59. Predicted mean and median number of weeks of TTD in SACT in the non-BRCA population

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean (weeks)
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted]
Niraparib	Exponential		[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; TTD, time to discontinuation; SACT, Systemic Anti-Cancer Therapy dataset
Bold indicates base case.

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Table 60. Statistical fit of all TTD parametric curve fits from SACT within non-BRCA population

	Rucaparib		Niraparib	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	3885.42	3890.13	**3298.40**	**3303.16**
Weibull	3880.15	3889.56	3269.49	3279.00
Gompertz	3886.76	3896.17	3298.71	3308.23
Log-logistic	3843.01	3852.42	3223.94	3233.46
Log-normal	**3829.91**	**3839.32**	3210.40	3219.91
Generalised gamma	3831.91	3846.02	3208.99	3223.26

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to discontinuation.
Bold indicates base case.

B.4.2.1.3 Overall Survival

B.4.2.1.3.1 OS for BRCA-mutated population – ARIEL3

The KM curve for OS in the ARIEL3 trial, displaying both active treatment and placebo arms in the BRCA population can be found in Section B3. An overview of all curve fits for rucaparib is presented in Figure 47.

Table 61 presents the observed median OS in weeks from ARIEL3, in addition to the median and mean as predicted by each fitted parametric survival model. Table 62 presents the AIC and BIC. Based on the goodness-of-fit statistics and the visual inspection of long-term extrapolations the log-normal distribution was selected for the base case.

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Figure 47. All parametric curve fits to rucaparib OS data from ARIEL3 BRCA population (projected survival curve)

BRCA, breast cancer gene; OS, overall survival

Table 61. Predicted mean and median of OS in ARIEL3 in the BRCA population – rucaparib

Extrapolation		**Observed median**	**Predicted**	
			Median	**Mean**
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted][a]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted][a]

BRCA, breast cancer gene; OS, overall survival.
[a]Estimated as restricted mean survival time at 99th percentile of the fitted distribution. No estimate is reported if the fitted distribution does not reach 99th percentile.
Bold indicates base case.

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Table 62. Statistical fit of all OS parametric curve fits within the ARIEL3 BRCA population - rucaparib

	AIC	BIC
Exponential	1110.6	1113.5
Weibull	1100.6	1106.4
Gompertz	1109.0	1114.7
Log-logistic	1093.6	1099.3
Log-normal	**1091.9**	**1097.6**
Generalised gamma	1093.4	1102.0

AIC, Akaike information criterion; BIC, Bayesian information criterion BRCA, breast cancer gene; OS, overall survival
Bold indicates base case.

B.4.2.1.3.2 OS for BRCA-mutated population – SACT

In addition to ARIEL3 data SACT data were also available for OS for the BRCA population for both niraparib (n=157) and rucaparib (n=70). For details on the SACT data see Section B.3.9.4 Comparisons using SACT data. An overview of all curve fits is presented in Figure 48.

Table 63 presents the observed and predicted median and mean by each fitted parametric survival model and Table 64 presents the AIC and BIC for each extrapolation. Log-logistic is selected as the preferred distribution for rucaparib, and log-normal is selected for niraparib based on fit statistics and visual inspection of the curves. As an alternative Weibull distribution was selected providing still a relatively good fit and conservative survival probabilities for both rucaparib and niraparib.

Figure 48. All parametric curve fits to rucaparib and niraparib OS data from the SACT BRCA population

BRCA, breast cancer gene; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset

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Table 63. Predicted mean and median number of weeks of OS in SACT in the BRCA population

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean (weeks)
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted]
Niraparib	Exponential		[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset
Bold indicates base case.

Table 64. Statistical fit of OS curve fits from SACT within BRCA population

	Rucaparib		Niraparib	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	263.2	265.4	514.4	517.4
Weibull	248.2	252.7	501.4	507.5
Gompertz	250.8	255.3	505.8	511.9
Log-logistic	**248.1**	**252.6**	500.8	506.9
Log-normal	250.0	254.5	**500.6**	**506.7**
Generalised gamma	250.1	256.8	502.4	511.6

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset
Bold indicates base case.

B.4.2.1.3.3 OS for non-BRCA mutated population – ARIEL3

The KM curve for OS in the ARIEL3 trial, displaying both active treatment and placebo arms in the non-BRCA population (Section B3). An overview of all curve fits for rucaparib is presented in Figure 49.

Table 65 presents the observed median OS in weeks from ARIEL3, in addition to the median and mean as predicted by each fitted parametric survival model. Table 66 presents the AIC and BIC. Based on the goodness-of-fit statistics and the visual inspection of long-term extrapolations the log-logistic distribution was selected for the base case.

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Figure 49.Overview of all parametric curve fits to the rucaparib OS data from the ARIEL3 non-BRCA population (projected survival curve)

BRCA, breast cancer gene; OS, overall survival

Table 65. Predicted mean and median number of weeks of OS in ARIEL3 in the non-BRCA population – rucaparib

		Observed median	Predicted	
Extrapolation			**Median**	**Mean**
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted]

BRCA, breast cancer gene; OS, overall survival
Bold indicates base case.

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Table 66. Statistical fit of all OS parametric curve fits within the ARIEL3 non-BRCA population - rucaparib

	AIC	BIC
Exponential	2381.9	2385.4
Weibull	2339.4	2346.4
Gompertz	2367.4	2374.4
Log-logistic	**2314.8**	**2321.8**
Log-normal	2321.6	2328.6
Generalised gamma	2322.7	2333.2

AIC, Akaike information criterion; BIC, Bayesian information criterion BRCA, breast cancer gene; OS, overall survival
Bold indicates base case.

B.4.2.1.3.4 OS for non-BRCA population – SACT

SACT data were also used to inform OS for the non-BRCA population treated with rucaparib (n=817) or niraparib (n=859). An overview of all curve fits is presented in Figure 50.

Table 67 presents the observed and predicted median and mean by each fitted parametric survival model and Table 68 presents the AIC and BIC. Log-logistic is selected as the preferred distribution for rucaparib, and generalised gamma is selected for niraparib based on fit statistics and visual inspection of the curves.

Figure 50. Overview of all parametric curve fits to the rucaparib and niraparib OS data from the SACT non-BRCA population

BRCA, breast cancer gene; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset

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Table 67. Predicted mean and median number of weeks of OS in SACT in the non-BRCA population

Extrapolation		Observed median (weeks)	Predicted	
			Median (weeks)	Mean (weeks)
Rucaparib	Exponential	[redacted]	[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma		[redacted]	[redacted]
Niraparib	Exponential		[redacted]	[redacted]
	Weibull		[redacted]	[redacted]
	Gompertz		[redacted]	[redacted]
	Log-logistic		[redacted]	[redacted]
	Log-normal		[redacted]	[redacted]
	Generalised gamma	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset
Bold indicates base case.

Table 68. Statistical fit of OS curve fits from SACT within the non-BRCA population

	Rucaparib		Niraparib	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	2966.9	2971.7	3817.9	3822.6
Weibull	2888.4	2897.8	3684.5	3694.0
Gompertz	2915.6	2925.0	3720.9	3730.4
Log-logistic	**2885.6**	**2895.0**	3681.7	3691.2
Log-normal	2887.9	2897.3	3688.2	3697.7
Generalised gamma	2884.7	2898.9	**3681.2**	**3695.5**

AIC, Akaike information criterion; BIC, Bayesian information criterion; BRCA, breast cancer gene; OS, overall survival; SACT, Systemic Anti-Cancer Therapy dataset
Bold indicates base case.

Mean predictions are aligned with expectations regarding RCT vs RWD (Appendix J).

B.4.2.2 Intervention and comparators' acquisition costs

The list price for rucaparib is £3,562 per pack of 60 tablets. Assuming a use of four tablets a day, the total drug acquisition cost for the intervention is £7,227.89 per month. Inclusive of the submitted prospective commercial discount, the NHS England acquisition cost for one month of rucaparib treatment is [redacted].

The list price of niraparib is £6,750 per pack of 84 capsules. Assuming a use of 3 tablets a day the total drug acquisition cost for niraparib is £7,337.61 per month. The SmPC for niraparib is for 300mg once daily, although in the NOVA trial this dosing was often reduced to 200mg per day. The clinical expert explained that clinicians favour starting treatment with

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a lower 200 mg daily dose of niraparib in clinical practice because it is associated with reduced toxicity and treatment stopping rates.[41] Individualised dosing for niraparib was not compared head-to-head against fixed dosing in the relapsed setting. In the 1L maintenance setting in the HR proficient subgroup, the individualised dose appeared to provide a lower treatment effect compared to the fixed 300 mg starting dose.[45] In the base case we use the dose recommended in the SmPC in 2L and investigate reduced dosing in line with that observed in NOVA trial in scenario analysis. Although the commercial discount agreed with NHS England is not known for niraparib we assumed a [redacted] discount was applied in the base case for a more accurate comparison to niraparib than using the list price. Details are shown in Table 69.

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Table 69. Acquisition costs of the intervention and comparator technologies

	Rucaparib	Niraparib
Pharmaceutical formulation	Film-coated tablets (300 mg/tablet)	Hard capsules (100 mg/capsule)
(Anticipated) care setting	Primary care	Primary care
Acquisition cost (excluding VAT) *	List price, per dose: £118.73	List price, per dose: £241.07
Method of administration	Oral	Oral
Doses	600 mg/dose	300 mg/dose
Dosing frequency	2 doses per day	1 dose per day
Dose adjustments	N/A	N/A
Average length of a course of treatment	The model assumes a cycle length of 1 month with a maximum time horizon of 30 years	
Average cost of a course of treatment (acquisition costs only)	Proposed discounted price, per month: [redacted][a]	Assumed discounted price per month: [redacted]
(Anticipated) average interval between courses of treatment	N/A	N/A
(Anticipated) number of repeat courses of treatment	N/A	N/A

N/A, not applicable

[a] The acquisition cost for a course of treatment with rucaparib follows a prospective discount of [redacted].

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B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

As both niraparib and rucaparib are oral medications no administration cost is assumed, which is in line with the administration costs assumed in TA784.[41] Resource use items and frequencies were informed by TA784[41] with all resource use frequencies being equal between rucaparib and niraparib except for blood tests where niraparib requires weekly tests during the first cycle. Unit costs for all resource use items were informed by 2023/24 NHS reference costs (Table 70).[92]

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Table 70. Resource costs of the intervention and comparator technologies

Resource	Rucaparib	Niraparib
CT scan		
Unit cost, £	93	93
Source reference for unit cost	RD22Z - Diagnostic Imaging - One area with pre and post contrast. NHS Payment Scheme 2023/2025.[92]	
Number of units in cycle 1 (progression-free on maintenance)	0	0
Number of units in cycle 2-15+ (progression-free on maintenance)	0.33	0.33
Number of units per model cycle (progression-free off maintenance)	0	0
Number of units per model cycle (progressed)	0	0
Source reference for number of units	TA784[41]	
Blood tests		
Unit cost, £	3.22	3.22
Source reference for unit cost	DAPS05 - Directly Accessed Pathology Services - Haematology. Resource use based on clinical expert opinion. NHS Payment Scheme 2023/2025 prices.[92]	
Number of units cycle1 (progression-free on maintenance)	1	4
Number of units in cycle 2-15+ (progression-free on maintenance)	1	1
Number of units per model cycle (progression-free off maintenance)	0	0
Number of units per model cycle (progressed)	0	0
Source reference for number of units	TA784[41]	
Medical oncologist		
Unit cost, £	158	158
Source reference for unit cost	370 Medical Oncology Service - WF01A Consultant Led, Non-Admitted Face-to-Face, single professional. Resource use based on clinical expert opinion. NHS Payment Scheme 2023/25.[92]	
Number of units per model cycle (progression-free on maintenance)	1	1
Number of units per model cycle (progression-free off maintenance)	0.33	0.33
Number of units per model cycle (progressed)	0.33	0.33
Source reference for number of units	TA784[41]	

CT computed tomography, NHS, National Health Service
Sources: NHS Payment Scheme 2023/25;[92]NICE TA784[41]

B.4.2.4 Adverse reaction unit costs and resource use

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

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& vomiting was suggested for inclusion with a UK clinical expert, and hypertension and thrombocytopenia were added for consistency with TA528.

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 71).

Table 71. Mean duration of adverse events applied in the economic model

	Mean duration (days)	Source
Combined ALT/AST	[redacted]	ARIEL2 statistical analyses – data on file[57,93]
Anaemia	[redacted]	
Fatigue/asthenia	[redacted]	
Neutropenia	[redacted]	
Thrombocytopenia	[redacted]	
Nausea/vomiting	[redacted]	
Hypertension	[redacted]	

AST, aspartate transaminase; ALT, alanine aminotransferase

The risks for rucaparib were taken from ARIEL3 data, while the risks for niraparib were taken from the NOVA trial. The resulting monthly risks of each AE, by treatment, are provided in Table 72.

Table 72. Adverse event risk per month on treatment

Adverse event	Rucaparib	Niraparib
Combined ALT/AST	[redacted]	0.00%
Anaemia	[redacted]	3.49%
Fatigue/asthenia	[redacted]	1.04%
Neutropenia	[redacted]	2.62%
Thrombocytopenia	[redacted]	4.90%
Nausea/vomiting	[redacted]	0.37%
Hypertension	[redacted]	1.04%

ALT, alanine aminotransferase; AST, aspartate transaminase
Source: Rucaparib, ARIEL3 data[56]; niraparib, NOVA trial.[41]

For consistency across appraisals, adverse event management costs were taken based on the resource use in TA528, which in turn were based on cost categorisations from TA381.[94,95] These values were taken from 2021-22 NHS reference costs and inflated to 2023.[96] The only AE cost not sourced in this way is ALT/AST; as part of TA611, validation with a UK clinical expert advised that standard treatment for this AE is monitoring via a liver

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function test.[42] For ALT/AST, the cost of testing was therefore sourced from 2021-22 NHS reference costs.[96] The costs for all AEs and the associated sources are summarised in Table 73.

Table 73. List of adverse reactions and summary of costs in the economic model

Adverse event	Average cost per patient episode	Reference
Combined ALT/AST	£ 11.77	DAPS04 - Clinical Biochemistry - Hepatic function panel include: Albumin; Bilirubin, total; Bilirubin, direct; Phosphatase, alkaline; Protein, total; Transferase, alanine amino (ALT); Transferase, aspartate amino (AST) = 7 TESTS. Resource use based on clinical expert opinion
Anaemia	£ 930.62	SA04G-SA04L (HRG costs for non-elective long and short stay, day case, and regular day or night admissions weighted by activity)
Fatigue/asthenia	£ 440.94	Assumed to require IV nutrition (XD26Z)
Neutropenia	£ 1,485.66	SA08G-SA08J (HRG costs, total weighted by activity)
Thrombocytopenia	£ 1,031.66	SA12G-SA12K (HRG costs for non-elective long and short stay, day case, and regular day or night admissions weighted by activity)
Nausea/vomiting	£ 348.07	Unit cost for N16AF (specialist nursing cost) plus HRG costs for regular day or night admission for Non-Malignant Gastrointestinal Tract Disorders
Hypertension	£ 831.53	Hypertenstion currency codes: EB04Z (HRG costs for non-elective long stay, non-elective short stay, day case and regular day or night admissions, weighted by activity)

ALT, alanine aminotransferase; AST, aspartate transaminase
Source: NHS Reference Costs 2021/2022[96]

B.4.2.5 Miscellaneous unit costs and resource use

B.4.2.5.1 Subsequent treatment

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. Subsequent therapy use in the CSR addendum of ARIEL3 were classified into broader categories.[56] The proportion of the broader therapeutical categories have been equally distributed to the specific therapies that belong to the therapeutical category. Within ARIEL3 some patients on rucaparib received PARPs as subsequent treatment[56], as PARP inhibitor after PARP inhibitor is not currently allowed within UK clinical practice, therefore subsequent treatment with PARPs in the active arm were not included in the subsequent treatment costs. Within the model, the average cost was applied to the newly progressed cohort for each intervention assessed at each model cycle. The administration cost of each regimen was dependent on the route of administration, according to costs provided in the 2023/25 NHS Payment Scheme (see Table 74)[92]. Oral therapies have an administration cost, assumed monthly. Infusion drugs are assumed to have an administration cost on each day of

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administration, according to the duration of administration. The total costs are summarised in Table 74.

The one-off cost of death (£4.226.07) was taken from the technology appraisal of niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (TA528) and inflated to 2023 prices.[94]

Table 74. Administration costs

Item	Description	Unit costs
Initial oral **administration cost**	Deliver Exclusively Oral Chemotherapy	£ 137.00
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**	£ 172.00
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.**	£ 343.00
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	£ 515.00
Subsequent elements of a chemotherapy cycle	Deliver Subsequent Elements of a Chemotherapy Cycle	£ 343.00

Source: NHS Payment Scheme 2023/25[92]

Table 75. One-off subsequent therapies cost by treatment by subgroups

	BRCA	Non-BRCA
Active treatments (rucaparib and niraparib)	£ 10,395.18	£ 9,942.40

BRCA, breast cancer gene

B.4.2.6 Uncertainties in the inputs and assumptions

Table 76 summarizes the base case inputs and uncertainty distribution around values varied in the PSA and DSA. Probabilistic sensitivity analysis (PSA) was undertaken using 1,000 iterations, varying inputs according to their distributions. For the DSA each parameter was varied to its upper and lower bound.

Table 76. Base case and uncertainty estimates for model parameters varied in DSA and PSA

Variable	Base case Value	Measurement of uncertainty and distribution: Distribution (alpha and beta); (lower and upper bound)
BRCA ARIEL 3 – rucaparib arm - Proportion of patients discontinuing	[redacted]	Beta(18,111); (9%, 20%)
BRCA NOVA – niraparib arm - Proportion of patients discontinuing	[redacted]	Beta(54,313); (11%, 19%)
Non-BRCA – ARIEL 3 – rucaparib arm - Proportion of patients discontinuing	[redacted]	Beta(53, 319); (11%, 18%)

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Variable	Base case Value	Measurement of uncertainty and distribution: Distribution (alpha and beta); (lower and upper bound)
Non-BRCA – NOVA – niraparib arm - Proportion of patients discontinuing	[redacted]	Beta(54, 313); (11%, 19%)
BRCA ARIEL 3 – rucaparib arm – Follow up period (weeks)	56	Normal(56.09, 11.22); (34.10, 78.08)
BRCA NOVA – niraparib arm - Follow up period (weeks)	54	Normal(54.00,10.80); (32.83, 75.17)
Non-BRCA – ARIEL 3 – rucaparib arm – Follow up period (weeks)	45.22	Normal(27.49, 62.95); (27.49, 62.95)
Non-BRCA – NOVA – niraparib arm - Follow up period (weeks)	42.84	Normal(26.05, 59.64); (26.05, 59.64)
Rucaparib – ARIEL 3 – AE risk for combined ALT/AST	[redacted]	Beta(37.94,334.06), (7%, 13)
Rucaparib – ARIEL 3 – AE risk for anaemia	[redacted]	Beta(68.82,303.18), (15%, 23%)
Rucaparib – ARIEL 3 – AE risk for fatigue/asthenia	[redacted]	Beta(24.92,347.08), (4%, 9%)
Rucaparib – ARIEL 3 – AE risk for neutropenia	[redacted]	Beta(20.83,351.17), (4%, 8%)
Rucaparib – ARIEL 3 – AE risk for thrombocytopenia	[redacted]	Beta(14.88,357.12), (2%, 6%)
Rucaparib – ARIEL 3 – AE risk for nausea/vomiting	[redacted]	Beta(23.06,348.94) , (4%, 9%)
Rucaparib – ARIEL 3 – AE risk for hypertension	[redacted]	Beta(1.86,370.14) , (0%, 1%)
Niraparib – NOVA – AE risk for combined ALT/AST	0.00	Beta(0,367) , (0%, 0%)
Niraparib – NOVA – AE risk for anaemia	0.25	Beta(92.85, 274.15) , (21%, 30%)
Niraparib – NOVA – AE risk for fatigue/asthenia	0.08	Beta(30.09, 336.91) , (6%, 11%)
Niraparib – NOVA – AE risk for neutropenia	0.20	Beta(71.93, 295.07) , (16%, 24%)
Niraparib – NOVA – AE risk for thrombocytopenia	0.34	Beta(124.05,242.95) , (29%, 39%)
Niraparib – NOVA – AE risk for nausea/vomiting	0.03	Beta(11.01,355.99) , (2%, 5%)
Niraparib – NOVA – AE risk for hypertension	0.08	Beta(30.09, 336.91) , (6%, 11%)
Duration of combined ALT/AST (days)	[redacted]	Normal(16.20,3.24), (9.85, 22.55)
Duration of anaemia (days)	[redacted]	Normal(9.38,1.88) , (5.71, 13.06)
Duration of fatigue/asthenia (days)	[redacted]	Normal(21.04,4.21) , (12.79, 29.29)
Duration of neutropenia (days)	[redacted]	Normal(11.20,2.24) , (6.81, 15.59)
Duration of thrombocytopenia (days)	[redacted]	Normal(9.33,1.87) , (5.67, 12.99)
Duration of nausea/vomiting (days)	[redacted]	Normal(5.14,1.03) , (3.13, 7.16)
Duration of hypertension (days)	[redacted]	Normal(49.50,9.90) , (30.10, 68.90)
Discount applied to drug acquisition cost, rucaparib	[redacted]	-
Discount applied to drug acquisition cost, niraparib	[redacted]	Assumption
One-off costs: Cost of death cost	£ 4226.07	gamma (25, 169.04); (2734.89, 6036.53)
Monitoring costs - Rucaparib - Progression-free (on maintenance, cycle 1)	£ 161.22	gamma (25, 6.45); (104.33, 230.29)

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Variable	Base case Value	Measurement of uncertainty and distribution: Distribution (alpha and beta); (lower and upper bound)
Monitoring costs - Rucaparib - Progression-free (on maintenance, cycle 2-14)	£ 191.91	gamma (25, 7.68); (124.19, 274.13)
Monitoring costs - Rucaparib - Progression-free (on maintenance, cycle 15+)	£ 86.05	gamma (25, 3.44); (55.69, 122.92)
Monitoring costs - Niraparib - Progression-free (on maintenance, cycle 1)	£ 170.89	gamma (25, 6.84); (110.59, 244.09)
Monitoring costs - Niraparib - Progression-free (on maintenance, cycle 2-14)	£ 191.91	gamma (25, 7.68); (124.19, 274.13)
Monitoring costs - Niraparib - Progression-free (on maintenance, cycle 15+)	£ 86.05	gamma (25, 3.44); (55.69, 122.92)
Monitoring costs - Rucaparib - Progression-free (off maintenance, cycle 1)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs - Rucaparib - Progression-free (off maintenance, cycle 2-14)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs – Rucaparib – Progression-free (off maintenance, cycle 15+)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs – Niraparib – Progression-free (off maintenance, cycle 1)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs – Niraparib – Progression-free (off maintenance, cycle 2-14)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs – Niraparib – Progression-free (off maintenance, cycle 15+)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs - Rucaparib - Progressed disease (cycle 1)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs - Rucaparib - Progressed disease (cycle 2-14)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs - Rucaparib - Progressed disease (cycle 14+)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs - Niraparib - Progressed disease (cycle 1)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Monitoring costs - Niraparib - Progressed disease (cycle 2-14)	£ 52.14	gamma (25, 2.09); (33.74, 74.48)
Total AE costs per month - Rucaparib	£ 35.97	gamma (25, 1.44); (23.28, 51.37)
Total AE costs per month - Niraparib	£ 136.42	gamma (25, 5.46); (88.28, 194.86)
Total Lump Sum Cost of Subsequent Therapy, per patient upon progression - BRCA 2L+ MTN - Rucaparib	£ 7060.03	gamma (25, 282.4); (4568.88, 10084.58)
Total Lump Sum Cost of Subsequent Therapy, per patient upon progression - BRCA 2L+ MTN - Niraparib	£ 7060.03	gamma (25, 282.4); (4568.88, 10084.58)
Total Lump Sum Cost of Subsequent Therapy, per patient upon progression - non-BRCA 2L+ MTN - Rucaparib	£ 7367.90	gamma (25, 294.72); (4768.12, 10524.34)

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Variable	Base case Value	Measurement of uncertainty and distribution: Distribution (alpha and beta); (lower and upper bound)
Total Lump Sum Cost of Subsequent Therapy, per patient upon progression - non-BRCA 2L+ MTN - Niraparib	£ 7367.90	gamma (25, 294.72); (4768.12, 10524.34)
BRCA 2L+ MTN - TTD - NOVA Niraparib Standard - Parameter 1	0.00	Multivariate normal / Cholesky
BRCA 2L+ MTN - TTD - NOVA Niraparib Standard - Parameter 2	-4.81	Multivariate normal / Cholesky
BRCA 2L+ MTN - TTD - NOVA Niraparib Standard - Parameter 3	0.00	Multivariate normal / Cholesky
BRCA 2L+ MTN - TTD - NOVA Niraparib Standard - Parameter 4	0.00	Multivariate normal / Cholesky
non-BRCA 2L+ MTN - TTD - NOVA Niraparib Standard - Parameter 1	0.00	Multivariate normal / Cholesky
non-BRCA 2L+ MTN - TTD - NOVA Niraparib Standard - Parameter 2	-4.14	Multivariate normal / Cholesky
non-BRCA 2L+ MTN - TTD - NOVA Niraparib Standard - Parameter 3	0.00	Multivariate normal / Cholesky
non-BRCA 2L+ MTN - TTD - NOVA Niraparib Standard - Parameter 4	0.00	Multivariate normal / Cholesky
BRCA 2L+ MTN - TTTD - ARIEL-3 Rucaparib Standard - Parameter 1	[redacted]	Multivariate normal / Cholesky
BRCA 2L+ MTN - TTTD - ARIEL-3 Rucaparib Standard - Parameter 2	[redacted]	Multivariate normal / Cholesky
BRCA 2L+ MTN - TTTD - ARIEL-3 Rucaparib Standard - Parameter 3	[redacted]	Multivariate normal / Cholesky
BRCA 2L+ MTN - TTTD - ARIEL-3 Rucaparib Standard - Parameter 4	[redacted]	Multivariate normal / Cholesky
non-BRCA 2L+ MTN - TTTD - ARIEL-3 Rucaparib Standard - Parameter 1	[redacted]	Multivariate normal / Cholesky
non-BRCA 2L+ MTN - TTTD - ARIEL-3 Rucaparib Standard - Parameter 2	[redacted]	Multivariate normal / Cholesky
non-BRCA 2L+ MTN - TTTD - ARIEL-3 Rucaparib Standard - Parameter 3	[redacted]	Multivariate normal / Cholesky
non-BRCA 2L+ MTN - TTTD - ARIEL-3 Rucaparib Standard - Parameter 4	[redacted]	Multivariate normal / Cholesky

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; BRCA, breast cancer gene; CA125, cancer antigen 125; CI, confidence interval; CT, computed tomography; DSA, deterministic sensitivity analysis; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PARPi; poly (ADP ribose) polymerase inhibitor; PSA, probabilistic sensitivity analysis; PET, positron emission tomography
Note, for brevity, inputs with value 0 and CI (0,0) were removed from this table.

B.4.2.7 Assumptions

The assumptions of the economic analysis and their justifications are detailed in Table 77. 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.

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Table 77. Summary of assumptions in the analysis

#	Assumption	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.	Model structure in line with previous NICE appraisals in this indication (TA784, TA908)
2	Rucaparib and niraparib can be assumed to have equivalent PFS and OS	See section on NMA and MAIC (Section B.3.9)
3	Patients who receive treatment with a maintenance PARP inhibitor will not receive a subsequent PARP inhibitor	Not currently approved in the UK (Section B.1.3.3 and Section B.4.2)
4	30 years is sufficiently long enough to capture all relevant outcomes	Assumed long enough to capture health and cost consequences over the entire patient lifetime of the populations of interest. (Section B.4.2)
5	No waning effect for PARP inhibitors	In line with previous submissions (TA784, TA908) (Section B.4.2)
6	AE durations from ARIEL2 can be generalised to maintenance indication, and are not treatment-specific	Section B.4.2
9	Relative dose intensity of rucaparib and niraparib assumed to be 100%	Section B.4.2
10	Dose of 300 mg per day for niraparib is most appropriate	Section B.4.2

AE, adverse event; NHS national health service; NICE, National Institute of Health and Care Excellence; MAIC, matching adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival; PSS, personal social services; UK, United Kingdom
Sources: NICE TA784;[41] NICE TA908[40]

B.4.3 Base case results

Results of the base case analysis are shown in Table 78 for the BRCA population and for the non-BRCA population. They demonstrate that in both populations, rucaparib is cost saving in comparison to niraparib, mainly driven by differences in drug acquisition cost.

Table 78. Base case results - BRCA population – list price

Technologies	Acquisition costs	Administration costs	Subsequent costs	Resource costs	Adverse event costs	Total costs
Rucaparib	£ 134,838.82	£ 0.00	£ 9,802.14	£ 8,397.50	£ 688.19	£ 153,726.64
Niraparib	£ 168,744.20	£ 0.00	£ 9,802.14	£ 8,637.43	£ 3,203.10	£ 190,386.87

BRCA, breast cancer gene

Table 79. Base case results – non-BRCA population – list price

Technologies	Acquisition costs	Administration costs	Subsequent costs	Resource costs	Adverse event costs	Total costs
Rucaparib	£ 80,191.09	£ 0.00	£ 9,705.35	£ 7,152.28	£ 416.65	£ 97,465.37
Niraparib	£ 87,663.34	£ 0.00	£ 9,705.35	£ 7,959.70	£ 1,697.19	£ 106,326.45

BRCA, breast cancer gene

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Table 80. Base case results - BRCA population – price inclusive of proposed PAS discount

Technologies	Acquisition costs	Administration costs	Subsequent costs	Resource costs	Adverse event costs	Total costs
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; PAS, patient access scheme

Table 81. Base case results – non-BRCA population – price inclusive of proposed PAS discount

Technologies	Acquisition costs	Administration costs	Subsequent costs	Resource costs	Adverse event costs	Total costs
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; PAS, patient access scheme

B.4.4 Sensitivity and scenario analyses

A sensitivity analysis was conducted as part of the Assessment Group report in TA188, considering a number of key variables and the impact on the ICER, based on lower and upper bounds. Variables, which are summarised in Table 82, included:

- Using alternative fits for TTD from ARIEL3 and NOVA (for rucaparib Weibull for BRCA and generalised gamma for non-BRCA and for niraparib Gompertz for BRCA and Weibull for non-BRCA)
- Using rucaparib SACT data as key efficacy data source with recommended and alternative fits
- Using niraparib SACT data source with recommended and alternative fits
- Using alternative assumptions for TTD for niraparib with ARIEL-3 key efficacy data source, including niraparib TTD assuming treat until progression and constant discontinuation rate scenarios
- Applying relative dose intensity for niraparib from NOVA (65%)
- Alternative resource use frequencies based on TA528 Table 50
- Alternative niraparib PAS ([redacted])

The deterministic sensitivity analysis suggest that the results were robust, with the majority of the scenarios not changing the conclusion that rucaparib is cost saving. The scenario with the largest impact on results is the one investigating PARPi dosing. However, that scenario assumes a very low average niraparib dose, reflecting what was taken in the NOVA trial and not what the prescribed dose would be for patients.[83]

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Utilizing niraparib and rucaparib SACT data and alternative assumptions for niraparib TTD did not change the conclusions.

The probabilistic sensitivity analysis and Table 85 and Table 86) and deterministic sensitivity analysis (Figure 51 and Figure 52) results also demonstrate the robustness of the base case conclusion. In the deterministic sensitivity analysis for both BRCA and non-BRCA populations, the cost of subsequent treatment for niraparib and rucaparib are the most influential parameters but in all results rucaparib remains cost saving.

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Table 82. Scenarios investigated for BRCA and non-BRCA populations

#	Scenario
Base case	OS and PFS: ARIEL3 – Recommended curves RDI: 100% RDI for rucaparib and niraparib, Prices – PAS [redacted] for rucaparib, [redacted] for niraparib TTD: niraparib Nova data, rucaparib – ARIEL3 data – Recommended curves
1	**ARIEL3 and NOVA TTD alternative fits** OS and PFS ARIEL3, TTD rucaparib: alternative fits, TTD niraparib: alternative fits Other settings same as base case
2	**SACT rucaparib data:** OS: SACT rucaparib OS data – Recommended curves TTD: Nira – SACT niraparib data, Ruca – SACT rucaparib data - Recommended curves PFS: PFS vs TTD HR from ARIEL3, applied to SACT rucaparib TTD Other settings same as base case
3	**SACT rucaparib data: Alternative fits** OS and PFS: SACT rucaparib data – Alternative curve TTD: Nira – SACT niraparib data, Ruca – SACT rucaparib data– Alternative curve PFS: PFS vs TTD HR from ARIEL3, applied to SACT rucaparib TTD **Other settings same as base case**
4	**SACT niraparib data:** OS and PFS: SACT niraparib data, TTD: Nira – SACT niraparib data, Ruca – SACT rucaparib data PFS: PFS vs TTD HR from ARIEL3, applied to SACT niraparib TTD Other settings same as base case
5	**SACT niraparib data: Alternative fits** OS and PFS: SACT niraparib data, – Alternative curve TTD: Nira – SACT niraparib data, Ruca – SACT rucaparib data– Alternative curve PFS: PFS vs TTD HR from ARIEL3, applied to SACT niraparib TTD **Other settings same as base case**
6	**Alternative TTD 1:** OS and PFS ARIEL3, TTD niraparib: treat until progression Other settings same as base case
7	**Alternative TTD 2:** OS and PFS ARIEL3, TTD niraparib: Constant discontinuation rate per cycle in PF Other settings same as base case
8	**PARPi dosing:** Niraparib 65% RDI. Other settings same as base case
9	**Alternative resource use:** TA528 table 50 Other settings same as base case
10	Alternative niraparib PAS [redacted]

OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; RDI, relative dose intensity; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to discontinuation

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Table 83. Scenario analysis results – BRCA population

Scenario	Overall cost for rucaparib	Overall cost for niraparib	Difference in cost
Base case	[redacted]	[redacted]	[redacted]
ARIEL3 and NOVA alternative TTD	[redacted]	[redacted]	[redacted]
SACT rucaparib	[redacted]	[redacted]	[redacted]
SACT rucaparib – Alternative fits	[redacted]	[redacted]	[redacted]
SACT niraparib	[redacted]	[redacted]	[redacted]
SACT niraparib– Alternative fits	[redacted]	[redacted]	[redacted]
Alternative TTD1	[redacted]	[redacted]	[redacted]
Alternative TTD2	[redacted]	[redacted]	[redacted]
PARPi dosing	[redacted]	[redacted]	[redacted]
Alternative niraparib PAS	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; PAS, patient access scheme; SACT, Systemic Anti-Cancer Therapy dataset; TTDD, time to discontinuation or death

Table 84. Scenario analysis results – non-BRCA population

Scenario	Overall cost for rucaparib	Overall cost for niraparib	Difference in cost
Base case	[redacted]	[redacted]	[redacted]
ARIEL3 and NOVA alternative TTD	[redacted]	[redacted]	[redacted]
SACT rucaparib	[redacted]	[redacted]	[redacted]
SACT rucaparib – Alternative fits	[redacted]	[redacted]	[redacted]
SACT niraparib	[redacted]	[redacted]	[redacted]
SACT niraparib– Alternative fits	[redacted]	[redacted]	[redacted]
Alternative TTD1	[redacted]	[redacted]	[redacted]
Alternative TTD2	[redacted]	[redacted]	[redacted]
PARPi dosing	[redacted]	[redacted]	[redacted]
Alternative niraparib PAS	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; PAS, patient access scheme; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to discontinuation

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Figure 51. Deterministic sensitivity analysis results - BRCA population

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Figure 52. Deterministic sensitivity analysis results - non-BRCA population

Table 85. Probabilistic sensitivity analysis results - BRCA population

Results	Mean	SD	Lower	Upper	Deterministic
Total costs - Rucaparib					
Total costs - Niraparib					
Incremental costs - Rucaparib vs Niraparib					

BRCA, breast cancer gene; SD, standard deviation

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Table 86. Probabilistic sensitivity analysis results - non-BRCA population

Total cost	Mean	SD	Lower	Upper	Deterministic
Total costs - Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs - Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs - Rucaparib vs Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; SD, standard deviation

B.4.5 Interpretation and conclusions of economic evidence

At the list price and assuming equal efficacy for therapies, rucaparib provides savings to the NHS in overall treatment costs. The level of confidential discount for niraparib is unknown. At an expected discount of [redacted], and the proposed discount for rucaparib of [redacted] there are expected savings to the NHS in most scenarios. In summary, the analyses clearly demonstrates that rucaparib is expected to be cost neutral to the NHS.

A key strength to the cost-comparison analysis is that it is supported by two sets of data: data from RCTs. The very large samples (over 800 patients for both rucaparib and niraparib) from real-world UK clinical practice in the non-BRCA population with a relatively long follow-up for rucaparib provides confidence in the underlying assumption of cost comparisons. To the extent baseline characteristics in SACT are reported, the patient populations receiving niraparib and rucaparib appear comparable and show very similar and possibly even better outcomes for overall survival, the ultimate clinical outcome of interest for payers. The findings of the cost comparison using clinical trial vs SACT data are aligned.

Limitations of the cost-comparison analysis include the fact that adjustment for patient characteristics between the two SACT data are not possible. SACT data does not include information on PFS and although PARP inhibitors should be taken until progression, trial data show some discrepancy. A previous submission considered a hazard ratio between PFS and TTD, however, due to the strongly supported assumption of equivalence and the fact that costs are driven by monitoring as well as treatment costs, and no difference is expected in subsequent therapies, it was not considered necessary. Furthermore, there is a lack of information on niraparib dosing in the SACT and its impact on efficacy. Niraparib has not demonstrated equivalence of efficacy of 200mg dose vs 300mg dose in recurrent advanced OC trial specifically. In 1st line therapies, there is evidence that a lower dose may not be as effective among the non-BRCA patients.

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The choice of PARP inhibitor in the treatment of recurrent advanced OC should be made on the basis of safety profile and dosing of therapies, in a discussion between the treating physician and the patient and/or their carer.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost comparison

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (Review of TA611) [ID4069]

Summary of Information for Patients (SIP)

File name	Version	Contains confidential information	Date
ID4069_pharma&_Rucaparib_SIP_ 19Dec2023_FINAL	v1.0	Yes	19 December 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the National Health Service (NHS) for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Rucaparib **Brand name:** Rubraca®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

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.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Rucaparib has a marketing authorisation in the United Kingdom (UK) 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. Authorisation by the European Commission for rucaparib as a maintenance therapy was granted in 01/2019. Documents related to regulatory approval can be found here: • Rubraca | European Medicines Agency (europa.eu)

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Not applicable

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is ovarian cancer?

- Ovarian cancer is a type of cancer arising from the ovaries, the female reproductive organ. The disease can develop when inherited or spontaneous genetic mutations accumulate within the cells of the ovary, resulting in uncontrolled cell growth.(1)
- This uncontrolled cell growth can result in the development of a mass, which is called an **ovarian tumour**. These types of tumours can remain confined to the ovary (i.e., benign) or they can spread beyond the ovary (**ovarian cancer**).(1)

What are the symptoms of ovarian cancer?

- In patients with ovarian cancer, the symptoms can frequently be debilitating. They include bloating, early satiety, loss of appetite, persistent pain in the abdomen or lower abdomen, increased need to urinate, changes in bowel habits, symptoms of irritable bowel syndrome, unexplained fatigue and unexplained weight loss.(2)
- Patient symptoms worsen when disease progresses.(3) Moreover, worsening symptoms negatively affect quality of life; which in turn can also be reduced following chemotherapy or when patients experience a relapse of illness.(4)

How many people have ovarian cancer?

- In 2021, 6,673 people in England were diagnosed with ovarian or fallopian tube cancer.(5)

What is the prognosis of ovarian cancer?

- At least 1 in 2 people with ovarian cancer in the UK have advanced disease at the time of diagnosis, which is characterised by spread outside the pelvis (classified as Stage III disease) or to a distant site (Stage IV).(6, 7)
- The prognosis of advanced ovarian cancer is poor. In the UK, only 32% of people with Stage III disease and 14% of people with Stage IV disease survive beyond five years of diagnosis.(8)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

- A diagnosis of ovarian cancer typically involves a general practitioner examination followed by blood tests and ultrasound scanning to determine aberrant protein levels or physical anomalies. If anything is observed, patients are referred to specialist oncologists who arrange for further assessment and biopsies to facilitate characterisation and staging of the tumour.(9) Additionally genetic testing is conducted to detect mutations in breast cancer (BRCA) genes that are drivers of ovarian cancer.[21,2220,23]
- In England, 60% of ovarian cancer patients in 2021 had advanced stage disease at the time of diagnosis (i.e., Stage III or IV disease), indicating an urgent need for treatment.(5)
- For rucaparib therapy, no additional tests or investigations will be required beyond monthly blood count monitoring that are already employed for all products in the poly (ADP-ribose) polymerase (PARP) inhibitor class.(10-12)

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

How is advanced ovarian cancer initially treated?

- The recommended initial treatment for advanced ovarian cancer includes:
  - **Surgery** to remove as much of the tumour as possible.(13)
  - **Chemotherapy** to destroy any remaining cancerous cells. Chemotherapy may also be given before surgery or without surgery.(13) The chemotherapeutic drugs recommended for advanced ovarian cancer are called platinum-based chemotherapy (typically carboplatin) and paclitaxel.(13) Chemotherapy acts by destroying cells that multiply quickly, including cancer cells, but also affects normal cells, such as those found in hair, skin, blood and the lining of the mouth/gastrointestinal tract.(14) This means that chemotherapy can cause debilitating side effects such as nausea, loss of appetite, weight loss, diarrhoea, constipation, fatigue, increased risk of infection and hair loss.(14)

- **Targeted therapy** with bevacizumab, which can be given in combination with chemotherapy. Targeted therapy acts by specifically attacking cancerous cells.(14)

How successful is initial treatment?

- Although most patients (70% to 80%) with advanced ovarian cancer respond to initial treatment with surgery and chemotherapy, 71% of patients will relapse ≥5 years after initial chemotherapy in the absence of maintenance therapy.(15, 16)

How is relapsed ovarian cancer treated?

- **Chemotherapy** (with paclitaxel or a drug called pegylated liposomal doxorubicin hydrochloride) is the recommended treatment for all patients with relapsed ovarian cancer who initially responded to platinum-based chemotherapy.(17)

How successful is the treatment of relapse?

- Almost all patients who relapse will eventually develop resistance to platinum-based chemotherapy. This means that the drug will lose its ability to destroy cancerous cells, and the cancer will typically relapse at increasingly shorter intervals until it no longer responds at all.(13, 18)
- The prognosis for patients with platinum-resistant ovarian cancer is extremely poor, and patients are not expected to survive beyond 12 months even with recommended treatment (non-platinum-based chemotherapy).(13, 18)

Can relapse of advanced ovarian cancer be prevented?

- **Maintenance therapy** is recommended for patients with advanced ovarian cancer after initial treatment to help prevent relapse and delay chemotherapy.(19, 20)
- Treatments recommended for the maintenance therapy of ovarian cancer include olaparib, niraparib and rucaparib.(15, 17, 21-23) These treatments belong to a group of drugs called PARP inhibitors, a type of targeted therapy.
- In England, access to PARP inhibitors for advanced ovarian cancer varies depending on where the patient lives, how many rounds of relapses the patient has had, and if the patient has a genetic mutation called BRCA:(15, 17, 21-23)
    - **First-line relapse**: Patients who relapse after one round of platinum-based chemotherapy can access the following drugs via the Cancer Drug Fund:
        - Olaparib (BRCA+ patients only) or
        - Niraparib (all patients, regardless of BRCA status)
    - **Second-line relapse and beyond**: Patients who relapse after two or more rounds of platinum-based chemotherapy can access the following drugs via the NHS (olaparib and niraparib) or the Cancer Drug Fund (rucaparib):
        - Olaparib (patients with BRCA mutation only) or

- Niraparib (all patients) or
- Rucaparib (all patients).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Not applicable.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Efficient deoxyribonucleic acid (DNA) repair is critical to cell survival. Cells that are unable to efficiently repair their DNA undergo cell death. One mechanism by which cells repair their DNA requires molecules referred to as PARPs.(12)

Rucaparib causes cancer cell death by:(12)

- Inhibiting PARPs, hindering the ability of the cell to repair damaged DNA, and
- Forming PARP-DNA structural complexes that increase the risk of DNA damage

In addition to PARPs, normal cells have other mechanisms of repairing DNA. Cancer cells can be deficient in these additional mechanisms, rendering them especially vulnerable to the effect of PARP inhibitors.(12)

Rucaparib is given as a maintenance therapy to patients whose ovarian cancer has responded (completely or partially) to platinum-based chemotherapy, in order to extend the length of time that a patient is disease-free. Information on the properties of rucaparib and how it works can be found here:

- Rubraca 200 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes/No • If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
No, rucaparib is not intended for use in combination therapy.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Rucaparib is provided as film-coated tablets (200 mg, 250 mg or 300 mg formulations), allowing treatment to take place in the convenience and comfort of the patient's home. The recommended starting dose of rucaparib is 600 mg (2 x 300 mg tablets) taken twice daily, to an equivalent daily dose of 1,200 mg.(12) Rucaparib can be taken with or without food, and the 2 daily doses should be taken approximately 12 hours apart. If a patient vomits after taking rucaparib, the patient should not retake the dose, and should take the next scheduled dose.(12) Rucaparib is started no later than 8 weeks following the final dose of platinum-based chemotherapy. Patients can continue treatment with rucaparib until their disease progresses, or if they experience unacceptable toxicity.(12)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
The clinical efficacy (i.e., how well rucaparib works) and safety of rucaparib has been studied for the treatment of relapsed ovarian cancer in the randomised, double-blind, placebo-controlled, phase III ARIEL3 study.(19) ARIEL3, which provided the pivotal basis for the regulatory approval of rucaparib, was conducted in 87 centres in 11 countries: Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, the UK and the United States. Adult patients were allowed to enrol in the study and needed to have had platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma. Patients were additionally required to have received at least two previous platinum-based chemotherapy treatments with either a complete or partial response to their last medication. The presence or absence of mutations in the BRCA gene was also established for study entrants via the use of genetic testing.(19)

Overall, 564 patients were recruited, with 375 receiving rucaparib and 189 given placebo. The primary efficacy endpoint in the trial was investigator-assessed progression-free survival (PFS). The benefit of this outcome being the evaluation and determination of disease progression in real time. This enables investigators to make timely decisions regarding the best clinical management for their patients.(19)

Other outcomes that were assessed included: overall length of survival; time periods where further subsequent chemotherapy was not needed or until the next treatment was required; the occurrence of adverse events; patient reports of their health-related quality of life. The treatment phase was double-blinded (i.e., neither doctors nor patients were aware of the agent being administered) and consisted of continuous 28-day maintenance treatment cycles until disease progression, death, or another reason for discontinuation. Patients were then followed up every 12 weeks.(19)

During the design of ARIEL3, it was decided that the clinical data would be assessed at certain pre-established times. Outside of these times, investigators were to remain blinded to the findings. The 'primary endpoint analysis' for ARIEL3 study was scheduled for after when 70% of patients with BRCA mutations had an investigator observed event disease progression or death. This was achieved by 15 April 2017. Similarly, the 'final analysis' of ARIEL3 was achieved as of 4 April 2022 and was due after approximately 70% of patients in the study had died.(19)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The primary endpoint of ARIEL3 was successfully met. Regardless of BRCA mutation status, rucaparib significantly reduced the risk of disease progression compared with placebo in patients with platinum-sensitive ovarian cancer who had responded to platinum-based chemotherapy at the primary endpoint analysis. For the overall ARIEL3 population, median investigator-assessed PFS in the rucaparib arm (10.8 months), was significantly longer than in the placebo arm (5.4 months) producing a hazard ratio (HR) of 0.36 (95%CI 0.30-0.45, p<0.0001).(19) This significant difference was also maintained in the subgroups of patients with BRCA mutations (16.6 vs 5.4 months; HR: 0.23 [95%CI 0.16-0.34], p<0.0001), and non-BRCA mutated individuals.(24) This benefit of rucaparib therapy was consistently observed when PFS was subsequently assessed as a key secondary endpoint by independent reviewers who were blinded to the underlying interventions.(19, 25)

At the end of the trial, no significant survival differences were observed between treatment arms of ARIEL3. However, when analyses adjusted for the confounding effect of subsequent PARP inhibitor treatment, it was found that overall survival (OS) in the rucaparib group was significantly longer for the trial as a whole than for placebo.(26)

ARIEL3 has also established that treatment with rucaparib also benefits patients with ovarian cancer in terms of lengthening the time needed before further chemotherapy (and in turn the potential adverse events associated with chemotherapy).(25) By the end of ARIEL3, the chemotherapy-free interval and the time to first anti-cancer treatment were significantly longer for rucaparib treatment in the overall study cohort and all subsets analysed than for placebo.(26)

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Patient health-related quality of life was assessed during ARIEL3 via the widely accepted, disease specific, Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index - 18 Item Version questionnaire and provided one of the secondary endpoints from the study. For the overall study cohort, and those with BRCA mutations, it was found that patients reported a shortening of the time to worsening of health-related quality of life in patients treated with rucaparib at the primary endpoint analysis. However, the difference was only found to be statistically different in the overall trial population.(25) ARIEL3 also utilised a generic tool (the EuroQol five-dimension) and it was established that health-related quality of life was not detrimentally impacted following rucaparib treatment, with no difference in patients' self-rated health observed across treatment groups from baseline to end of treatment.(25)

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

At the time of the final analysis of ARIEL3, the median duration of treatment was 8.3 months for rucaparib group and 5.5 months for placebo. Further, 78.1% of patients in the rucaparib group and 88.9% of the placebo group had received at least one subsequent anti-cancer treatment.(27)

Most patients in the safety population experienced at least one treatment-emergent adverse event (TEAE; rucaparib: 100%; placebo: 96.3%).(26, 27) the most common TEAEs that occurred in the rucaparib group were nausea, combined asthenia/fatigue and abdominal pain. 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 combined asthenia/fatigue, abdominal pain and nausea .(26) In the rucaparib group, 20.2% of patients had a TEAE that led to study drug discontinuation, compared with 2.1% in the placebo group. The incidence of TEAEs leading to dose reduction was greater for the rucaparib group (56.2%) than the placebo group (4.2%).(27)

Overall, rucaparib was generally well tolerated with adverse events observed in the ARIEL3 trial consistent with the known safety profile of rucaparib.(19, 20, 25-28) There was no meaningful increase in mortality or morbidity in the rucaparib group compared with the placebo group. The rucaparib treatment discontinuation rate due to TEAEs was low at the final analysis (20.2%), with TEAEs generally managed through dose modifications and supportive care.(19, 20, 27)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Rucaparib prolongs response to platinum-based chemotherapy and extends the chemotherapy-free interval and time to subsequent first and second anti-cancer treatments without negatively impacting health-related quality of life.(13, 29) In clinical practice, postponing subsequent platinum-based chemotherapy is expected to have a positive impact on daily life. Overall, rucaparib has a consistent and manageable safety profile; the side effect profile observed in the ARIEL3 trial was similar to the side effects recorded in previous studies of maintenance treatment with PARP inhibitors.(30)

No meaningful differences were observed in analyses comparing rucaparib to olaparib and niraparib. This suggests that rucaparib provides at least similar clinical benefits to current PARP inhibitor maintenance treatments. Moreover, rucaparib offers patients and physicians a reduced administration burden and a safety profile that differs from the safety profile of olaparib and niraparib.(10, 11, 31)

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The majority of patients treated with rucaparib in the ARIEL3 study experienced at least one treatment-related TEAE. The most common TEAEs that occurred in the rucaparib group were nausea, combined asthenia/fatigue and abdominal pain. Approximately one in five patients treated with rucaparib discontinue treatment due to TEAEs.(19, 20, 25-28)

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Rucaparib is not anticipated to require any changes to the current service provision and management. Rucaparib is orally administered twice daily with or without food. Niraparib and olaparib are also orally administered once daily therefore there are minimal differences in dosing and administration. Similar to other PARP inhibitors, rucaparib requires monthly monitoring of blood counts. Niraparib requires complete blood count weekly during the first month of treatment and blood pressure monitored weekly for the first two months. Therefore, rucaparib has lower blood count and blood pressure monitoring requirements in comparison to niraparib. Rucaparib is subject to additional monitoring for patients with either moderate or severe renal impairment. Patients with moderate hepatic impairment should be carefully monitored for hepatic function and adverse reactions. Patients with moderate or severe renal impairment should be carefully monitored for renal function and adverse reactions.(10, 11, 31)

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Not applicable.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Not applicable.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
• ARIEL3 – Phase 3 Study of Rucaparib as Switch Maintenance After Platinum in Relapsed High Grade Serous or Endometrioid Ovarian Cancer (ARIEL3). Available at: https://clinicaltrials.gov/study/NCT01968213 **Further information on NICE and the role of patients:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe. **Clinical trial:** A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study. **HTA (Health Technology Assessment) (bodies):** Bodies that make recommendations groups regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones. **Median**: The value separating the higher half from the lower half of a set of data **MHRA (Medicines and Healthcare products Regulatory Agency):** The body that regulates medicines, medical devices and blood components for transfusion in the UK.

Primary Endpoint: The outcome measured to answer the key question in a clinical trial.
Quality of life: The overall enjoyment of life. Many clinical trials assess it to measure aspects of an individual's sense of wellbeing and ability to carry out activities of daily living.
Secondary Endpoint: An outcome measured to answer an additional question of interest in a clinical trial.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [Review of TA611] [ID4069]

Clarification questions

Received: 20 December 2023

Submitted: 17 January 2024

(updated 19 January 2024)

File name	Version	Contains confidential information	Date
ID4069_pharma&_Rucaparib_Clarification Question Responses_17Jan2024 [redacted]	V1.0	Yes	17 January 2024
ID4069_pharma&_Rucaparib_Clarification Question Responses_19Jan2024 [redacted]	V1.1	Yes	19 January 2024

Section A: Clarification on effectiveness data

Network meta-analyses

A1. Priority question: Please provide the working OpenBUGS code files used for each of the outcomes in the network meta analyses (NMAs) presented in the company submission (CS), including the study data, and all other model inputs (such as initial values for each chain, number of burn ins and any other inputs required for the NMA to run) to enable validation of the company results?

The EAG expressed concerns about including Study 19 in the NMAs in Question A2. The company fully agrees that conducting NMAs without including Study19 in the study network is more appropriate and considers NMAs without Study 19 as the preferred approach.

In line with the EAG request, all programming codes including OpenBUGS code and R codes with all requested inputs such as initial values for each chain, number of burn ins, and input tables with HRs and CIs used in the updated analysis using only ARIEL3, SOLO2 and NOVA are provided in the company's response to Question A2.

A2. Priority question: The External Assessment Group (EAG) is concerned that the data from Study 19 relate to a retrospective analysis and has concerns about the inclusion of Study 19 in the company NMAs. Please re-run the NMAs using only ARIEL3, SOLO2 and NOVA (i.e. excluding Study 19) and provide the results.

Study 19 was included in the NMA analysis to preserve consistency with the original submission in 2017. However, in agreement with the EAG's concern that Study 19 is outdated and that NMA based only on ARIEL3, SOLO2 and NOVA is more appropriate, the NMA was re-run after excluding Study 19 from the study network. Please find the results from the updated analysis in Table 1 (as an update of Table 32 in Document B of the original company submission) below, showing revised NMA outcomes from the base case network for BRCA mutated and non-BRCA mutated cohorts.

All programming codes (OpenBUGS and R) and input files for each outcome of interest (including PFS-IRC and TTD) are provided in a separate folder named *A2 code -ARIEL3 NMA updated*.

Table 1. NMA outcomes, BRCA mutated and non-BRCA mutated cohorts (base case network, updated after excluding Study 19 and adding PFS-IRC and TTD)

	Rucaparib vs. olaparib[a]	Rucaparib vs. niraparib[b]
BRCA mutated cohort		
INV-PFS, HR (95% CI)	[redacted]	[redacted]

	Rucaparib vs. olaparib[a]	Rucaparib vs. niraparib[b]
BRCA mutated cohort		
IRC-PFS, HR (95% CI)	[redacted]	[redacted]
OS, HR (95% CI)	[redacted]	[redacted]
PFS2, HR (95% CI)	[redacted][c]	[redacted]
TSST, HR (95% CI)	[redacted]	[redacted]
TTD[d], HR (95% CI)	[redacted]	[redacted]
Non-BRCA mutated cohort		
INV-PFS, HR (95% CI)	[redacted]	[redacted]
IRC-PFS, HR (95% CI)	[redacted]	[redacted]
OS, HR (95% CI)	[redacted]	[redacted]
PFS2, HR (95% CI)	[redacted]	[redacted]
TSST, HR (95% CI)	[redacted]	[redacted]
TTD[d], HR (95% CI)	[redacted]	[redacted]

BRCA, BReast CAncer gene; CI, confidence interval; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; NMA, network meta-analysis; OS, overall survival; PFS2, progression-free survival on a subsequent line of treatment; TSST, time to start of second subsequent therapy, TTD, time to treatment discontinuation
Note: ARIEL3, Study 19, SOLO2 and NOVA were included in the base case analysis
[a] Olaparib is a relevant comparator in the BRCA mutated cohort only
[b] Niraparib is a relevant comparator in both the BRCA mutated and non-BRCA mutated cohorts
[c] Only immature PFS2 data were available in SOLO2 and mature PFS2 was not reported for that trial.
[d] Death event was treated as TTD event.

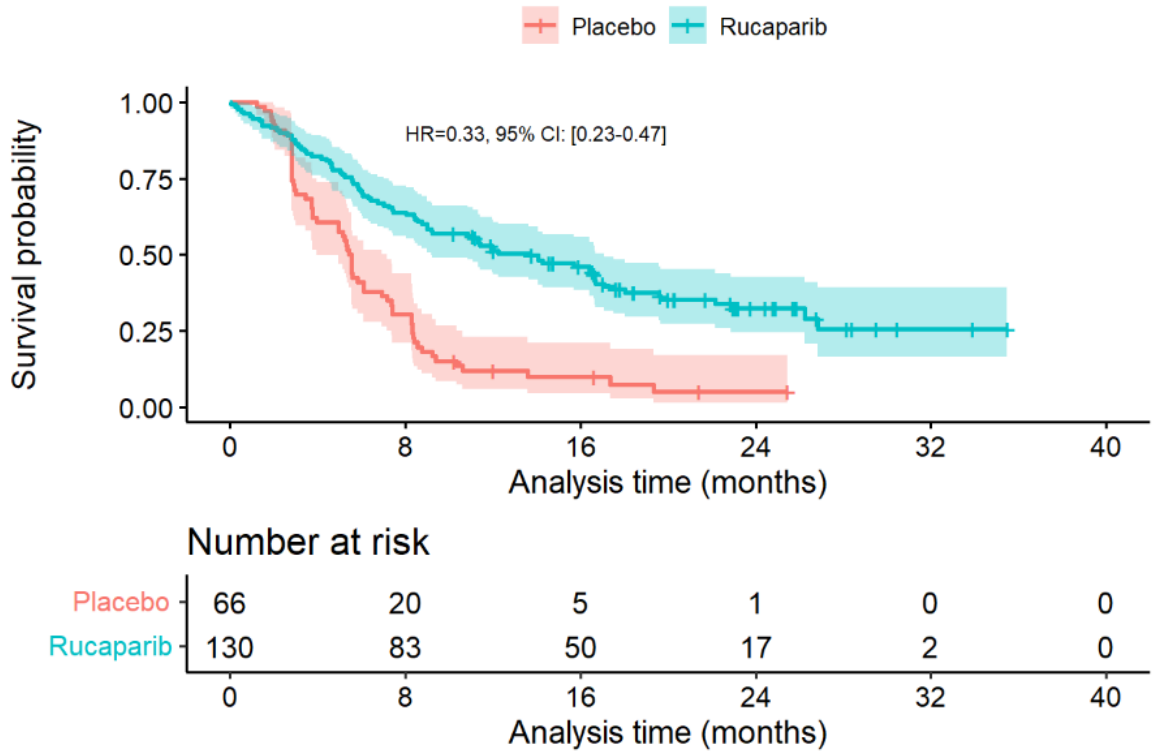
A3. Priority question: Please provide NMAs in the BRCA mutated cohort using ARIEL3, SOLO2 and NOVA and the non-BRCA mutated cohort using ARIEL3 and NOVA for the outcome of time-to-treatment discontinuation (TTD).

The HR for TTD was only available for olaparib vs placebo in SOLO2[1] in the BRCA cohort, while TTD was not reported for niraparib vs placebo in NOVA for BRCA or non-BRCA cohorts. Therefore, a potential NMA could only be conducted for the BRCA cohort including input data from ARIEL3 and SOLO2.

Additional programming codes, inputs and results are provided in the company's response to Question A2. above. Please note that since TTD KM curves are not reported in SOLO2, diagnostic procedures investigating PH assumption cannot be conducted.

Post-hoc subgroup analysis: stratified Cox HR for TTD in ARIEL3 is provided below in Figure 1. NMA results for TTD in BRCA mutated and non-BRCA mutated cohorts (in Table 2) have been added to the summary of NMA results provided in Table 1 for Question A2. Programming codes for the additional analysis have also been provided under Question A2.

Figure 1. New post-hoc analysis of TTD in the BRCA mutated cohort of ARIEL3



BRCA, BReast CAncer gene; TTD, time to treatment discontinuation

Table 2. NMA outcomes, BRCA mutated and non-BRCA mutated cohorts (base case network, TTD)

	Rucaparib vs. olaparib[a]	Rucaparib vs. niraparib[b]
BRCA mutated cohort		
TTD[c], HR (95% CI)	[redacted]	[redacted]
Non-BRCA mutated cohort		
TTD[c], HR (95% CI)	[redacted]	[redacted]

BRCA, BReast CAncer gene; CI, confidence interval; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; NMA, network meta-analysis; OS, overall survival; PFS2, progression-free survival on a subsequent line of treatment; TSST, time to start of second subsequent therapy, TTD, time to treatment discontinuation;
Note: ARIEL3, Study 19, SOLO2 and NOVA were included in the base case analysis
[a] Olaparib is a relevant comparator in the BRCA mutated cohort only
[b] Niraparib is a relevant comparator in both the BRCA mutated and non-BRCA mutated cohorts
[c] Death event was treated as TTD event.

A4. Priority question: Please provide NMAs in the BRCA mutated cohort using ARIEL3, SOLO2 and NOVA and non-BRCA mutated cohort using ARIEL3 and NOVA for the outcome of overall survival (OS) with crossover adjustment. Please prioritise the comparison of rucaparib versus niraparib using ARIEL3 and NOVA given the focus of the cost comparison analysis.

Methods for cross-over adjustment vary across trials. Previous analyses have either applied IPCW or RPSFT methodology. The key assumption in the IPCW method is the assumption

of “no unmeasured confounders”, which states that data must be available on all baseline and time-dependent prognostic factors for mortality that independently predict informative censoring, and models of censoring risk must be correctly specified. This assumption cannot be verified using trial data, and there is always a risk that some key predictors of treatment switching are not collected in a trial. Also, at high levels of treatment switching and small sample size IPCW can lead to bias.[2] There is no evidence that the NOVA trial had all required characteristics at the time of switching, and OS follow-up itself was not complete in NOVA. Due to the likely bias with IPCW adjustment, we do not think it is appropriate to conduct an NMA with these values.

The RPSFT adjusted HR is available from SOLO2, and an RPSFT adjusted acceleration factor is calculated in ARIEL3 for the BRCA mutated cohort. However, the extent of switching to PARPi therapy differ markedly between the two trials, up from 38.4% in SOLO2 to 65.2% in ARIEL3 (Table 20 in Document B of the original company submission). Given that details of the RPSFT analyses are unknown, an NMA on the cross-over adjusted HRs is not conducted.

A5. Priority question: Regarding the NMAs, please could the company clarify/provide the following:

a) **Please clarify if separate BRCA/non-BRCA subgroups from ARIEL 3 were used in the BRCA and non-BRCA NMAs, respectively, or if the full population from ARIEL 3 was used to inform rucaparib data for both BRCA and non-BRCA NMAs?**

    i) **If the latter, please provide NMAs where the BRCA and non-BRCA subgroups from ARIEL 3 (and comparator studies where applicable) are used in the respective NMAs, instead of the full trial population.**

The NMAs presented in the original submission were performed using the subgroup data as suggested. Please see Table 3 for outcomes for the BRCA mutated and non-BRCA mutated cohorts in ARIEL3 that were used in the ITCs. Therefore, there is no need to include a scenario on this.

Table 3. Summary of outcomes for the BRCA mutated and non-BRCA mutated cohorts[1,3-13]

HR (95% CI)	Rucaparib vs. placebo	Olaparib vs. placebo	Niraparib vs. placebo	
	ARIEL3	**SOLO2**	**NOVA**	**NORA**
BRCA mutated cohort[a]				
INV-PFS	0.23 (0.16, 0.34)	0.30 (0.22, 0.41)	Not reported	Not reported
IRC-PFS	0.20 (0.13, 0.32)	0.27 (0.17, 0.41)	0.25 (0.18, 0.35)	Not reported
OS	0.832 (0.581, 1.192)	0.74 (0.54, 1.00)	0.85 (0.61, 1.20)	0.764 (0.398, 1.464)
PFS2	0.672 (0.48, 0.941)	0.5 (0.34, 0.72)	0.7 (0.500, 0.968)	Not reported
TSST	0.635 (0.453, 0.891)	0.51 (0.39, 0.68)	0.63 (0.451, 0.878)	Not reported
TTD	0.33 (0.23, 0.47)	0.37 (0.28, 0.49)	Not reported	Not reported
Non-BRCA mutated cohort[a]				
INV-PFS	LOH^{high}: 0.44 (0.29, 0.66) LOH^{low}: 0.58 (0.40, 0.85) $LOH^{unknown}$: 0.25 (0.11, 0.56)	Not applicable	Not reported	Not reported
IRC-PFS	0.44 (0.33, 0.58)	Not applicable	0.45 (0.34, 0.61)	Not reported
OS	1.096 (0.852, 1.411)	Not applicable	1.06 (0.81, 1.37)	0.855 (0.529, 1.381)
TSST	0.73 (0.577, 0.923)	Not applicable	0.84 (0.654, 1.077)	Not reported
PFS2	0.713 (0.563, 0.903)	Not applicable	0.8 (0.627, 1.022)	Not reported

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; OS, overall survival; PFS2, progression-free survival on a subsequent line of treatment
[a] The ARIEL3 BRCA mutated cohort included patients with somatic and germline BRCA mutations, while the SOLO2, NOVA and NORA BRCA mutated cohorts included only patients with germline BRCA mutations
Source: Coleman et al. 2017[3]; Ledermann et al. 2012[4]; Ledermann et al. 2014[5]; Pujade-Lauraine et al. 2017[6]; Mirza et al. 2016[7]; Wu et al. 2021[8]; ARIEL3 CSR 2017[9]; ARIEL3 CSR addendum[10]; Poveda et al. 2021[1]; Friedlander et al. 2018[11]; Matulonis, 2023[12]; Wu et al. 2023[13]

b) Please provide a breakdown of baseline characteristics across studies included in BRCA and non-BRCA NMAs separately, for the populations that were actually included in the NMA from each trial. The EAG notes that Table 30 in the company submission (CS) provides some comparison, but it does not present a comparison between studies for BRCA and non-BRCA subgroups that may have been used in the NMAs rather than full trial populations.

Please include all of the characteristics listed in Table 30 of the CS in this new

table, in addition to homologous recombination deficiency (HRD) status and stage III vs stage IV disease.

Table 4. Patient characteristics at baseline for studies considered for ITC – BRCA population[a]

	ARIEL3		SOLO2		NOVA		NORA
	Rucaparib (n=130)	**Placebo (n=66)**	**Olaparib (n=196)**	**Placebo (n=99)**	**Niraparib (n=138)**	**Placebo (n=65)**	Not reported[b]
Age in years, median (range)	58 (42,81)	59 (36,84)	56 (51, 63)	56 (49, 63)	57 (36, 83)	58 (38, 73)	
Race, white %	81.5	72.7	88.3	91.9	89.1	84.6	
BMI, mean (SD)	27.9 (5.84)	26.9 (5.21)	NR	NR	NR	NR	
ECOG PS ≥1, %	22.3	36.4	16.3	22.2	34.1	26.2	
FIGO ≥III, %	91.4	81.8	NR	NR	83.3	84.6	
FIGO, III, %	IIIA: 3.8 IIIB: 6.9 IIIC: 61.5	IIIA: 1.5 IIIB: 9.1 IIIC: 51.5	NR	NR	68.8	70.8	
FIGO IV, %	19.2	19.7	NR	NR	14.5	13.8	
Ovarian tumour site, %	80.8	84.8	83.7	86.9	88.4	81.5	
Serous histology, %	97.7	90.9	100	100	100	100	
Prior lines of platinum chemotherapy, median (range)	2 (2,5) Lines, %: 2: 59.2 3: 30.8 >3: 10.0	2 (2,5) Lines, %: 2: 62.1 3: 27.3 >3: 10.6	Lines, %: 2: 56.1 3: 30.6 4: 9.2 ≥5: 3.6	Lines, %: 2: 62.6 3: 20.2 4: 12.1 ≥5: 5.0	Lines, %: 1: 0.7 2: 50.7 ≥3: 48.6	Lines, %: 1: 0 2: 46.2 ≥3: 53.8	
Platinum-free interval >12 months, %	58.5	59.1	59.7	59.6	≥12 months: 60.9	≥12 months: 60.0	
Response to most recent platinum chemotherapy, %	CR: 35.4 PR: 64.6	CR: 36.4 PR: 63.6	CR: 46 PR: 54	CR: 47 PR: 53	CR: 51 PR: 49	CR: 51 PR: 49	
HRD, %	100	100	100	100	100	100	

[a] The ARIEL3 BRCA mutated cohorts included patients with somatic and germline BRCA mutations, while the SOLO2, NOVA and NORA BRCA mutated cohorts included only patients with germline BRCA mutations
[b] Population characteristics available only for ITT population of NORA trial (pooled gBRCA and non-gBRCA)

Table 5. Patient characteristics at baseline for studies considered for ITC – non-BRCA population

	ARIEL3	SOLO2		NOVA		NORA	
	Rucaparib (n=245)	**Placebo (n=123)**	--	**Niraparib (n=234)**	**Placebo (n=116)**	--	
Age in years, median (range)	63 (39, 84)	63 (41, 85)	Not applicable[a]	63 (33, 84)		61 (34, 82)	Not reported[b]
Race, white %	75.9	78.0		85.9		87.1	
BMI, mean (SD)	27.862 (8.001)	26.354 (5.179)		NR		NR	
ECOG PS ≥1, %	26.9	23.6		31.6		32.8	
FIGO ≥III, %	86.1	89.4		90.1		94.8	

	ARIEL3	SOLO2		NOVA		NORA	
	Rucaparib (n=245)	**Placebo (n=123)**	--	**Niraparib (n=234)**	**Placebo (n=116)**	--	
FIGO, III, %	IIIA: 3.7 IIIB: 6.1 IIIC: 64.5	IIIA: 0.8 IIIB: 4.9 IIIC: 69.9		III-IIIB: 10.3 IIIC: 63.7	III-IIIB: 17.2 IIIC: 56.9		
FIGO IV, %	11.8	13.8		16.2	20.7		
Ovarian tumour site, %	84.5	84.6		82.1		82.8	
Serous histology, %	94.3	96.7		100		100	
Prior lines of platinum chemotherapy, median (range)	2 (2,6) Lines, %: 2: 64.9 3: 28.2 >3: 6.9	2 (2,4) Lines, %: 2: 69.1 3: 23.6 >3: 7.3		Lines, %: 1: 0 2: 66.2 ≥3: 33.8		Lines, %: 1: 0 2: 66.4 ≥3: 32.8	
Platinum-free interval >12 months, %	60.4	60.2		≥12 months: 61.5		≥12 months: 62.1	
Response to most recent platinum chemotherapy, %	CR: 31.4 PR: 68.2 SD: 0.4	CR: 29.3 PR: 70.7		CR: 50 PR: 50		CR: 52 PR: 48	
HRD, %	43.3	42.3		45.3[c]		48.3[c]	

[a] All patients enrolled in SOLO2 study carried gBRCA mutation.
[b] Population characteristics available only for ITT population of NORA trial (pooled gBRCA and non-gBRCA).
[c] Calculated based on Mirza 2016, Fig 2b.

A6. Please conduct an NMA for independent review committee assessed progression-free survival (IRC-PFS) in the BRCA mutated and non-BRCA mutated cohorts.

An NMA for PFS-IRC has been conducted in the BRCA mutated and non-BRCA cohorts. Results (Table 6) have been added to the summary of NMA results provided in Table 1 for Question A2. Programming codes for the additional analysis have also been provided under Question A2.

Table 6. NMA outcomes, BRCA mutated and non-BRCA mutated cohorts (base case network, PFS-IRC)

	Rucaparib vs. olaparib[a]	Rucaparib vs. niraparib[b]
BRCA mutated cohort		
IRC-PFS, HR (95% CI)	[redacted]	[redacted]
Non-BRCA mutated cohort		
IRC-PFS, HR (95% CI)	[redacted]	[redacted]

CI, confidence interval; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; NMA, network meta-analysis; OS, overall survival; PFS2, progression-free survival on a subsequent line of treatment; TSST, time to start of second subsequent therapy
Note: ARIEL3, Study 19, SOLO2 and NOVA were included in the base case analysis
[a] Olaparib is a relevant comparator in the BRCA mutated cohort only
[b] Niraparib is a relevant comparator in both the BRCA mutated and non-BRCA mutated cohorts

Matching-adjusted indirect comparisons

A7. Please conduct matching-adjusted indirect comparisons (MAICs) for TTD in the BRCA mutated and non-BRCA mutated cohorts and provide the baseline characteristics after matching, and the results including Kaplan-Meier survival plots.

An anchored MAIC for TTD has been calculated between rucaparib in ARIEL3 and olaparib in SOLO2 using the same set of adjustment factors as in the other MAICs presented in the submission for PFS-INV, PFS2, and OS. However, after population adjustment the HR changed in favour of olaparib, it remained numerically in favour of rucaparib (HR<1). Neither the naïve nor adjusted comparisons showed significant differences in TTD between the two treatments. Results of TTD MAIC are presented in Table 7.

Please note KM curves were not reported for TTD in SOLO2. In addition, HRs for TTD were not available for niraparib in NOVA. Therefore, due to a lack of data for niraparib, a corresponding MAIC between rucaparib and niraparib could not be conducted.

Table 7. Anchored MAIC for TTD[a] between rucaparib in ARIEL3 and olaparib in SOLO2

Naïve comparison, HR (95% CI)	Naïve p-value	MAIC, HR (95% CI)	MAIC p-value
[redacted]	[redacted]	[redacted]	[redacted]

[a] Death event was treated as TTD event.
CI, confidence interval; HR, hazard ratio.

A8. Please conduct matching-adjusted indirect comparisons (MAICs) for crossover adjusted OS in the BRCA mutated and non-BRCA mutated cohorts and provide the baseline characteristics after matching, and the results including Kaplan-Meier survival plots.

See our responses above. Since the cross-over adjustment applied in the case of OS from the NOVA trial has a very high risk of bias given the small sample size and the underlying assumptions required for IPCW (reference DSU), such an analysis would be inappropriate.

The company produced acceleration factors, however, did not produce adjusted OS curves based on the adjusted RPSFT for the BRCA population, therefore such an analysis cannot be conducted.

A9. Please explain the rationale for including body mass index (BMI) as a treatment effect modifier in the MAICs presented in the company submission.

The list of effect modifiers in the MAICs was discussed with a clinical expert in the UK. Given all patients received the same treatment dose in clinical trials, the expert noted patients with

lower BMI may be exposed to a larger dose relative to their body size, which could impact treatment efficacy.

Subsequent treatments

A10. Priority question: Please provide a table with full details of the subsequent treatments received for each arm of ARIEL3 and the number of patients receiving each treatment including details of the chemotherapy regimens used.

Full details of subsequent treatments that were administered during ARIEL3 are presented in the CSR addendum. Page numbers for the relevant information are as follows:[10]

- ITT population: pages 895 to 906 (all subsequent therapies) and pages 907 to 936 (subsequent treatments broken down by regimen)
- tBRCA mutated population: pages 838 to 843 (all subsequent therapies) and pages 844 to 861 (subsequent treatments broken down by regimen)

Systematic literature review

A11. Please provide a list of studies excluded from the systematic literature review (SLR), with a brief rationale for exclusion for each.

A list of the studies excluded at the full text level from the SLR that was conducted for this submission, including the reasons for exclusion, is presented in a separate file named *Excluded Studies_Full Text*.

A12. Please provide the inclusion/exclusion criteria applied for studies to be considered relevant for inclusion in the indirect treatment comparisons for this appraisal, and a full list of studies that were considered to meet these criteria initially (before being excluded for other *reasons).*

A global SLR designed to identify and select evidence on the efficacy and safety of rucaparib and comparator maintenance therapies for patients with advanced or metastatic ovarian cancer (OC) or fallopian tube or primary peritoneal carcinomas after two or more prior lines of chemotherapy was conducted (Table 8). Nine RCTs met the criteria for this global SLR. Out of these nine studies, seven studies (reported in 89 articles) met this appraisal inclusion criteria (Table 9) in that they investigated rucaparib, olaparib, niraparib and/or routine surveillance for the maintenance treatment of locally advanced or metastatic OC: ARIEL3, NOVA, Study 19, NCT01081951, SOLO2, NORA and OReO/ENGOT Ov-38. The list of the studies considered for the inclusion for this appraisal and inclusion/exclusion status is presented in Table 10.

Table 8. Eligibility criteria – global SLR

Category	Inclusion criteria	Exclusion criteria
Population	Women with de novo locally advanced or metastatic OC or fallopian tube or primary peritoneal carcinomas who: Have platinum-sensitive* disease Had two or more prior lines of chemotherapies Have responded to prior platinum therapy	Women in the following categories: Early OC (Stage I) Without previous platinum-based chemotherapy With central nervous system metastasis that remains untreated
Interventions/ Comparators	Targeted treatments PARP inhibitors (e.g., rucaparib, olaparib, niraparib, veliparib*) Monoclonal antibodies (bevacizumab) Chemotherapy (platinum-based and non-platinum-based) No treatment/placebo/"wait-and-see" approach Best supportive care	Non-pharmacologic treatments, such as surgery or radiotherapy alone Alternative doses, schedules, or formulations of the intervention as the only comparator arms
Outcomes	Efficacy: PFS using RECIST criteria, time on treatment, time to treatment discontinuation, ORR, OS, and duration of response, time to progression to second treatment, PFS on the subsequent line of treatment. Safety/tolerability: any adverse event, adverse events by grade, discontinuation due to adverse events, including tolerability for dose. HRQL and PROs, including symptom assessment (for example, FACT-O, FOSI, and TOI)	Publications that do not report data on relevant outcomes Publications that report only interim trial results
Study designs	Systematic reviews and meta-analyses of RCTs RCTs in any country (Phases II/III) for efficacy, safety, and PROs	Non-randomised, single-arm, or observational (non-interventional) studies for efficacy, safety, PROs Open-label extension phases of RCTs Pre-clinical studies (animal, in vitro) Case reports, expert opinion articles, letters, narrative (non-systematic reviews)
Duplicate	NA	Publications that are duplicates of other publications in the search yield
Publication types	NA	Publications of the following types: Narrative publications Non-systematic reviews Case studies Case reports Editorials
Other criteria	Only English-language articles/conference abstracts will be included No time limit	Journal articles and conference abstracts without English full text

HRQL, health-related quality of life; OC; ovarian cancer; ORR, overall response rate; OS, overall survival; PARP, poly ADP ribose polymerase; PFS, progression-free survival; PRO, patient-reported outcome; RCT, randomised controlled trial; SLR, systematic literature review.

Table 9. Eligibility criteria – indirect treatment comparisons for this appraisal

Category	Inclusion criteria	Exclusion criteria
Population	Women with de novo locally advanced or metastatic OC or fallopian tube or primary peritoneal carcinomas who: Have platinum-sensitive* disease Had two or more prior lines of chemotherapies Have responded to prior platinum therapy	Women in the following categories: Early OC (Stage I) Without previous platinum-based chemotherapy With central nervous system metastasis that remains untreated
Interventions/ Comparators	Rucaparib, olaparib, niraparib and/or routine surveillance	Non-pharmacologic treatments, such as surgery or radiotherapy alone Alternative doses, schedules, or formulations of the intervention as the only comparator arms
Outcomes	Efficacy: PFS using RECIST criteria, time on treatment, time to treatment discontinuation, ORR, OS, and duration of response, time to progression to second treatment, PFS on the subsequent line of treatment. Safety/tolerability: any adverse event, adverse events by grade, discontinuation due to adverse events, including tolerability for dose. HRQL and PROs, including symptom assessment (for example, FACT-O, FOSI, and TOI)	Publications that do not report data on relevant outcomes Publications that report only interim trial results
Study designs	Systematic reviews and meta-analyses of RCTs RCTs in any country (Phases II/III) for efficacy, safety, and PROs	Non-randomised, single-arm, or observational (non-interventional) studies for efficacy, safety, PROs Open-label extension phases of RCTs Pre-clinical studies (animal, in vitro) Case reports, expert opinion articles, letters, narrative (non-systematic reviews)
Duplicate	NA	Publications that are duplicates of other publications in the search yield
Publication types	NA	Publications of the following types: Narrative publications Non-systematic reviews Case studies Case reports Editorials
Other criteria	Only English-language articles/conference abstracts will be included No time limit	Journal articles and conference abstracts without English full text

HRQL, health-related quality of life; OC; ovarian cancer; ORR, overall response rate; OS, overall survival; PARP, poly ADP ribose polymerase; PFS, progression-free survival; PRO, patient-reported outcome; RCT, randomised controlled trial.

Table 10. Primary and secondary publications of included studies included in the global SLR, and their appraisal inclusion/exclusion status

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
ARIEL3	Coleman, RL, Oza, AM, Lorusso, D et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2017.	Ledermann, J., Oza, A.M., Lorusso, D., et al. ARIEL3: A phase 3, randomised, double-blind study of rucaparib vs placebo following response to platinum-based chemotherapy for recurrent ovarian carcinoma (OC). Annals of Oncology, Volume 28, Issue suppl_5, 1 September 2017. Lorusso, D., Coleman, R. L., Oza, A. M., et al. Subgroup analysis of rucaparib in platinum-sensitive recurrent ovarian carcinoma: Effect of prior chemotherapy regimens in ARIEL3. ESMO Congress. 2018. Coleman, R. L., Oza, A. M, Lorusso, D, et al. Erratum: rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial (The Lancet (2017) 390(10106) (1949-1961) (S0140673617324406) (10.1016/S0140-6736(17)32440-6)). Lancet. 2017. 390:1948. Coleman, R. L., Oza, A. M., Lorusso, C., et al. ARIEL3: a phase 3, randomized, double-blind study of rucaparib vs placebo following response to platinum-based chemotherapy for recurrent ovarian cancer (OC). Clinical cancer research. Conference: AACR special conference "addressing critical questions in ovarian cancer research and treatment". United states. 2018. 24:#pages#. Khan, A. O'Malley, D. M. Ariel3: a phase 3, randomized, double-blind study of rucaparib vs placebo following response to platinum-based chemotherapy for recurrent ovarian carcinoma. Journal of oncology pharmacy practice. Conference: 14th annual meeting for the hematology/oncology pharmacy association. United states. 2018. 24:9-10. Ledermann, J. A. Oza, A. M., Lorusso, C., et al. Ariel3: phase 3, randomised, double-blind study of rucaparib vs placebo following response to platinum-based chemotherapy for recurrent ovarian carcinoma (OC). International journal of gynecological cancer. Conference: 20th international meeting of the european society of gynaecological oncology. Austria. 2017. 27:10-11. O'Malley, D. M., Coleman, R. L., Oza, A. M., et al. Results from the phase 3 study ARIEL3: mutations in non-BRCA homologous recombination repair genes confer sensitivity to maintenance treatment with the PARP inhibitor rucaparib in patients with recurrent platinum-sensitive highgrade ovarian carcinoma. Molecular cancer therapeutics. Conference: AACR-NCI-EORTC international conference: molecular targets and cancer therapeutics 2017. United states. 2018. 17:#pages#.	**Included**

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Oza, A. M., Coleman, R. L., Lorusso, C., et al. Effect of prior bevacizumab therapy in patients with platinum-sensitive recurrent ovarian carcinoma (roc) in the phase 3 study ariel3. International journal of gynecological cancer. Conference: 17th biennial meeting of the international gynecologic cancer society. Japan. 2018. 28:45-46. Leary, A., Ledermann, J. A., Oaknin, A., et al. Use of the Poly (ADP-Ribose) Polymerase Inhibitor Rucaparib in Women with Recurrent Ovarian Carcinoma with Endometrioid and Other Nonserous Histopathologic Subtypes. International Journal of Gynecological Cancer. 2018. 28:200-201. Clamp AR, Lorusso D, Oza AM, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Scambia G, Leary A, Holloway RW, Amenedo Gancedo M, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Banerjee S, García-Donas J, Swisher EM, Cameron T, Goble S, Coleman RL, Ledermann JA. Rucaparib maintenance treatment for recurrent ovarian carcinoma: the effects of progression-free interval and prior therapies on efficacy and safety in the randomized phase III trial ARIEL3. Int J Gynecol Cancer. 2021 Jul;31(7):949-958. doi: 10.1136/ijgc-2020-002240. Epub 2021 Jun 8. PMID: 34103386; PMCID: PMC9445915. Colombo N, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Weberpals JI, Clamp AR, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Banerjee S, García-Donas J, Swisher EM, Meunier J, Cameron T, Maloney L, Goble S, Bedel J, Ledermann JA, Coleman RL. The effect of age on efficacy, safety and patient-centered outcomes with rucaparib: A post hoc exploratory analysis of ARIEL3, a phase 3, randomized, maintenance study in patients with recurrent ovarian carcinoma. Gynecol Oncol. 2020 Oct;159(1):101-111. doi: 10.1016/j.ygyno.2020.05.045. Epub 2020 Aug 26. PMID: 32861537; PMCID: PMC8450972. Ledermann JA, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp AR, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Banerjee S, García-Donas J, Swisher EM, Cameron T, Maloney L, Goble S, Coleman RL. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 May;21(5):710-722. doi: 10.1016/S1470-2045(20)30061-9. PMID: 32359490; PMCID: PMC8210534.	

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Oaknin A, Oza AM, Lorusso D, Aghajanian C, Dean A, Colombo N, Weberpals JI, Clamp AR, Scambia G, Leary A, Holloway RW, Amenedo Gancedo M, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Banerjee S, García-Donas J, Swisher EM, Cameron T, Maloney L, Goble S, Ledermann JA, Coleman RL. Maintenance treatment with rucaparib for recurrent ovarian carcinoma in ARIEL3, a randomized phase 3 trial: The effects of best response to last platinum-based regimen and disease at baseline on efficacy and safety. Cancer Med. 2021 Oct;10(20):7162-7173. doi: 10.1002/cam4.4260. Epub 2021 Sep 21. PMID: 34549539; PMCID: PMC8525125. O'Malley DM, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp AR, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, Swisher EM, Maloney L, Goble S, Lin KK, Kwan T, Ledermann JA, Coleman RL. Clinical and molecular characteristics of ARIEL3 patients who derived exceptional benefit from rucaparib maintenance treatment for high-grade ovarian carcinoma. Gynecol Oncol. 2022 Dec;167(3):404-413. doi: 10.1016/j.ygyno.2022.08.021. Epub 2022 Oct 20. PMID: 36273926; PMCID: PMC10339359. Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp AR, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Banerjee S, García-Donas J, Swisher EM, Cella D, Meunier J, Goble S, Cameron T, Maloney L, Mörk AC, Bedel J, Ledermann JA, Coleman RL. Patient-Centered Outcomes in ARIEL3, a Phase III, Randomized, Placebo-Controlled Trial of Rucaparib Maintenance Treatment in Patients With Recurrent Ovarian Carcinoma. J Clin Oncol. 2020 Oct 20;38(30):3494-3505. doi: 10.1200/JCO.19.03107. Epub 2020 Aug 24. PMID: 32840418; PMCID: PMC7571791. Peipert JD, Goble S, Isaacson J, Tang X, Wallace K, Coleman RL, Ledermann JA, Cella D. Patient-reported outcomes of maintenance rucaparib in patients with recurrent ovarian carcinoma in ARIEL3, a phase III, randomized, placebo-controlled trial. Gynecol Oncol. 2023 Aug;175:1-7. doi: 10.1016/j.ygyno.2023.05.060. Epub 2023 May 30. PMID: 37262961. https://clinicaltrials.gov/study/NCT01968213	

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Robert L. Coleman, Amit M. Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew R. Clamp, Giovanni Scambia, Alexandra Leary, Robert W. Holloway, Margarita Amenedo Gancedo, Peter C.C. Fong, Jeffrey C. Goh, David M. O'Malley, Sandra M. Goble, Lara Maloney, and Jonathan A. Ledermann. Efficacy and safety of rucaparib maintenance treatment in patients from ARIEL3 with platinum-sensitive, recurrent ovarian carcinoma not associated with homologous recombination deficiency. Journal of Clinical Oncology 2022 40:16_suppl, 5544-5544. Coleman RL, Oza AM, Lorusso D, et al 2022-RA-249-ESGO Overall survival results from ariel3: a phase 3 randomised, double-blind study of rucaparib vs placebo following response to platinum-based chemotherapy for recurrent ovarian carcinomaInternational Journal of Gynecologic Cancer 2022;32:A226. Ledermann J, Oza A, Lorusso D, et al1 Analysis of patients who derived exceptional benefit from rucaparib maintenance treatment for high-grade ovarian cancer in the phase 3 ARIEL3 studyInternational Journal of Gynecologic Cancer 2021;31:A192-A193. Coleman R, Oza A, Lorusso D, et alO016/#233 Clinical and molecular characteristics of ariel3 patients who derived exceptional benefit from rucaparib maintenance treatment for high-grade ovarian cancer (HGOC)International Journal of Gynecologic Cancer 2021;31:A10.	
SOLO2	Pujade-Lauraine, E, Ledermann, JA, Selle, F et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology. 2017.	Friedlander, M., Gebski, V., Gibbs, E., et al. Health-related quality of life (HRQOL) and patient-centered outcomes with maintenance olaparib compared with placebo following chemotherapy in patients with germline (g) BRCA-mutated (m) platinum-sensitive relapsed serous ovarian cancer (PSR SOC): SOLO2 phase III trial. Journal of Clinical Oncology. 2017. 35:#pages# Friedlander, M., Pujade-Lauraine, E., Ledermann, J. A., et al. Treatment with maintenance olaparib significantly improves progression-free survival in patients with platinum-sensitive relapsed ovarian cancer: Results of SOLO2 study. Asia-Pacific Journal of Clinical Oncology. 2017. 13:51 Ledermann, J. A., Lortholary, A., Penson, R. T., et al. Adverse events (AEs) with maintenance olaparib tablets in patients (pts) with BRCA-mutated (BRCAm) platinum-sensitive relapsed serous ovarian cancer (PSR SOC): Phase III SOLO2 trial. Journal of Clinical Oncology. 2017. 35:#pages#	**Included**

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Pujade-Lauraine, E., Ledermann, J. A., Penson, R. T., et al. Treatment with olaparib monotherapy in the maintenance setting significantly improves progression-free survival in patients with platinum-sensitive relapsed ovarian cancer: Results from the phase III SOLO2 study. Gynecologic Oncology. 2017. 145:219-220 Penson, R., Kaminsky-Forrett M.C., Ledermann J. , et al. Efficacy of olaparib maintenance therapy in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) by lines of prior chemotherapy: Phase III SOLO2 trial (ENGOT Ov-21). Annals of Oncology, Volume 28, Issue suppl_5, 1 September 2017. Friedlander, M., Gebski, V., Gibbs, E., et al. Health-related quality of life (HRQOL) and patient-centred outcomes with olaparib maintenance post-chemotherapy in patients with germline BRCA-mutated platinum-sensitive relapsed serous ovarian cancer (PSR SOC). International journal of gynecological cancer. Conference: 20th international meeting of the european society of gynaecological oncology. Austria. 2017. 27:1941. Friedlander, M., Gebski, V., Gibbs, E., et al. Health-related quality of life and patient-centred outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT Ov-21): a placebo-controlled, phase 3 randomised trial. Lancet oncology. 2018. 19:1126-1134. Hasenburg, A., Harter, P., Park-Simon, W., et al. Health-related quality of life (HRQOL) and patient-centered outcomes with maintenance olaparib compared with placebo following chemotherapy in patients with germline BRCA mutated platinum-sensitive relapsed serous ovarian cancer: sOLO2 Phase III. Oncology research and treatment. Conference: 33. Deutscher krebskongress, DKK. Germany. 2018. 41:88-89. Liu, J., Yin, R., Wu, L., et al. Olaparib maintenance monotherapy improves progression-free survival (PFS) in patients with platinum-sensitive relapsed ovarian cancer (PSROC): solo2 study-China cohort. International journal of gynecological cancer. Conference: 17th biennial meeting of the international gynecologic cancer society. Japan. 2018. 28:49-50. Oza, A. M., Combe, P., Ledermann, J. A., et al. Evaluation of tumour responses and olaparib efficacy in platinum sensitive relapsed ovarian cancer (PSROC) patients (pts) with or without measurable disease in the SOLO2 trial (ENGOT Ov-21). Annals of oncology. Conference: 42nd ESMO congress, ESMO 2017. Spain. 2017. 28:v344.	

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		M. Friedlander, V. Gebski, E. Gibbs, R. Bloomfield, F. Hilpert, L. B. Wenzel, F. Joly, D. Eek, M. Rodrigues, A. Clamp,et al.. Health-related quality of life (HRQOL) and patient-centred outcomes with olaparib maintenance post-chemotherapy in patients with germline BRCA-mutated platinum-sensitive relapsed serous ovarian cancer (PSR SOC). International journal of gynecological cancer. Conference: 20th international meeting of the european society of gynaecological oncology. Austria. 2017. 27:1941 M. Friedlander, V. Gebski, E. Gibbs, L. Davies, R. Bloomfield, F. Hilpert, L. B. Wenzel, D. Eek, M. Rodrigues, A. Clamp,et al.. Health-related quality of life and patient-centred outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT Ov-21): a placebo-controlled, phase 3 randomised trial. Lancet oncology. 2018. 19:1126-1134 A. Hasenburg, P. Harter, T. W. Park-Simon, M. Gropp-Meier, F. Heitz, P. Soergel, B. Ataseven, M. Friedlander, F. Hilpert, E. Pujade-Lauraine. Health-related quality of life (HRQOL) and patient-centered outcomes with maintenance olaparib compared with placebo following chemotherapy in patients with germline BRCAmutated platinum-sensitive relapsed serous ovarian cancer: sOLO2 Phase III. Oncology research and treatment. Conference: 33. Deutscher krebskongress, DKK. Germany. 2018. 41:88-89 J. Liu, R. Yin, L. Wu, J. Zhu, G. Lou, X. Wu, Q. Zhou, Y. Gao, B. Kong, X. Lu,et al.. Olaparib maintenance monotherapy improves progression-free survival (PFS) in patients with platinum-sensitive relapsed ovarian cancer (PSROC): solo2 study-China cohort. International journal of gynecological cancer. Conference: 17th biennial meeting of the international gynecologic cancer society. Japan. 2018. 28:49-50 A. M. Oza, P. Combe, J. Ledermann, S. Marschner, A. Amit, T. Huzarski, N. Lainez Milagro, A. Savarese, C. Scott, M. O. Nicoletto,et al.. Evaluation of tumour responses and olaparib efficacy in platinumsensitive relapsed ovarian cancer (PSROC) patients (pts) with or without measurable disease in the SOLO2 trial (ENGOT Ov-21). Annals of oncology. Conference: 42nd ESMO congress, ESMO 2017. Spain. 2017. 28:v344	

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Frenel JS, Kim JW, Aryal N, Asher R, Berton D, Vidal L, Pautier P, Ledermann JA, Penson RT, Oza AM, Korach J, Huzarski T, Pignata S, Colombo N, Park-Simon TW, Tamura K, Sonke GS, Freimund AE, Lee CK, Pujade-Lauraine E. Efficacy of subsequent chemotherapy for patients with BRCA1/2-mutated recurrent epithelial ovarian cancer progressing on olaparib versus placebo maintenance: post-hoc analyses of the SOLO2/ENGOT Ov-21 trial. Ann Oncol. 2022 Oct;33(10):1021-1028. doi: 10.1016/j.annonc.2022.06.011. Epub 2022 Jun 27. PMID: 35772665. Tjokrowidjaja A, Lee CK, Friedlander M, Gebski V, Gladieff L, Ledermann J, Penson R, Oza A, Korach J, Huzarski T, Manso L, Pisano C, Asher R, Lord SJ, Kim SI, Lee JY, Colombo N, Park-Simon TW, Fujiwara K, Sonke G, Vergote I, Kim JW, Pujade-Lauraine E. Concordance between CA-125 and RECIST progression in patients with germline BRCA-mutated platinum-sensitive relapsed ovarian cancer treated in the SOLO2 trial with olaparib as maintenance therapy after response to chemotherapy. Eur J Cancer. 2020 Nov;139:59-67. doi: 10.1016/j.ejca.2020.08.021. Epub 2020 Sep 23. PMID: 32977221. Trillsch F, Mahner S, Ataseven B, Asher R, Aryal N, Dubot C, Clamp A, Penson RT, Oza A, Amit A, Huzarski T, Casado A, Scambia G, Friedlander M, Colombo N, Fujiwara K, Sonke GS, Denys H, Lowe ES, Lee CK, Pujade-Lauraine E. Efficacy and safety of olaparib according to age in BRCA1/2-mutated patients with recurrent platinum-sensitive ovarian cancer: Analysis of the phase III SOLO2/ENGOT-Ov21 study. Gynecol Oncol. 2022 Apr;165(1):40-48. doi: 10.1016/j.ygyno.2022.01.024. Epub 2022 Jan 31. PMID: 35115180. Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM, Korach J, Huzarski T, Pignata S, Friedlander M, Baldoni A, Park-Simon TW, Tamura K, Sonke GS, Lisyanskaya A, Kim JH, Filho EA, Milenkova T, Lowe ES, Rowe P, Vergote I, Pujade-Lauraine E; SOLO2/ENGOT-Ov21 investigators. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2021 May;22(5):620-631. doi: 10.1016/S1470-2045(21)00073-5. Epub 2021 Mar 18. PMID: 33743851.	

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Ledermann JA, Ray-Coquard I, Penson R, et al#66 Survival of PARP inhibitor (PARPi) naïve ovarian cancer patients with a BRCA-mutation receiving maintenance olaparib after chemotherapy for first recurrence. An exploratory analysis of the solo2/engot-ov21 trialInternational Journal of Gynecologic Cancer 2023;33:A243. https://classic.clinicaltrials.gov/ct2/show/NCT01874353	
Study 19	Ledermann, J, Harter, P, Gourley, C et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. New England Journal of Medicine. 2012. 366:1382-1392	Gourley, C., Friedlander, M., Matulonis, U. A., et al. Clinically significant long-term maintenance treatment with olaparib in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). Journal of Clinical Oncology. 2017. 35:#pages# Ledermann, Ja., Harter, P., Gourley, C et al. Quality of life during olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer. British journal of cancer. 2016. 115:1313-1320 Ledermann, J. A.., Harter, P., Gourley, C et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. The lancet. Oncology. 2016. 17:1579-1589 Ledermann, J A.., Harter, P., Gourley, C., et al. Phase II randomized placebo-controlled study of olaparib (AZD2281) in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). Journal of clinical oncology. 2011. 29:#pages# Matulonis, U., Friedlander, M., Du, Bois A., et al. Frequency, severity and timing of common adverse events (AEs) with maintenance olaparib in patients (pts) with platinum sensitive relapsed serous ovarian cancer (PSR SOC). Journal of clinical oncology. 2015. 33:#pages# Matulonis, U. A.., Harter, P., Gourley, C., et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer and a BRCA mutation: Overall survival adjusted for post-progression PARP inhibitor therapy. Gynecologic oncology. 2015. 137:8 Matulonis, U. A.., Harter, P., Gourley, C., et al. Olaparib maintenance therapy in patients with platinum-sensitive, relapsed serous ovarian cancer and a BRCA mutation: overall survival adjusted for post progression poly(adenosine diphosphate ribose) polymerase inhibitor therapy. Cancer. 2016. 122:1844-1852 Ledermann, J. A., Harter, P., Gourley, C. et al. (2016). Overall survival (OS) in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) receiving olaparib maintenance monotherapy: An interim analysis.	**Included**

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Friedlander, M., Gourlety, C., Matulonis, U., et al. Clinically significant long-term maintenance treatment with olaparib in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). International journal of gynecological cancer. Conference: 20th international meeting of the european society of gynaecological oncology. Austria. 2017. 27:13. Friedlander, M., Matulonis, U,. Gourley, C., et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. British journal of cancer. 2018. (no pagination):#pages#. Martinez Bueno, A., Molina, M. A., Fielding, A., et al. Disruptive mutations in TP53 associate with survival benefit in a PARPi trial in ovarian cancer. Annals of oncology. Conference: 42nd ESMO congress, ESMO 2017. Spain. 2017. 28:v626. Dougherty, B. A., Lai, Z,. Hodgson, D. R., et al. Biological and clinical evidence for somatic mutations in BRCA1 and BRCA2 as predictive markers for olaparib response in high-grade serous ovarian cancers in the maintenance setting. Oncotarget. 2017. 8:43653-43661. https://clinicaltrials.gov/study/NCT00753545	
NCT01081951	Oza, AM, Cibula, D, Benzaquen, A et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. The Lancet. Oncology. 2015. 16:87-97	https://classic.clinicaltrials.gov/ct2/show/NCT01081951	**Included**
ICON6	Ledermann, J, Embleton, A, Raja, F et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016. 387:1066-1074	Ledermann, J. A., Embleton, A. C., Perren, T. et al. Overall survival results of ICON6: A trial of chemotherapy and cediranib in relapsed ovarian cancer. Journal of Clinical Oncology. 2017. 35:#pages# Ledermann, J. A.,Embleton, A. C.,Raja, F. Erratum: On behalf of the ICON6 collaborators. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): A randomised, double-blind, placebo-controlled phase 3 trial. (Lancet (2016) 387 (1066-74)). The Lancet. 2016. 387:1722 Stark, D. P., Cook, A., Brown, J. M., et al. Quality of life with cediranib in relapsed ovarian cancer: The ICON6 phase 3 randomized clinical trial. Cancer. 2017. 123:2752-2761	**Excluded: Not relevant intervention/comparator**

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Ledermann JA, Embleton-Thirsk AC, Perren TJ, Jayson GC, Rustin GJS, Kaye SB, Hirte H, Oza A, Vaughan M, Friedlander M, González-Martín A, Deane E, Popoola B, Farrelly L, Swart AM, Kaplan RS, Parmar MKB; ICON6 collaborators. Cediranib in addition to chemotherapy for women with relapsed platinum-sensitive ovarian cancer (ICON6): overall survival results of a phase III randomised trial. ESMO Open. 2021 Apr;6(2):100043. doi: 10.1016/j.esmoop.2020.100043. Epub 2021 Feb 18. PMID: 33610123; PMCID: PMC7903311.	
NOVA/ ENGOTOV16	Mirza, MR, Monk, BI, Herrstedt, J et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. New England journal of medicine. 2016. 375:2154-2164	Campo, J. M., Mirza, M. R. ,Berek, J. S., et al. The successful phase 3 niraparib ENGOT-OV16/NOVA trial included a substantial number of patients with platinum resistant ovarian cancer (OC). Journal of clinical oncology. Conference: 2017 annual meeting of the American Society Of Clinical Oncology, ASCO. United states. 2017. 35:#pages# Matulonis, U. A., Herrstedt, J., Tinker, A., et al. Long-term benefit of niraparib treatment of recurrent ovarian cancer (OC). Journal of clinical oncology. Conference: 2017 annual meeting of the American Society Of Clinical Oncology, ASCO. United states. 2017. 35:#pages# Mirza, M. R., Monk, B. J., Oza, A., et al. PR A randomized, double-blind phase 3 trial of maintenance therapy with niraparib vs placebo in patients with platinum-sensitive recurrent ovarian cancer (ENGOT-OV16/NOVA trial). Annals of oncology. Conference: 41st european society for medical oncology congress, ESMO 2016. Denmark. Conference start: 20161007. Conference end: 20161011. 2016. 27:#pages# Mirza, M. R., Monk, B. J., Gil-Martin, M., et al. Efficacy of niraparib on progression-free survival (PFS) in patients (pts) with recurrent ovarian cancer (OC) with partial response (PR) to the last platinum based chemotherapy. Journal of Clinical Oncology. 2017. 35:#pages# Ledermann J., Mirza M., Monk B., et al. Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer (engot-ov16/nova trial). British Gynaecological Cancer Society Annual Scientific Meeting. 2017. Matulonis U., Herrstedt J., Oza A., et al. ENGOT-OV16/NOVA: A maintenance study with niraparib versus placebo in patients with platinum-sensitive ovarian cancer. 16th Biennial Meeting of the International Gynecologic Cancer Society. 2016. Oza, U.A. Matulonis, S. Malander, J., et al. Quality of life in patients with recurrent ovarian cancer (OC) treated with niraparib: Results from the ENGOT-OV16/NOVA Trial. Annals of Oncology, Volume 28, Issue suppl_5, 1 September 2017.	**Included**

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Mirza, M. R., Walder, L., Monk, B. J., et al. A time without symptoms or toxicity analysis of niraparib compared with routine surveillance in the maintenance treatment of patients with recurrent ovarian cancer. ISPOR 21st Annual European Congress. 2018. Lord, R., Mirza, M. R., Woelber, L., et al. Safety and dose modification for patients with low body weight receiving niraparib in the ENGOT-OV16/NOVA phase III trial. SGO Annual Meeting. 2018. Fabbro, M., Moore, K. N., Dorum, A., et al. Safety and Efficacy of Niraparib in Elderly Patients (Pts) with Recurrent Ovarian Cancer (OC). Annals of oncology. Conference: 42nd ESMO congress, ESMO 2017. Spain. 2017. 28:v332. Ison, G., Howie, L. J., Amiri-Kordestani, L. et al. FDA approval summary: niraparib for the maintenance treatment of patients with recurrent ovarian cancer in response to platinum-based chemotherapy. Clinical cancer research. 2018. 24:4066-4071. Mirza, M. R., Benigno, B., Dorum, A., et al. Long-term safety of niraparib in patients with recurrent ovarian cancer (ROC): results from the ENGOT-OV16/NOVA trial. International journal of gynecological cancer. Conference: 17th biennial meeting of the international gynecologic cancer society. Japan. 2018. 28:21-22. Oza, A. M., Matulonis, U. A., Malander, S., et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. Lancet oncology. 2018. 19:1117-1125. Del Campo JM, Matulonis UA, Malander S, Provencher D, Mahner S, Follana P, Waters J, Berek JS, Woie K, Oza AM, Canzler U, Gil-Martin M, Lesoin A, Monk BJ, Lund B, Gilbert L, Wenham RM, Benigno B, Arora S, Hazard SJ, Mirza MR. Niraparib Maintenance Therapy in Patients With Recurrent Ovarian Cancer After a Partial Response to the Last Platinum-Based Chemotherapy in the ENGOT-OV16/NOVA Trial. J Clin Oncol. 2019 Nov 10;37(32):2968-2973. doi: 10.1200/JCO.18.02238. Epub 2019 Jun 7. PMID: 31173551; PMCID: PMC6839909. Fabbro M, Moore KN, Dørum A, Tinker AV, Mahner S, Bover I, Banerjee S, Tognon G, Goffin F, Shapira-Frommer R, Wenham RM, Hellman K, Provencher D, Harter P, Vázquez IP, Follana P, Pineda MJ, Mirza MR, Hazard SJ, Matulonis UA. Efficacy and safety of niraparib as maintenance treatment in older patients (≥ 70 years) with recurrent ovarian cancer: Results from the ENGOT-OV16/NOVA trial. Gynecol Oncol. 2019 Mar;152(3):560-567. doi: 10.1016/j.ygyno.2018.12.009. Epub 2019 Jan 9. PMID: 30638768.	

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Matulonis UA, Walder L, Nøttrup TJ, Bessette P, Mahner S, Gil-Martin M, Kalbacher E, Ledermann JA, Wenham RM, Woie K, Lau S, Marmé F, Casado Herraez A, Hardy-Bessard AC, Banerjee S, Lindahl G, Benigno B, Buscema J, Travers K, Guy H, Mirza MR. Niraparib Maintenance Treatment Improves Time Without Symptoms or Toxicity (TWiST) Versus Routine Surveillance in Recurrent Ovarian Cancer: A TWiST Analysis of the ENGOT-OV16/NOVA Trial. J Clin Oncol. 2019 Dec 1;37(34):3183-3191. doi: 10.1200/JCO.19.00917. Epub 2019 Sep 16. PMID: 31518175; PMCID: PMC6881097. Mirza MR, Benigno B, Dørum A, Mahner S, Bessette P, Barceló IB, Berton-Rigaud D, Ledermann JA, Rimel BJ, Herrstedt J, Lau S, du Bois A, Herráez AC, Kalbacher E, Buscema J, Lorusso D, Vergote I, Levy T, Wang P, de Jong FA, Gupta D, Matulonis UA. Long-term safety in patients with recurrent ovarian cancer treated with niraparib versus placebo: Results from the phase III ENGOT-OV16/NOVA trial. Gynecol Oncol. 2020 Nov;159(2):442-448. doi: 10.1016/j.ygyno.2020.09.006. Epub 2020 Sep 25. PMID: 32981695. Mirza MR, Lindahl G, Mahner S, Redondo A, Fabbro M, Rimel BJ, Herrstedt J, Oza AM, Canzler U, Berek JS, González-Martín A, Follana P, Lord R, Azodi M, Estenson K, Wang Z, Li Y, Gupta D, Matulonis U, Feng B. Ad hoc Analysis of the Phase III ENGOT-OV16/NOVA Study: Niraparib Efficacy in Germline BRCA Wild-type Recurrent Ovarian Cancer with Homologous Recombination Repair Defects. Cancer Res Commun. 2022 Nov 15;2(11):1436-1444. doi: 10.1158/2767-9764.CRC-22-0240. PMID: 36970052; PMCID: PMC10035404. https://classic.clinicaltrials.gov/ct2/show/NCT01847274 Matulonis, U., Herrstedt, J., Oza, A., Mahner, S., Redondo, A., Berton, D., ... & Mirza, M. (2021). Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase III trial of niraparib in recurrent ovarian cancer. Gynecologic oncology, 162, S24-S25. Mirza MR, Herrstedt J, Oza A, et al#161 Final overall survival and long-term safety in the ENGOT-OV16/NOVA phase 3 trial of niraparib in patients with recurrent ovarian cancerInternational Journal of Gynecologic Cancer 2023;33:A15-A16. Supplementary data in: Matulonis, 2023, Final Overall Survival and Long-Term Safety in the ENGOT-OV16/NOVA Phase 3 Trial of Niraparib in Patients with Recurrent Ovarian Cancer (A21)	

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Gonzalez Martin, A., Matulonis, U. A., Korach, J., Mirza, M. R., Moore, K. N., Gupta, D., ... & Monk, B. J. (2021). Niraparib efficacy and safety in patients with BRCA mutated (BRCA m) ovarian cancer: Results from three phase 3 niraparib trials. J Clin Oncol 39, (suppl 15; abstr 5518).	
NORA	Wu XH, Zhu JQ, Yin RT, Yang JX, Liu JH, Wang J, Wu LY, Liu ZL, Gao YN, Wang DB, Lou G, Yang HY, Zhou Q, Kong BH, Huang Y, Chen LP, Li GL, An RF, Wang K, Zhang Y, Yan XJ, Lu X, Lu WG, Hao M, Wang L, Cui H, Chen QH, Abulizi G, Huang XH, Tian XF, Wen H, Zhang C, Hou JM, Mirza MR. Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial☆. Ann Oncol. 2021 Apr;32(4):512-521. doi: 10.1016/j.annonc.2020.12.018. Epub 2021 Jan 14. PMID: 33453391.	Jing Wang, Xiaohua Wu, Jianqing Zhu, Rutie Yin, Jiaxin Yang, Qidan Huang, Lingying Wu, Ziling Liu, Yunong Gao, Danbo Wang, Ge Lou, Hongying Yang, Qi Zhou, Beihua Kong, Yi Huang, Lipai Chen, Guiling Li, Ruifang An, Tao Tan, and Juan Dong. Safety assessment of niraparib individualized starting dose in patients with platinum-sensitive recurrent ovarian cancer: A randomized, double-blind, placebo-controlled, phase III NORA trial. Journal of Clinical Oncology 2021 39:15_suppl, 5535-5535. Lingying Wu, Xiaohua Wu, Jianqing Zhu, Rutie Yin, Jiaxin Yang, Jihong Liu, Jing Wang, Ziling Liu, Yunong Gao, Danbo Wang, Ge Lou, Hongying Yang, Qi Zhou, Beihua Kong, Yi Huang, Lipai Chen, Guiling Li, Ruifang An, Tao Tan, and Juan Dong. Efficacy of niraparib maintenance therapy in Chinese women with platinum-sensitive recurrent ovarian cancer with and without secondary cytoreductive surgery: Results from the NORA trial. Journal of Clinical Oncology 2021 39:15_suppl, 5534-5534. Wu, X., Zhu, J., Yin, R., Yang, J., Liu, J., Wang, J., ... & Mirza, M. R. (2023). 35O Overall survival of niraparib with individualized starting dose as maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer adjusted for subsequent PARPi use in placebo group: Results from an ad hoc interim analysis for the phase III NORA study. ESMO Open, 8(1). Liu Z, Wu X, Zhu J, et al29 Dose modification for Chinese patients on niraparib maintenance treatment for platinum-sensitive recurrent ovarian cancer: A post hoc analysisInternational Journal of Gynecologic Cancer 2021;31:A193-A194.	**Included**
OReO/ENGOT Ov-38	Pujade-Lauraine, E., Selle, F., Scambia, G., Asselain, B., Marmé, F., Lindemann, K., ... & Redondo, A. (2021). LBA33 Maintenance olaparib rechallenge in patients (pts) with ovarian carcinoma (OC) previously treated with a PARP inhibitor (PARPi): Phase IIIb OReO/ENGOT Ov-38 trial. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741	https://classic.clinicaltrials.gov/ct2/show/NCT03106987 Frederic Selle, Bernard Asselain, François Montestruc, Fernando Bazan, Beatriz Pardo, Vanda Salutari, Frederik Marmé, Anja Ør Knudsen, Alessandra Bologna, Radoslaw Madry, Rosalind Glasspool, Stéphanie Henry, Jacob Korach, Stephanie Lheureux, Bob Shaw, Ana Santaballa, Raffaella Cioffi, Ulrich Canzler, Alain Lortholary, and Eric Pujade-Lauraine. OReO/ENGOT Ov-38 trial: Impact of maintenance olaparib rechallenge according to ovarian cancer patient prognosis—An exploratory joint analysis of the BRCA and non-BRCA cohorts. Journal of Clinical Oncology 2022 40:16_suppl, 5558-5558.	**Included**

Trial	Primary publication	Secondary publication(s)	Appraisal inclusion/exclusion status
		Redondo A, Follana P, Scambia G, et alO025/#522 Maintenance olaparib rechallenge in patients with ovarian cancer previously treated with a parp inhibitor: patient-reported outcomes from the phase IIIB OReO/engot-ov38 trialInternational Journal of Gynecologic Cancer 2022;32:A15. Salutari V, Lotz J, Manso L, et al2022-RA-1290-ESGO Maintenance olaparib rechallenge in patients with ovarian cancer previously treated with a PARP inhibitor: detailed safety results from the Phase IIIb OReO/ENGOT-ov38 trialInternational Journal of Gynecologic Cancer 2022;32:A318.	
FZOCUS-2	Li N, Zhang Y, Wang J, Zhu J, Wang L, Wu X, Yao D, Wu Q, Liu J, Tang J, Yin R, Lou G, An R, Zhang G, Xia X, Li Q, Zhu Y, Zheng H, Yang X, Hu Y, Zhang X, Hao M, Huang Y, Lin Z, Wang D, Guo X, Yao S, Wan X, Zhou H, Yao L, Yang X, Cui H, Meng Y, Zhang S, Qu J, Zhang B, Zou J, Wu L. Fuzuloparib Maintenance Therapy in Patients With Platinum-Sensitive, Recurrent Ovarian Carcinoma (FZOCUS-2): A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Trial. J Clin Oncol. 2022 Aug 1;40(22):2436-2446. doi: 10.1200/JCO.21.01511. Epub 2022 Apr 11. PMID: 35404684.	Li, N., Zhang, Y., Wang, J., Zhu, J., Wang, L., Wu, X., ... & Wu, L. (2021). Fuzuloparib maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer: A multicenter, randomized, double-blind, placebo-controlled, phase III trial. Gynecologic Oncology, 162, S57-S58.	**Excluded: Not relevant intervention/comparator**

BRCA mutations

A13. Please provide subgroup results for patients with somatic and germline BRCA mutations for INV-PFS, OS, PFS2 and TTD.

In the ITT population, median INV-PFS was [redacted] in patients with germline BRCA treated with rucaparib (n=[redacted]) vs. [redacted]) in patients with germline BRCA treated with placebo (n=[redacted]). Median INV-PFS was [redacted]) in patients with somatic BRCA treated with rucaparib (n=[redacted]) vs. [redacted]) in patients with somatic BRCA treated with placebo (n=[redacted]). Results from the Cox proportional hazard model found rucaparib significantly improved INV-PFS compared to placebo in both the germline BRCA [redacted]) and somatic BRCA ([redacted]) populations.[9]

Subgroup analyses for somatic and germline BRCA mutations were not performed for OS, PFS2 and TTD outcomes. Note that findings are in line with results for niraparib results presented in Table 35 and Figure 15 of the September 2017 niraparib EPAR, available here.[14]

A14. ARIEL3 included patients with both somatic and germline BRCA mutations. Please explain what impact the inclusion of somatic BRCA mutations from ARIEL3 may have on the results of the indirect comparisons for the BRCA mutant population when NOVA and SOLO2 only included germline BRCA mutations.

There is no evidence of a difference in rucaparib treatment effect based on INV-PFS outcomes in patients with germline BRCA ([redacted]) and somatic BRCA [redacted]).[9]

Since the NOVA trial included patients with somatic BRCA mutation in the non-germline BRCA population, the only impact expected is bias favoring niraparib in the non-BRCA population.

A15. If a difference in treatment effect is identified for any outcome in response to the subgroup analyses requested in question A13, then please provide NMAs in the BRCA mutated cohort using ARIEL3, SOLO2 and NOVA for all outcomes excluding the somatic BRCA mutation patients from NOVA (i.e. please conduct an NMA consistently using the germline BRCA mutated cohort for all studies).

There is no evidence of a difference in rucaparib treatment effect based on INV-PFS outcomes in patients with germline BRCA ([redacted]) and somatic BRCA [redacted]).[9]

Please note that the NOVA trial included patients with somatic BRCA mutation in the non-germline BRCA population.

From NOVA results of PFS (likely IRC) were reported separately for the sBRCA population (see above) and for the g+sBRCA population. These suggest similar results between sBRCA and gBRCA. As a result, non-gBRCA results in NOVA are likely more favorable than they would be without the sBRCA patients. Results for a non-BRCA population that excludes sBRCA patients (i.e. comparable to the non-BRCA population in ARIEL3) could not be identified, therefore such an analysis is not feasible.

Therefore, somatic BRCA mutation patients cannot be excluded from NOVA in the NMA.

Section B: Clarification on cost-effectiveness data

Treatment acquisition costs

B1. Priority question: Based on the SACT data provided in the company submission, time on treatment for rucaparib and niraparib for both the BRCA and non-BRCA populations are very similar. Additionally, the EAG's clinical experts consider that treatment to treatment discontinuation (TTD) is likely to be similar for all PARP inhibitors and furthermore, is likely to closely track PFS.

a) ***The network-meta analysis (NMA) requested in question A3 should produce a hazard ratio (HR) for niraparib vs rucaparib. Please explore a scenario where the NMA TTD HR is applied to a preferred parametric curve for rucaparib based on ARIEL-3 that supports the proportional hazards assumption to produce a TTD curve for niraparib.***

b) ***Please explore a scenario where TTD for niraparib is equal to TTD for rucaparib for both the BRCA and non-BRCA populations.***

c) ***For the BRCA population, please explore an alternative scenario where the Weibull curve is used to model TTD for rucaparib and assume TTD for niraparib is equal to rucaparib.***

We have included the requested scenario for Question B1b and Question B1c in Section D: Appendix, however as discussed in priority Question A3 an NMA against NOVA is not feasible so a scenario for Question B1a is not possible. Assuming equal TTD between niraparib and rucaparib reduces the acquisition costs for niraparib from £168,744.20 to £136,885.68 and therefore reduces the incremental costs from -£ 117,563.52 to -£ 84,882.77. However, the conclusion that rucaparib is cost saving compared to niraparib is maintained. For the scenario where TTD is assumed to be equal between rucaparib and niraparib and a Weibull distribution assumed based on ARIEL3, there is a small increase in the acquisition costs rucaparib compared to the base case and a similar reduction in acquisition costs for niraparib as the previous scenario.

B2. Please provide data on the relative dose intensity (RDI) for rucaparib from ARIEL-3 and run a scenario that includes RDI for both rucaparib and niraparib.

No data are available for RDI from ARIEL3 therefore this scenario is not possible.

Adverse events

B3. Priority question: In the model, rates of adverse events from ARIEL-3 are taken from the ARIEL-3 CSR (2017), Table 14.3.1.1.9.1, p. 1562. However, in Table 72 of the company submission, reference is made to the ARIEL-3 CSR addendum (2023), which represents a later data cut of April 2022 for incidence of Grade 3 or higher treatment emergent AEs (Table 17 and Table 14.3.4.1).

a) **Please clarify why data from the ARIEL-3 CSR from 2017 was used instead of data from the ARIEL-3 CSR addendum from 2023?**

As the rates are similar between the two data cuts, there is minimal impact on the base case results.

b) **Please clarify why data for grade 3 or higher nausea and hypertension occurring in ≥5% of patients are not reported in Table 17 of the ARIEL-3 CSR addendum, given that they were present in the data from the ARIEL-3 CSR from 2017.**

The incidence of nausea and hypertension are below the 5% threshold for inclusion in Table 17 of the CSR addendum; however their rates are reported in Table 14.3.4.1 in the CSR addendum. The rates were below 5% in the 2017 CSR, and therefore appear in Table 14.3.1.1.8.1 but not Table 25.

c) **Please provide a scenario where rates of AEs for rucaparib are based on Table 17 of the ARIEL-3 CSR addendum. Please note data for grade 3 or higher nausea and hypertension occurring in ≥5% of patients are not reported in Table 17 of the ARIEL-3 CSR addendum, therefore for the scenario, please continue to use the data already provided in the model for these AEs.**

A scenario utilizing AE rates from the CSR amendment has been presented in Section D: Appendix. AE rates did not differ substantially between the data cuts and therefore this scenario has minimal impact on adverse event costs for rucaparib and very limited impact on incremental costs.

B4. In Table 72 of the company submission, combined ALT/AST for niraparib per month on treatment is reported as 0%, but in the model it is 0.5%. Please confirm which value is correct?

a) *Please clarify the source of the estimate for combined ALT/AST for niraparib included in the model (4%), as it is not reported in TA784 (original company submission in TA528).*

The 4% combined AST/ALT evaluation for niraparib is based on adverse events reported in Table 8 (page 11) of the niraparib US FDA prescribing information, available here.[15]

B5. The HRG code for hypertension (EB04Z) is available from the NHS Payment Scheme 2023/25. Please explore a scenario using the EB04Z cost from the NHS Payment Scheme 2023/25.

A scenario using the suggested HRG code has been included in Section D: Appendix. changing the cost of hypotension increases adverse event costs and total costs in both rucaparib and niraparib arms but has a minimal impact on incremental costs.

Monitoring resource use

B6. Priority question: In TA784, no difference was made for monitoring resource use for progression-free patients on or off treatment. Additionally, the EAG's clinical experts considered that after the initial few months of treatment with dose adjustments made, in the long-term patients only discontinue treatment because of

disease progression, thus monitoring of progression-free patients is likely to be the same, irrespective of treatment status.

a) **Please justify why monitoring resource use is assumed to differ for progression-free patients based on treatment status.**

We assumed that monitoring was associated with treatment, and when patients cease treatment, the monitoring would resemble that seen in the post-progression period. This is also in line with the assumptions made in TA611.

b) **Please provide a scenario where monitoring resource use costs are the same for patients who are progression-free irrespective of whether they are on or off treatment.**

We have provided the results of the suggested scenario is Section D: Appendix. Changing the pre-progression monitoring resource use to be equal on and off treatment, results in a substantial increase in monitoring costs in both rucaparib and niraparib arms but has minimal impact on incremental costs.

Other costs

B7. In TA528, the cost of death was estimated to be £7,238, which was based on a unit cost of £4,789.73 (2000/2001 prices) inflated to 2015/2016 prices. In the company submission, a one off cost of death of £4,226.07 was estimated based on TA528 and inflated to 2023 prices. Please clarify how the one off cost of death was calculated given the estimate in TA528 was £7,238 in 2016 prices.

TA528 did use the £7,238 value in their cost-effectiveness analysis but used a value of £3,692 was applied. To quote TA528 Section B.3.5.6.2, “The terminal care costs associated with OC were estimated to be £7,238 (inflated from 2000/01 price of £4,789 to 2015/16 prices using inflation indices from the Personal Social Services Research Unit) for an average time period of 399 days. Gao and colleagues reported that only 51% of terminal care in England is administered in a health service setting. Therefore, the total end-of-life care costs applied at death in the model were £3,692”. The value of £3,692 was also applied in TA611. For this submission we inflated the value from TA528 and TA611 to 2023 prices. Therefore, we believe the one-off cost of death applied is correct and no adjustment is required.

B8. Priority question: Figure 2 of the company submission presents 3L treatment for relapsed ovarian cancer to be platinum-based chemotherapy (paclitaxel + platinum or

PLDH + platinum). The EAG's clinical experts agreed that 3L treatment for relapsed ovarian cancer would be platinum-based chemotherapy.

a) **Please clarify why subsequent treatment costs only include bevacizumab, carboplatin monotherapy and PLDH monotherapy? In the economic model, tab "Subseq Therapy", cells D12:H34, subsequent treatments received in ARIEL-3 include additional treatments, such as gemcitabine + carboplatin, hormonal therapy, paclitaxel + carboplatin and PLDH + carboplatin.**

This has been rectified in the CIC marked version of the model submitted to NICE on the 20th December and details have been provided in Appendix H of the original company submission.

b) **Based on Figure 2 of the CS, please remove the cost of bevacizumab from the one-off cost of subsequent treatment included in the company base case.**
c) **Please provide a scenario where the one-off cost of subsequent treatment is based only on the cost of paclitaxel + carboplatin and PLDH + carboplatin (as per Figure 2 of the company submission), assuming a 50:50 split. Please ensure associated administration costs for treatment are included.**

The base case has been updated so that there is no cost of bevacizumab included in the one-off cost of subsequent treatments, additionally the requested scenario has been included in the scenarios presented in Section D: Appendix. Utilizing a 50/50 split of paclitaxel + carboplatin and PLDH + carboplatin reduces the subsequent treatment costs and total costs for both arms equally and therefore has no impact on incremental costs.

B9. For subsequent treatment drug acquisition costs sourced from the Drugs and pharmaceutical electronic market information (eMIT), please update the model with the latest costs and provide updated base case results.

Thank you for pointing out that updated values were available, these have been updated in the base case results presented in Section D: Appendix.

Section C: Textual clarification and additional points

C1. Priority question: Please provide all results presented in Section B.4.3 and B.4.4 of the company submission and scenarios requested in Section B of this document with the PAS discount for rucaparib included and the assumed discount for niraparib excluded. Please also present the incremental costs.

These result are presented in Section D: Appendix.

Section D: Appendix. Updated base case and scenario results

Results of the base case analysis are shown in Table 11 for the BRCA population and Table 12 for the non-BRCA population. Updates to the base case are as follows.

- Niraparib discount 0%
- Rucaparib discount [redacted]
- Cost of bevacizumab removed from subsequent treatments.
- Costs of adverse events updated using the latest version of eMIT

These changes to the base case do not change the conclusion that in both populations, rucaparib is cost saving in comparison to niraparib, mainly driven by differences in drug acquisition cost.

Table 11. Base case results - BRCA population

Technologies	Acquisition costs	Administration costs	Subsequent costs	Resource costs	Adverse event costs	Total costs
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene

Table 12. Base case results – non-BRCA population

Technologies	Acquisition costs	Administration costs	Subsequent costs	Resource costs	Adverse event costs	Total costs
Rucaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene

All scenarios presented in the original submission have been rerun to reflect the updated base case. In addition, scenarios requested in the EAG clarification questions have been included:

- Using alternative fits for TTD from ARIEL3 and NOVA (for rucaparib Weibull for BRCA and generalised gamma for non-BRCA and for niraparib Gompertz for BRCA and Weibull for non-BRCA)
- Using rucaparib SACT data as key efficacy data source with recommended and alternative fits
- Using niraparib SACT data source with recommended and alternative fits

- Using alternative assumptions for TTD for niraparib with ARIEL-3 key efficacy data source, including niraparib TTD assuming treat until progression and constant discontinuation rate scenarios
- Applying relative dose intensity for niraparib from NOVA (65%)
- Updated adverse event risks based ARIEL-3 CSR addendum (2023)
- Using updated cost for hypertension based on the EB04Z cost from the NHS Payment Scheme 2023/25
- Assuming pre-progression resource use is the same for those on and off treatment
- Alternative subsequent treatments assuming 50/50 split between paclitaxel + carboplatin and PLDH + carboplatin
- Assuming equal TTD for rucaparib and niraparib
- Employing a Weibull distribution for rucaparib TTD for BRCA population and assuming niraparib TTD is equal to rucaparib

Table 13. Scenario analysis results – BRCA population

	Scenario	Overall cost for rucaparib	Overall cost for niraparib	Difference in cost
	Base case	[redacted]	[redacted]	[redacted]
1	ARIEL3 and NOVA alternative TTD	[redacted]	[redacted]	[redacted]
2	SACT rucaparib	[redacted]	[redacted]	[redacted]
3	SACT rucaparib – Alternative fits	[redacted]	[redacted]	[redacted]
4	SACT niraparib	[redacted]	[redacted]	[redacted]
5	SACT niraparib– Alternative fits	[redacted]	[redacted]	[redacted]
6	Alternative TTD1	[redacted]	[redacted]	[redacted]
7	Alternative TTD2	[redacted]	[redacted]	[redacted]
8	PARPi dosing	[redacted]	[redacted]	[redacted]
9	Update AE incidence	[redacted]	[redacted]	[redacted]
10	Updated hypotension cost	[redacted]	[redacted]	[redacted]
11	Same pre-progression resource use on and off treatment	[redacted]	[redacted]	[redacted]
12	Alternative subsequent treatments	[redacted]	[redacted]	[redacted]
13	Assuming equal TTD	[redacted]	[redacted]	[redacted]
14	Equal TTD assuming Weibull TTD for BRCA	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; SACT, Systemic Anti-Cancer Therapy dataset; TTDD, time to discontinuation or death

Table 14. Scenario analysis results – non-BRCA population

	Scenario	Overall cost for rucaparib	Overall cost for niraparib	Difference in cost
	Base case	[redacted]	[redacted]	[redacted]
1	ARIEL3 and NOVA alternative TTD	[redacted]	[redacted]	[redacted]

	Scenario	Overall cost for rucaparib	Overall cost for niraparib	Difference in cost
2	SACT rucaparib	[redacted]	[redacted]	[redacted]
3	SACT rucaparib – Alternative fits	[redacted]	[redacted]	[redacted]
4	SACT niraparib	[redacted]	[redacted]	[redacted]
5	SACT niraparib– Alternative fits	[redacted]	[redacted]	[redacted]
6	Alternative TTD1	[redacted]	[redacted]	[redacted]
7	Alternative TTD2	[redacted]	[redacted]	[redacted]
8	PARPi dosing	[redacted]	[redacted]	[redacted]
9	Update AE incidence	[redacted]	[redacted]	[redacted]
10	Updated hypotension cost	[redacted]	[redacted]	[redacted]
11	Same pre-progression resource use on and off treatment	[redacted]	[redacted]	[redacted]
12	Alternative subsequent treatments	[redacted]	[redacted]	[redacted]
13	Assuming equal TTD	[redacted]	[redacted]	[redacted]

BRCA, breast cancer gene; SACT, Systemic Anti-Cancer Therapy dataset; TTD, time to discontinuation

Section E: Errata

E1. Document B: Table 13. Baseline characteristics of the ITT population in ARIEL3

A number of patient baseline characteristics for ARIEL3 were incorrectly reported in Table 13 of Document B of the original company submission. These characteristics have been corrected in the Table 15 below.

Table 15. Updated table of baseline characteristics of the ITT population in ARIEL (erratum: Table 13 of Document B of the original company submission)

	Rucaparib (n=375)	Placebo (n=189)	Total (n=564)
Median age, years (range)	61.0 (39.0, 84.0)	62.0 (36.0, 85.0)	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	[redacted]	[redacted]	[redacted]
Non-white	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
ECOG PS, n (%)			
0	280 (74.7)	136 (72.0)	416 (73.8)
1	95 (25.3)	53 (28.0)	148 (26.2)
Type of OC, n (%)			
EOC	312 (83.2)	[redacted]	[redacted]
Fallopian tube cancer	32 (8.5)	10 (5.3)	42 (7.4)
Primary peritoneal cancer	31 (8.3)	19 (10.1)	50 (8.9)

	Rucaparib (n=375)	Placebo (n=189)	Total (n=564)
Histology, n (%)			
Serous	[redacted]	179 (94.7)	[redacted]
Endometrioid	16 (4.3)	7 (3.7)	23 (4.1)
Mixed	1 (0.3)	3 (1.6)	4 (0.7)
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)
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	[redacted]	25 (13.2)	[redacted]
>24 months	[redacted]	164 (86.8)	[redacted]
Number of prior previous chemotherapy regimens			
Median (range)	2 (2, 6)	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]	[redacted]
≥3, n (%)	[redacted]	[redacted]	[redacted]
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 (%)	[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]

BRCA, breast cancer gene; CA-125, cancer antigen 125; CR, complete response; CSR, clinical study report; CTA, clinical trial assay; ECOG PS, Eastern Cooperative Oncology Group performance status; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; ITT, intent-to-treat; LOH, loss of heterozygosity; OC, ovarian cancer; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Source: ARIEL3 CSR[9]; ARIEL3 CSR addendum[10]

E2. Document B: Table 21. Additional analysis of OS, adjusting for subsequent treatment with PARP inhibitors in placebo patients

The RPSFTM result for rucaparib vs. placebo was presented as a hazard ratio in Table 21 of Document B of the original company submission. 'HR (95% CI)' has been removed from the header row of the RPSFTM column and a footnote has been added to clarify that the rucaparib vs. placebo result is an acceleration factor (Table 16).

Table 16. Updated table of additional analysis of OS, adjusting for subsequent treatment with PARP inhibitors in placebo patients (erratum: Table 21 of Document B of the original company submission)

	Unadjusted OS analysis based on the study protocol	**Intervention vs. placebo (RPSFTM)[a]**	**Intervention vs. placebo (IPCW) HR (95% CI)**
BRCA mutated cohort			
ARIEL3	[redacted]	[redacted]	[redacted]
SOLO2	0.740 (0.54, 1.00)	0.56 (0.35, 0.97)	Not available[b]
NOVA	0.85 (0.61, 1.20)	Not available[c]	0.66 (0.44, 0.99)
Non-BRCA mutated cohort			
ARIEL3	1.096 (0.852, 1.411)	-	-
SOLO2	Not applicable[d]	Not applicable[d]	Not applicable[d]
NOVA	1.06 (0.81, 1.37)	Not available[c]	0.97 (0.74, 1.26)

BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; OS, overall survival; PARPi, poly (ADP-ribose) polymerase; RPSFTM, Rank-Preserving Structural Failure Time Model; IPCW, Inverse Probability of Censoring Weighting model

[a] [redacted] is an acceleration factor for rucaparib vs. placebo in the BRCA mutated cohort; 0.56 (0.35, 0.97) is a HR for olaparib vs. placebo in the BRCA mutated cohort

[b] Only RPSFT analysis was presented for adjustment for the SOLO2 trial

[c] Only IPCW adjustment was presented for the NOVA trial

[d] SOLO2 did not enrol any patients without BRCA mutation

Source: Matulonis et al. 2021[16]; Galbraith et al. 2020[17]

E3. Document B: Table 30. Patient characteristics at baseline for studies considered for ITC (total trial population data)

A number of patient baseline characteristics for ARIEL3 were incorrectly reported in Table 30 of Document B of the original company submission. These characteristics have been corrected in Table 17 below.

Table 17. Updated table of patient characteristics at baseline for studies considered for ITC (total trial population data; erratum: Table 30 of Document B of the original company submission)

	ARIEL3		SOLO2		Study 19		NOVA (germline BRCA mutation)		NOVA (no germline BRCA mutation)		NORA	
	Rucaparib (n=375)	Placebo (n=189)	Olaparib (n=196)	Placebo (n=99)	Olaparib (n=136)	Placebo (n=129)	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)	Niraparib (n=177)	Placebo (n=88)
Age in years, median (range)	61 (39, 84)	62 (36, 85)	56 (51, 63)	56 (49, 63)	58 (21, 89)	59 (33, 84)	57 (36, 83)	58 (38, 73)	63 (33, 84)	61 (34, 82)	53 (35, 78)	55 (38, 72)
Race, white %	[redacted]	[redacted]	88.3	91.9	95.6	97.7	89.1	84.6	85.9	87.1	NR	NR
BMI, mean	27.9	26.6	NR	NR	NR	NR	NR	NR	NR	NR	24.4	24.2
ECOG PS ≥1, %	25.3	28.0	16.3	22.2	17.6	24.8	34.1	26.2	31.6	32.8	60.5	60.2
FIGO ≥III, %	88.0	86.8	NR	NR	88.2	89.1	83.3	84.6	90.1	94.8	84.2	80.7
Ovarian tumour site, %	83.2	[redacted]	83.7	86.9	87.5	84.5	88.4	81.5	82.1	82.8	NR	NR
Serous histology, %	[redacted]	94.7	100	100	100	100	100	100	100	100	98.3	97.7
BRCA mutation[a], %	34.7	34.9	100	100	54.4	48.1	100	100	0	0	36.7	39.8
Prior lines of platinum chemotherapy, median (range)	2 (2, 6)	2 (2, 5)	Lines, %: 2: 56.1 3: 30.6 4: 9.2 ≥5: 3.6	Lines, %: 2: 62.6 3: 20.2 4: 12.1 ≥5: 5.0	2 (0, 7)	2 (2, 7)	Lines, %: 1: 0.7 2: 50.7 ≥3: 48.6	Lines, %: 1: 0 2: 46.2 ≥3: 53.8	Lines, %: 1: 0 2: 66.2 ≥3: 33.8	Lines, %: 1: 0 2: 66.4 ≥3: 32.8	2 (2, 2)	2 (2, 2)

	ARIEL3		SOLO2		Study 19		NOVA (germline BRCA mutation)		NOVA (no germline BRCA mutation)		NORA	
	Rucaparib (n=375)	**Placebo (n=189)**	**Olaparib (n=196)**	**Placebo (n=99)**	**Olaparib (n=136)**	**Placebo (n=129)**	**Niraparib (n=138)**	**Placebo (n=65)**	**Niraparib (n=234)**	**Placebo (n=116)**	**Niraparib (n=177)**	**Placebo (n=88)**
Platinum-free interval >12 months, %	59.2	64.0	59.7	59.6	61.0	58.1	≥12 months: 60.9	≥12 months: 60.0	≥12 months: 61.5	≥12 months: 62.1	≥12 months: 68.4	≥12 months: 68.2
Response to most recent platinum chemotherapy, %	[redacted]	[redacted]	CR: 46 PR: 54	CR: 47 PR: 53	CR: 42 PR: 58	CR: 49 PR: 51	CR: 51 PR: 49	CR: 51 PR: 49	CR: 50 PR: 50	CR: 52 PR: 48	CR: 51 PR: 49	CR: 52 PR: 48

BRCA, breast cancer gene; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; ITC, indirect treatment comparison; NR, not reported; PBO, placebo; PR, partial response.

[a] The ARIEL3 and Study 19 BRCA mutated cohorts included patients with somatic and germline BRCA mutations, while the SOLO2, NOVA and NORA BRCA mutated cohorts included only patients with germline BRCA mutations

Source: Coleman et al. 2017[3]; ARIEL3 CSR addendum[10]; Ledermann et al. 2016[18]; Pujade-Lauraine et al. 2017[6]; Mirza et al. 2016[7]; Wu et al. 2021[8]

E4. Document B: Table 32. NMA outcomes, BRCA mutated and non-BRCA mutated cohorts (base case network)

The TSST HR values in the BRCA mutated cohort were incorrectly reported as [redacted] and [redacted] the rucaparib vs. olaparib and rucaparib vs. niraparib, respectively, in Table 32 of Document B of the original company submission. Moreover, the INV-PFS for rucaparib vs. niraparib was incorrectly reported as [redacted]. These values have been corrected in Table 18 below.

Table 18. Updated table of NMA outcomes, BRCA mutated and non-BRCA mutated cohorts (base case network; erratum: Table 32 of Document B of the original company submission)

	Rucaparib vs. olaparib[a]	Rucaparib vs. niraparib[b]
BRCA mutated cohort		
INV-PFS, HR (95% CI)	[redacted]	[redacted]
OS, HR (95% CI)	[redacted]	[redacted]
PFS2, HR (95% CI)	[redacted][c]	[redacted]
TSST, HR (95% CI)	[redacted]	[redacted]
Non-BRCA mutated cohort		
INV-PFS, HR (95% CI)	[redacted]	[redacted]
OS, HR (95% CI)	[redacted]	[redacted]
PFS2, HR (95% CI)	[redacted]	[redacted]
TSST, HR (95% CI)	[redacted]	[redacted]

CI, confidence interval; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; NMA, network meta-analysis; OS, overall survival; PFS2, progression-free survival on a subsequent line of treatment; TSST, time to start of second subsequent therapy
Note: ARIEL3, Study 19, SOLO2 and NOVA were included in the base case analysis
[a] Olaparib is a relevant comparator in the BRCA mutated cohort only
[b] Niraparib is a relevant comparator in both the BRCA mutated and non-BRCA mutated cohorts
[c] Only immature PFS2 data were available in SOLO2 and mature PFS2 was not reported for that trial.

Section F: References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [Review of TA611] [ID4069]

Clarification questions

January 2024

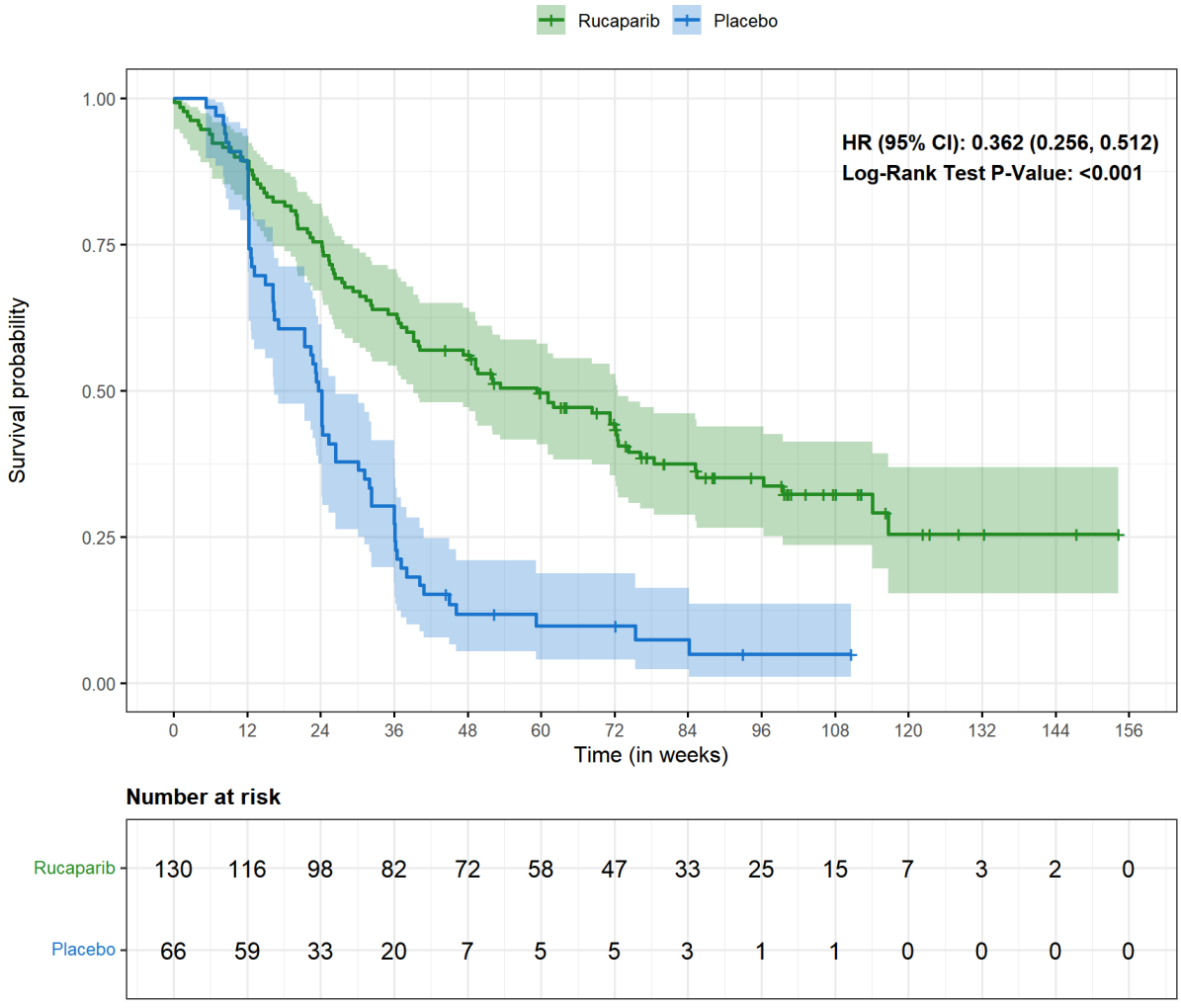
File name	Version	Contains confidential information	Date
		Yes/no	

Section A: Clarification on effectiveness data

A16. For the BRCA mutant subgroup of ARIEL3, please provide the median TTD and 95% confidence interval for the rucaparib and placebo groups, and the resulting hazard ratio with 95% confidence interval.

The median TTD for rucaparib is 59.3 weeks (CI 39.1-72.6) and for placebo is 23.0 weeks (CI 16.4-26.4).

The plot of the KM curves HR and with confidence interval is shown below.



Section B: Clarification on cost-effectiveness data

B9. The EAG notes that as part of the scenario for question B5, the company updated the costs for anaemia, neutropenia, and thrombocytopenia, in addition to hypertension.

a) **Confirm if the costs in the scenario for the additional AEs (presented in the below table) are also from the 2023/25 NHS payment scheme; and**

Yes, that is correct.

b) **Explain how the AE costs for the scenario have been estimated, filling in the below table, as the EAG cannot verify the company's estimation.**

An explanation of the calculations used has been provided in the table below.

Adverse event	Cost used in CQ B5 scenario	Company explanation of cost calculation and source
Anaemia	£1,595.30	Average of 'Unit price' and 'Guide price' of 'Non-elective spell (£)' for SA04G, SA04H, SA04J, SA04K, SA04L
Neutropenia	£1,612	Average of 'Unit price' and 'Guide price' of 'Non-elective spell (£)' for SA08G, SA08H, SA08J
Thrombocytopenia	£1,801.50	Average of 'Unit price' and 'Guide price' of 'Non-elective spell (£)' for SA12G, SA12H, SA12J, SA12K
Hypertension	£520.50	Average of 'Unit price' and 'Guide price' of 'Non-elective spell (£)' for EB04Z

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (Review of TA611) ID4069

Patient Organisation Submission

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. [Please note that declarations of interests relevant to this topic are compulsory].

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	Head of Support Services
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovacome is the national UK ovarian cancer charity focused on providing support and information to anyone affected by ovarian cancer. This includes people who have either been diagnosed with the disease or think that they might be at risk, as well as their friends and family and healthcare professionals. We provided direct support to 6,200 people in the last year. and have 5,000 members. We have 12 full time members of staff and 5 part-time members of staff. We are funded through charitable donations, trusts and foundations donations, community fundraising donations and earned income.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Details for last 12 months pharma funding at 28 November 2023

Company	Amount Received	Date received money	Funding for:
Clovis Oncology	£1,372.00	01/12/2022	PARP inhibitor clinic delivery survey (1st payment)
GSK	£1,740.00	06/12/2022	PATRON project (29 hours at £60 per hour)
Inceptua	£1,020.00	13/12/2022	Review of Apealea patient support material, the Apealea Patient Booklet by Ovacome experts and 8-12 representatives from the Ovacome patient panel (15 hours)

	GSK	£900.00	14/12/2022	PATRON project (Additional 15 hours at £60 per hour)
	Pfizer	£250.00	30/01/2023	National Conference 23 Video Recording
	GSK	£75.00	31/07/2023	Insights from attendee after the GSK Knowledge Lab workshop for patient organisations
	Gilead	£10,000.00	23/08/2023	Grant towards reducing inequalities in ovarian cancer diagnosis and care
	GSK	£15,000.00	31/08/2023	Grant to support to support the Health Inequalities community project
	GSK	£525.00	13/09/2023	Preparation and delivery of presentation "Diversity & under-represented groups in the ovarian cancer community"

4c. 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 providing support to those affected by ovarian cancer. With regards to this submission, we have also used feedback from members sought through the My Ovacome online forum.

Current treatment of the condition in the NHS

6. Do people using the technology feel that it works in the same way as the comparator(s)?	Yes, They feel it works the same way as other PARP inhibitors but offers a further choice of PARPi should the side effects of comparators be unmanageable.
7. Are there any key differences?	There can be different side effects and drug interactions so this offers a further choice of PARPi.
8. Will this technology be easier, the same, or more difficult to take than the comparator(s)? If so, please explain why	It will broadly be the same. It is an oral medication taken at home, as both comparators. Like Olaparib the dose is twice daily. Niraparib is once daily which can be more convenient. Ongoing monitoring is often the same or similar.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	They are pleased to have a maintenance therapy that is manageable in terms of administration and side effects. It enables good quality of life while receiving ongoing treatment and increases the time between chemotherapy treatments. Ongoing regular contact with oncology teams can be reassuring and have psychological benefits. Please see comments below from our members: “I had some tiredness for the first few months, but no other side effects. It was stopped after a routine scan showed a lymph node close to my aorta had continued to increase in size and was surrounding it putting significant pressure on it. So I had some urgent palliative radiotherapy and rucaparib discontinued.” “I was on this for just under 18 months when it stopped working. […] I started rucaparib on 600mg twice a day, side effects made me feel really unwell and I could not eat. So I was advised to come off of them for a week, and then restarted on a low dose, and built up quite quickly to 500mg twice a day which was OK. I never suffered side effects at this level.”

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	For some the side effects are harder to manage. Please see comment below from one of our members: "I began Rubraca this past June after completing chemo. I began with 1200 mg/day. Unfortunately, it decimated my haemoglobin and platelets and had to have a transfusion. I stopped Rubraca for two months and restarted the medication in late August, but the same thing happened even at the lowered dose of 800 mg/day. My platelets decreased to 26,000, so I stopped it for another two months. I am currently taking 500 mg/day and my platelets have dropped to 109,000 and I expect that I will, again, have to stop taking Rubraca. If my platelets drop below 75,000, I will no longer be able to take the drug."

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.	See section 12.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We know that some people with ovarian cancer can struggle to access treatments if they don't fully understand treatment options and choices. This may include people with learning disabilities, people who have English as a second language or who have low levels of literacy. It is important that all patients have equal access to this treatment option where clinically appropriate, and that includes detailed understanding of risk-benefits. It is essential that all patients' information and support needs are assessed on an individual basis and that risk-benefit conversations take place in an appropriate and accessible manner. These should take into consideration patient preferences such as preferred language and preference for face to face, or over the phone appointments.

Key messages

13. 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 the choice of maintenance therapies for this group of patients is vital. • For patients with advanced ovarian cancer knowing their cancer is likely to recur, having maintenance therapy which extends progression-free survival and continued input from oncology teams offers significant psychological as well as health benefits. • Rucaparib is convenient in terms of administration, offering good quality of life for patients whose side effects are manageable. • For patients (particularly those who may have barriers to accessing information) it is essential that information and support needs are assessed on an individual basis and that risk-benefit conversations take place in an appropriate and accessible manner.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (Review of TA611) ID4069

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Target Ovarian Cancer
3. Job title or position	Head of Policy and Campaigns
4a. Brief description of the organisation (including who funds it). How many members does it have?	Target Ovarian Cancer is the UK's leading ovarian cancer charity. We work to: • improve early diagnosis • fund life-saving research • provide much needed support to women with ovarian cancer We are the only national charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. We are 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 Target Ovarian Cancer is funded through voluntary donations and in the last 12 months we have been in receipt of one grant from a manufacturers which is outlined below
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	**Yes** GSK June 2023 £14,000 for the development of patient information guides

If so, please state the name of the company, amount, and purpose of funding.	
4c. 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?	• Anecdotal feedback from patients and their families. • Patient survey on access to cancer drugs and patient feedback as part of our Pathfinder research • Calls to the Target Ovarian Cancer support line and questions and comments on our online communities

Current treatment of the condition in the NHS

6. Do people using the technology feel that it works in the same way as the comparator(s)?	Patients in the NHS currently usually have access to one type PARP inhibitor so it is difficult for those that have taken PARPs to be able to offer a view on comparisons. What is vital to patients is having choice so that if they are not able to tolerate the side effects on one type of PAR inhibitor, they can haves access to another option
7. Are there any key differences?	There can be differences in side effect profiles between PARP inhibitors
8. Will this technology be easier, the same, or more difficult to take than the comparator(s)? If so, please explain why	They are broadly the same

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	*I feel now and when I was going through my treatment that ovarian cancer is the poor relation of women's cancers. No screening programme, reduction in research funding, with a high recurrence. Having ovarian cancer doesn't fill you with high hopes by the time you are diagnosed*." Woman with ovarian cancer. **Choice** – rucaparib gives clinicians and women another option for extending progression free survival (PFS for those who have had a recurrence. Many women welcome the opportunity to be involved in making decisions about their care and treatments they receive, and feel they are able to take some control at what a very uncertain time is typically. There is currently only one option for women who do not have a BRCA mutation (niraparib) meaning that if side effects for that treatment are not tolerated there are no other options *'Women with ovarian cancer usually have very little time to live. My mum would have liked six months to put her affairs in order and say goodbye to people. If a drug can do this, she should have been able to access it.'* Family member of a woman with ovarian cancer **Best possible care** – often women are aware of the poor outcomes associated with ovarian cancer. By accessing rucaparib part of their treatment plan, they may feel they are giving themselves the best possible chance of prolonging the disease-free interval. This is extremely important to those who have experienced a recurrence. '*Second time was more frightening. I think ladies in this situation need encouragement, reassurance about the treatment and to feel that this is not the end of the line'* Woman who had a recurrence. **Physical wellbeing** - once a woman has recurrent ovarian cancer, she will inevitably go through further treatment cycles for subsequent recurrences. Rucaparib offers women the opportunity to extend their PFS and therefore the interval between chemotherapy, this benefit is likely for many to outweigh the possible side effects associated with rucaparib. A longer PFS may be beneficial in terms of supporting a better physical recovery from chemotherapy, enabling the individual to successfully undergo subsequent treatment. It is thought that prolonging the interval between treatments is likely to make subsequent treatment more effective.

	Emotional/mental health – once a woman has been diagnosed with recurrent ovarian cancer, further recurrence will be expected as the cancer runs its course. For many, receiving the news that their cancer has returned can be more devastating than the initial ovarian cancer diagnosis. Improvement in PFS offered by rucaparib will allow give women valuable time to recover from the mental impact of recurrence and treatment, allowing them to resume normality, and live their lives as fully as possible. **Mode of delivery** – rucaparib is administered orally which is well tolerated.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	**Side effects** – Side effects are associated with rucaparib, some women will find these more difficult to tolerate, depending upon the side-effect and its severity

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.	Current treatment options both in routine commissioning and the Cancer Drugs Fund offer more options of those that have a BRCA mutation or are positive for HRD. Having options for those that do not have any genomic variations is vital.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Key messages

13. 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.

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Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (Review of TA611) [ID4069]

Cost-comparison Technology Appraisal

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 136191.

Title:	Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (Review of TA611) [ID4069]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
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Date completed:	06/02/2024
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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 Systematic Reviews Programme. Any errors are the responsibility of the authors.
Report reference:	Edwards SJ, Wakefield V, Jhita T, and Downes N. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (Review of TA611): A Cost-comparison Technology Appraisal. BMJ Technology Assessment Group, 2024.

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Contribution 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
Victoria Wakefield	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
Nicole Downes	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; critical appraisal of the economic evidence; and drafted the economic sections

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

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List of Abbreviations

AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BRCA	breast cancer susceptibility gene
CDF	Cancer Drugs Fund
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CS	Company submission
DRS-P	Disease-related symptoms–physical
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D	Euro-Quality of Life 5 Dimensions
ESMO	European Society for Medical Oncology
FIGO	International Federation of Gynaecology and Obstetrics
FOSI	FACT/NCCN Ovarian Symptom Index
HR	hazard ratio
INV-PFS	Investigator-assessed progression-free survival
IRR	Independent radiology review
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KM	Kaplan-Meier
LOH	Loss of heterozygosity
MAIC	Matching adjusted indirect comparison
Mg	Milligrams
NMA	Network meta-analysis
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PARP	Poly-ADP-ribose polymerase
PAS	Patient access scheme
PFS	Progression-free survival
PFS2	Time from randomisation to second progression or death
PLDH	Pegylated liposomal doxorubicin hydrochloride

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
SACT	Systemic Anti-Cancer Therapy
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
TSST	Time to second subsequent anticancer treatment
TTD	Time to treatment discontinuation

1 Summary of EAG's view of the company's CCE case

A cost-comparison analysis was developed by the company to assess rucaparib compared with niraparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer. To be considered for a cost-comparison technology appraisal, the National Institute for Health and Care Excellence (NICE) requires the intervention under review to be clinically similar to one treatment that NICE has previously recommended in technology appraisal guidance for the same indication. Niraparib has previously been recommended by NICE as an option for treating relapsed, platinum-sensitive high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to the most recent course of platinum-based chemotherapy in adults (TA784).

Based on analyses of the clinical evidence for rucaparib versus niraparib and the advice of clinical experts, the External Assessment Group (EAG) does not consider it unreasonable to assume that rucaparib and niraparib are clinically similar. Therefore, the EAG considers that a cost-comparison of rucaparib and niraparib may be appropriate. However, the EAG notes that there is [redacted] in the clinical analyses and this is discussed below.

In November 2019, rucaparib was recommended by NICE in TA611 for use within the Cancer Drugs Fund (CDF) as an option for maintenance treatment of relapsed, platinum-sensitive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to platinum-based chemotherapy in adults if the conditions in the managed access agreement for rucaparib were followed. At this time it was considered that there was clinical uncertainty associated with rucaparib due to the immaturity of the overall survival (OS) data, and that this could be addressed through the collection of additional data from ARIEL3.

In the company submission (CS), the company uses OS data from the final data analysis of OS from ARIEL3 in support of the clinical efficacy of rucaparib. The EAG notes that the results from these final analyses in ARIEL3 for rucaparib versus placebo demonstrate [redacted] the EAG also notes that the primary endpoint in ARIEL3 was investigator assessed progression-free survival (INV-PFS) and rucaparib significantly reduced the risk of disease progression or death compared with placebo in patients with platinum-sensitive ovarian cancer who had responded to platinum-based chemotherapy at the 15 April 2017 data cut in the ITT population and BRCA mutant subgroup. The hazard ratio for the non-BRCA subgroup suggested [redacted]

[redacted]

In the CS, the company has provided analysis of clinical efficacy data for rucaparib versus niraparib, and also for rucaparib versus olaparib. The marketing authorisation and NICE approval for olaparib restricts its use to only BRCA mutation positive patients, whereas rucaparib and niraparib have marketing authorisation for use in both BRCA, and non-BRCA patients. The company has conducted analyses of clinical efficacy separately for the BRCA and non-BRCA populations, and has also used these two populations in the cost-comparison versus niraparib. The EAG considers that this approach appears to be reasonable, and the EAG's clinical experts did not express any concerns.

The EAG notes that rucaparib, niraparib and olaparib are all oral treatments with a similar mechanism of action; they are all poly-ADP ribose polymerase (PARP) inhibitors. The dose and frequency of administration differs between the three drugs, with rucaparib and olaparib recommended in their MHRA summary of product characteristics (SmPC) as twice daily whereas niraparib is a once daily treatment. The EAG's clinical experts reported that all three treatments (rucaparib, niraparib and olaparib) are currently used in England and they did not consider there to be any notable difference between rucaparib, niraparib and olaparib in terms of efficacy or safety aside from the limitations around the eligible patient populations (in particular, olaparib use is limited to BRCA mutant patients).

There are no randomised controlled trials (RCTs) directly comparing rucaparib with niraparib or olaparib and so the company has conducted various indirect treatment comparisons (ITCs) including network meta-analyses (NMAs) and matching adjusted indirect treatment comparisons (MAICs) using the ARIEL3 trial for rucaparib, the NOVA trial for niraparib and the SOLO2 trial for olaparib. The EAG considers these trials to match the population in the NICE final scope and decision problem well, and considers the NMAs to be the most robust source of efficacy data for rucaparib versus niraparib and rucaparib versus olaparib in the absence of head-to-head RCT data. There were some differences in trial baseline characteristics noted (Section 4.4.1), but the EAG's clinical experts did not consider these differences to be substantial enough to impact outcomes for rucaparib, niraparib or olaparib.

The EAG notes [redacted] in all of the results from the NMAs, although the base case NMA [redacted] for rucaparib versus niraparib or rucaparib versus olaparib. The point estimates for rucaparib compared to niraparib [redacted]

[redacted]. Based on these data and the advice of clinical experts, the EAG doesn't consider it unreasonable to conclude that rucaparib and niraparib have broadly similar efficacy. [redacted] However, the EAG notes that for a cost-comparison, the company only needs to be able to demonstrate convincing evidence of similar efficacy to one previously approved NICE technology according to the NICE health technology evaluation manual. The EAG considers this threshold to have been met with rucaparib and niraparib.

With regards to safety, it should be noted that there was no statistical comparison of adverse effects between the treatments reported in the CS. The EAG also considers it important to highlight that Grade 3 or above raised ALT/AST adverse events (AEs) were not included in the economic modelling of the NICE appraisals for niraparib (TA528) or olaparib (TA908) and safety data from ARIEL3 demonstrate that rucaparib is associated with a [redacted] proportion of patients with Grade 3 or above combined ALT/AST treatment-emergent adverse events (TEAEs) compared with niraparib in NOVA. However, the EAG's clinical experts reported that, while there are differences in the individual AEs for the PARP inhibitors, there were no major safety concerns regarding differences in AEs between rucaparib, niraparib and olaparib. Overall, based on naïve comparison and the advice of the EAG's clinical experts, the EAG does not consider it to be unreasonable to assume the safety profiles of rucaparib and niraparib are broadly similar.

For the cost-comparison economic analysis, several parameters and assumptions have been varied by the company and the EAG in scenario analyses, and based on a proposed patient access scheme (PAS) discount of [redacted] for rucaparib and the list price for niraparib, rucaparib continues to be cost saving in each instance. However, a confidential PAS discount is available for niraparib and so results that include this discount will be used by the committee for decision making. The EAG has produced a confidential appendix to this report, which presents the company base case results, scenario analyses and EAG base case and scenario analyses with the niraparib PAS discount included.

The fundamental driver of the cost differences between rucaparib and niraparib, related to drug acquisition, AEs and monitoring costs is the company's approach to time to treatment discontinuation (TTD). As well as being used to estimate drug acquisition costs, TTD affects AE costs as a monthly risk of AEs is applied to patients while on treatment and it affects monitoring costs as

the company assumed a difference in resource use dependent on whether a progression-free patient is on or off treatment.

The company estimated that patients are on treatment longer with niraparib compared to rucaparib, based on a naïve comparison of TTD, but also estimated that patients incur greater costs associated with AEs while on niraparib, which the EAG considers to be incoherent. It seems clinically implausible that the less well tolerated treatment should have a longer TTD. Both rucaparib and niraparib are treatments that are given until disease progression or unacceptable toxicity.

Thus, by estimating niraparib patients remain on treatment for longer than patients with rucaparib, drug acquisition costs are lower for rucaparib, but also monitoring and AE costs are lower. Data from the Systemic Anti-Cancer Therapy (SACT) database suggests that TTD is similar between rucaparib and niraparib and this is also supported by the EAG's clinical experts experience of both drugs. The EAG considers that a naïve comparison of TTD for both treatments is not robust and is driving the cost differences in the model. As such, the EAG considers that for the cost-comparison analysis, it is more appropriate and more clinically plausible to assume that TTD for niraparib is equal to TTD for rucaparib.

Additionally, assuming TTD is equivalent for both treatment is in line with guidance for cost-comparison analysis in the NICE health technology evaluation manual, which advises that if there are substantial in costs directly relating to health outcomes (such as adverse events), this may suggest that the technologies may not provide similar overall health benefits. However, under the EAG's preferred assumption that TTD is equivalent between treatments, the cost differences associated with AEs reduces and the approach is more in line with guidance for cost-comparison analysis. Furthermore, differences in monitoring costs due to being on or off treatment are eliminated.

2 Background

Herein is a critique of the evidence submitted to the Cost-comparison Technology Appraisal in support of the clinical and cost-effectiveness of rucaparib (Rubraca®; pharma&) for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (Review of TA611). European Commission marketing authorisation for rucaparib use in this indication was granted on 23 January 2019 following an application from Clovis Oncology, and on 19 June 2023 the marketing authorisation of rucaparib was transferred from Clovis Oncology Ireland Ltd. to pharmaand GmbH (pharma&). The EAG notes that pharmaand GmbH (pharma&) also holds marketing authorisation for the use of rucaparib in this indication with the Medicines and Healthcare products Regulatory Agency (MHRA) and that the wording of the therapeutic indication is as follows: "*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*".[1]

In November 2019, rucaparib was recommended by National Institute for Health and Care Excellence (NICE) in TA611[2] for use within the Cancer Drugs Fund as an option for maintenance treatment of relapsed, platinum-sensitive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to platinum-based chemotherapy in adults if the conditions in the managed access agreement for rucaparib were followed. At this time it was considered that there was clinical uncertainty associated with rucaparib due to the immaturity of the overall survival (OS) data currently available and that this could be addressed through the collection of additional data from ARIEL3[3]. The ARIEL3 trial is the primary source of clinical efficacy data for rucaparib in both TA611, and the company submission (CS) for this appraisal.[3] In the CS, the company presents OS data from April 2022 - the final data analysis of OS from ARIEL3.

The company outlines in the CS that their rationale for submitting for a cost-comparison is that they consider rucaparib provides similar health benefits at similar or lower cost than technologies in the same therapeutic class previously recommended in published NICE technology appraisal guidance for this indication:

- Olaparib for maintenance treatment of recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer after two or more courses of platinum-based chemotherapy (2023) NICE technology appraisal guidance 908 (TA908).[4]
- Niraparib for maintenance treatment of relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer (2022): NICE technology appraisal guidance 784 (TA784).[5]

The External Assessment Group (EAG) notes that the company provides clinical efficacy data for rucaparib versus the two comparators listed in the NICE final scope (olaparib and niraparib), using indirect treatment comparisons (ITCs), but has focused only on niraparib for the cost-comparison. The EAG's conclusion regarding the appropriateness of a cost-comparison for this treatment and indication is summarised in Section 1 of this report and discussed in more detail throughout.

The EAG notes that rucaparib, niraparib and olaparib are all the same class of drug (poly adenosine diphosphate-ribose [ADP-ribose] polymerase [PARP] inhibitors) and therefore have similar modes of action. However, the EAG considers it important to highlight that olaparib's use as a maintenance therapy for recurrent, platinum-sensitive ovarian, fallopian tube and peritoneal cancer after two or more courses of platinum-based chemotherapy is restricted to patients with BRCA mutations. In contrast, neither rucaparib or niraparib are restricted for this treatment indication based on BRCA mutations, and thus they are available for a broader patient population than olaparib.

In the CS it is reported that on 15 November 2023, the European Medicines Agency approved an extension of the rucaparib marketing authorisation to include an indication for first-line maintenance treatment in advanced ovarian cancer (OC).[6] The EAG notes that the NICE website suggests that rucaparib for this indication is currently under review in a single-technology appraisal: rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID5100].

2.1 Disease overview and treatment pathway

Within Section B.1.3 of the CS, the company provides an overview of the disease condition, focusing on ovarian cancer which is the most common out of ovarian, fallopian tube and peritoneal cancers. The EAG considers it important to highlight that people with mutations in the BRCA1 or BRCA2 genes are at increased risk of ovarian cancer than the general population. Also, the BRCA1 and BRCA2 mutations can be subdivided into germline and somatic mutations. This is important to note because there are differences between the three key trials informing the ITC in terms of the enrolment of patients with different BRCA mutations; this is discussed further in Section 3.3.

Figure 2 in the CS document B provides an overview of the treatment pathway for patients with platinum-sensitive advanced OC and the current maintenance therapy treatment options. The EAG notes that the treatment options available as first line maintenance therapy are all restricted to use in the Cancer Drugs Fund (CDF). In terms of second line and beyond (2L+) maintenance therapies, there are three PARP inhibitors available. Of these, there are some differences in the

recommendations which include that rucaparib is only available via the CDF, niraparib is restricted to use in patients with serous carcinoma and olaparib is restricted to patients with BRCA mutations. The EAG's clinical experts reported that the company overview of the current treatment pathway and the company's positioning of rucaparib as a 2L+ maintenance therapy appeared to be consistent with clinical practice in England and the marketing authorisation for rucaparib. The EAG's clinical experts also reported that in their clinical practice the exact choice of PARP inhibitor would depend partly on the presence of a BRCA mutation or homologous recombination deficiency (HRD) and the final decision out of the eligible options would generally be determined on an individual basis by the patient and the treating clinician. The EAG's clinical experts also highlighted that the availability of first-line maintenance therapies is now reducing the number of patients eligible for PARP inhibitors at 2L+ maintenance as re-treatment with a PARP inhibitor at later lines of therapy is not permitted in clinical practice in England.

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

The company provided a summary of the final scope issued by the National Institute for Health and Care Excellence (NICE) in Section B.1.1 of the company submission (CS),[7] together with a summary of the decision problem addressed in the CS (Table 1 of the CS). The company highlights that the decision problem addressed is in line with the NICE final scope for all parameters. Comments from the External Assessment Group (EAG) are provided in the subsections that follow; overall, the EAG considers the decision problem addressed and the evidence used to address it to be reasonable.

3.1 Population

Clinical effectiveness data for rucaparib are derived from the ARIEL3 trial[3], which enrolled adults with platinum sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients in ARIEL3 were required 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 EAG considers the population in ARIEL3 to be consistent with the population specified in the NICE final scope (people with relapsed, platinum-sensitive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that is in response [complete or partial] to platinum-based chemotherapy).

The EAG notes that in the indirect treatment comparisons (ITCs), and the cost-comparison analyses, the company has split the population into BRCA-mutation positive (BRCA population) and patients without a BRCA mutation (non-BRCA population). The EAG considers this to be reasonable to enable comparisons with both the comparators in the NICE final scope (olaparib and niraparib). The EAG also notes that the primary efficacy analyses of ARIEL3 are in the intention-to-treat (ITT) population and therefore the EAG focuses its critique on the ITT, BRCA and non-BRCA populations.

The EAG also considers that a relatively small proportion of the ARIEL3 trial population (N=67 from 10 sites) were enrolled and treated in the UK. The EAG's clinical experts reported that patients were possibly slightly younger and potentially had a better performance status in ARIEL3 than would be expected in clinical practice in England, although they considered the full trial population largely representative of people in England eligible for rucaparib 2L+ maintenance treatment.

The EAG also notes that the subsequent therapies in ARIEL3 do not align with clinical practice in England, in particular it is noted that [redacted]% of the rucaparib group received subsequent PARP inhibitors, whereas the EAG's clinical experts reported that re-treatment with PARP inhibitors is not permitted in clinical practice. The company also highlighted that [redacted]% of the placebo group

received subsequent treatment with PARP inhibitors and that they considered this may bias the results for OS in ARIEL3 against rucaparib. In the CS (CS Section B.3.6.2.3.1) the company conducted exploratory analyses adjusting for the subsequent PARP inhibitor use in the placebo arm of ARIEL3 and the results of this are discussed in section 4.3.2.1. However, the EAG notes that if patients haven't received a PARP inhibitor then they would potentially be eligible to receive one as a subsequent treatment in UK clinical practice (conditional on responding to platinum-based chemotherapy).

In summary, the EAG considers ARIEL3 aligns with the population in the NICE final scope and that the population is broadly consistent with clinical practice in England but it is noted that subsequent treatment usage in the trial may differ to clinical practice and is likely to impact on the results of OS.

3.2 Intervention

Rucaparib is an inhibitor of PARP enzymes, which are involved in DNA repair. Through the inhibition of PARP enzymes, rucaparib leads to increased DNA damage, apoptosis, and tumour cell death.

The intervention in the NICE final scope matches the intervention in ARIEL3 (rucaparib) and the EAG notes that the rucaparib treatment regimen in ARIEL3 is consistent with the marketing authorisation recommended dose detailed in the summary of product characteristics for rucaparib:

- *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.*
- *The recommended dose is 600 mg rucaparib taken twice daily, equivalent to a total daily dose of 1,200 mg, until disease progression or unacceptable toxicity.*
- *Patients should start the maintenance treatment with Rubraca no later than 8 weeks after completion of their final dose of the platinum containing regimen.*

The EAG's clinical experts reported that the dose of rucaparib in ARIEL3 was consistent with clinical practice in England, and that similar to in the trial, dose reductions may be required in clinical practice.

In summary, the EAG considers the intervention (rucaparib) to be appropriate in both the key clinical trial (ARIEL3) and the cost-comparison presented in the CS.

3.3 Comparators

The NICE final scope specifies that at least 1 of the following treatments, according to NICE guidance should be considered:

- niraparib;
- olaparib (only for people who have a BRCA mutation).

As discussed in Section 2, the company has chosen to focus on niraparib for the cost-comparison but the company has also provided clinical efficacy data in the CS for the comparison versus olaparib in the BRCA mutated population. The EAG notes that ITCs were conducted by the company for both the comparison of rucaparib versus niraparib and rucaparib versus olaparib. The methods and results of these are discussed in Section 4.4 The EAG's clinical experts reported that both olaparib (only for people who have a BRCA mutation) and niraparib are reasonable comparators for rucaparib and that all three treatments are currently available for use in the 2L+ maintenance setting in clinical practice in England.

There are differences in the NICE recommendations for olaparib, niraparib and rucaparib usage as 2L+ maintenance therapies, with the main ones being that olaparib is only recommended in patients with BRCA mutations and niraparib is only recommended for use in patients with serous carcinomas. Further details and comparison of the differences between the three PARP inhibitors is provided in Table 5 of the CS document B. The EAG's clinical experts reported that serous carcinomas account for the majority of high-grade ovarian cancer and therefore niraparib can be used in most patients assuming they meet the other criteria for treatment. However, the non-BRCA population accounts for a large proportion of ovarian cancer patients and therefore if olaparib was considered the main comparator for rucaparib in the cost-comparison then comparator data for a large group of patients would not be available from SOLO2,[8] the key study of olaparib. This is because SOLO2 restricted enrolment to patients with BRCA mutations.

The EAG notes that in the cost-comparison, the BRCA mutant and non-BRCA populations have been considered separately and that subgroup data from these two populations have been used in the ITCs for niraparib and rucaparib from the NOVA[9] and ARIEL3 trials, respectively. Another issue relating to the BRCA mutation data is that for rucaparib the BRCA population data comprise a mix of patients with germline and somatic mutations whereas the niraparib BRCA population data in NOVA and the olaparib BRCA population data from SOLO2 comprise only of patients with germline BRCA mutations. In addition, the EAG notes that the non-BRCA population data in NOVA (n = 350) includes

47 patients with somatic BRCA mutations (according to Supplemental Figure A1 from Mirza *et al.* 2016). The EAG's clinical experts reported that in keeping with the enrolment in ARIEL3, more patients would be expected to have germline BRCA mutations in clinical practice than somatic mutations. However, the impact of these differences in the BRCA populations of ARIEL3, NOVA and SOLO2, and the non-BRCA populations of NOVA and ARIEL3 is unknown.

3.4 Outcomes

The outcomes presented in the CS match those in the final scope well and all outcomes are covered in the ARIEL3 trial. The EAG notes that data for progression-free survival (PFS) and health-related quality of life (HRQL) remain unchanged from TA611 (April 2017 data-cut). Data for overall survival (OS) and other relevant outcomes including adverse events are reported in the CS using the April 2022 data from the final analysis of ARIEL3.

The company presented ITCs for the outcomes of investigator-assessed progression-free survival (INV-PFS), OS, progression-free survival on a subsequent line of treatment (PFS2) and time to start of second subsequent therapy (TSST). The EAG notes that OS, PFS and time-to-treatment discontinuation (TTD) were key drivers in the cost-effectiveness analyses for TA784 and TA908. The EAG therefore also requested the company conduct ITCs for TTD during the clarification stage but the company reported that it was not possible to conduct NMAs or MAICs for TTD for the comparison of rucaparib versus niraparib due to the absence of suitable data for niraparib (company response to clarification questions A3 and A7).

The EAG notes that adverse events (AEs) were also included in the modelling in TA784 and TA908; AEs for rucaparib and niraparib have been included in the cost-comparison analysis (Section 5.4.2). The EAG notes that there are differences between the PARP inhibitors (rucaparib, niraparib and olaparib) in some of the AEs, but the EAG's clinical experts did not raise any particular safety concerns regarding differences in AEs between the different drugs. Please see Section 4.6 for further critique of AEs.

In summary, the EAG considers data on all key outcomes has been presented for rucaparib in the CS but notes that suitable data for TTD were not available from NOVA to enable a statistical comparison between rucaparib and niraparib using NMA or MAIC methods.

3.5 Subgroup analyses and other relevant factors

The company presented the results of various subgroup analysis within the CS and CS appendices although the EAG notes that no subgroup analyses were specified in the NICE final scope. The EAG considers the results from the subgroup analyses of BRCA and non-BRCA patients to be of relevance as the company has conducted cost-comparisons for these two populations. The EAG therefore discusses the results of these subgroups for ARIEL3 in Section 4.3 and for the ITC in Section 4.4.2.1.

The EAG notes that the company has proposed a confidential patient access scheme (PAS) discount for rucaparib (Section 5).

4 Summary of the EAG's critique of clinical effectiveness evidence submitted

4.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify clinical evidence on the efficacy and safety of rucaparib and comparator maintenance therapies for patients with advanced or metastatic ovarian cancer (OC), or fallopian tube or primary peritoneal carcinomas, after two or more prior lines of chemotherapy. Searches were specifically for the identification of randomised controlled trials (RCTs). Studies identified as relevant to this SLR were considered for inclusion in indirect treatment comparisons (ITCs), which are detailed Section 4.4. Detailed methods involved in this SLR are described in Appendix D.1 of the company submission (CS) appendices. These methods were stated to be in line with the National Institute for Health and Care Excellence (NICE) health technology evaluation manual. The External Assessment Group (EAG) discusses features of the SLR in more detail in Table 27 of Appendix 10.1.

The EAG considers these searches to be robust and likely to have captured all relevant RCTs up to the search date, and the methods used for screening, data extraction and quality assessment are considered to be appropriate. Searches were last updated in July 2023 (~5 months prior to the EAG receiving the submission), which the EAG considers to be reasonable. As discussed in Table 27, the EAG has some concerns about the changes described for the most recent update searches compared to the original and first update searches (change of database and, therefore, search terms) and whether the study design filter was validated, but considers the risk of having missed relevant studies to be low. Furthermore, the EAG notes that, for comparators considered applicable to the decision problem (see Section 3), the SLR identified all comparator studies that were key to their respective NICE appraisals (TA908 and TA784 for olaparib and niraparib, respectively).[4, 5]

The searches and inclusion criteria used for the SLR were in line with the population outlined in the decision problem (people with relapsed, platinum-sensitive high-grade OC or fallopian tube or primary peritoneal cancer, with at least two prior chemotherapy treatments; Section 3) but the SLR covered a wider range of comparators than outlined in the decision problem (for example, studies covering chemotherapy agents other than niraparib and olaparib were included). The EAG has no major concerns about any of the inclusion or exclusion criteria applied to the SLR based on the excluded studies list provided in response to clarification question (CQ) A11.

Inclusion and exclusion criteria used to determine studies relevant for the ITCs from those included in the overall SLR were provided in Table 9 of the company's response to CQ A12 and are considered reasonable by the EAG. The rationale provided for studies being included in the global SLR but excluded from the ITCs (response to CQ A12 and Section B.3.9.1 of the CS) is considered to be reasonable by the EAG. ARIEL3 (rucaparib), SOLO2 and Study 19 (olaparib), and NOVA and NORA (niraparib) were considered for inclusion in ITCs.[3, 8-11] SOLO2 and NOVA were favoured by the company for matching-adjusted indirect comparisons (MAICs) but Study 19 was additionally included in the original network meta-analyses (NMAs). In response to CQ A2, the company updated its preferred NMAs to include only SOLO2 and NOVA as comparator studies, with ARIEL3 included for rucaparib. The EAG's preferences in terms of studies included in ITCs are described in more detail in Section 4.4; overall, the EAG considers that NORA and Study 19 have additional limitations and may be less appropriate for inclusion in ITCs.

4.2 Critique of ARIEL3

One randomised controlled trial (RCT) comparing rucaparib vs placebo was used in the CS to provide data for the efficacy and safety of rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer. This was ARIEL3, that evaluated the efficacy and safety of rucaparib vs 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 2L or later platinum-based chemotherapy. At the time of TA611, data for OS were immature and the study was ongoing. The ARIEL3 study was completed on 7 July 2022 and the final visit data cut was 4 April.[12, 13]

ARIEL3 is a phase III double-blind RCT with patients (N=564) randomised in a 2:1 ratio to receive oral rucaparib (n=375; 600mg twice daily) or matching placebo (n=189). The EAG's assessment of the design, conduct, and internal validity of the ARIEL3 trial and the representativeness of the trial population is described in Table 28 of Appendix 10.2 and Section 3.1. The EAG's clinical experts considered ARIEL3 to be a reasonable reflection of the eligible patient population in UK clinical practice (Section 3.1) and that the dosing regimen of rucaparib was broadly consistent with clinical practice in England (Section 3.2). However, the EAG notes that the subsequent treatments used in ARIEL3 do not align with clinical practice in England and considers this may impact on the results for the analyses of OS.

A total of 78.1% of patients in the rucaparib group and 88.9% of the placebo group had received at least one subsequent anti-cancer treatment at the final data analysis (ITT population). The most common subsequent treatments received were platinum-based chemotherapy (rucaparib: [redacted]; placebo: [redacted]), non-platinum chemotherapy (rucaparib: [redacted]; placebo: [redacted]) and PARP inhibitors (rucaparib: [redacted]; placebo: [redacted]); the EAG's clinical experts reported that patients would not usually receive a PARP inhibitor as a subsequent therapy if they had already received one in the UK.

Quality assessment performed by the company for ARIEL3 is presented in Table 27 of Appendix D of the CS. The company's critique suggests a low risk of bias for all domains, although the company has flagged a potential high risk of bias for OS associated with the number of patients in the placebo arm that went onto receive PARP inhibitor treatment post-progression. The EAG broadly agrees with the company's quality assessment and comment regarding the unadjusted analyses of OS (Table 28).

4.3 Clinical effectiveness results

The EAG notes that subgroup analyses of the patients without a BRCA mutation in the ARIEL3 study were conducted *post-hoc* with results presented in the CS and used to inform the clinical efficacy estimated for the non-BRCA mutant cohort in the ITC and the cost-comparison. In addition, the pre-specified subgroup analysis of BRCA mutant patients in ARIEL3 is used to inform the equivalent subgroup in the ITCs and economic model. The EAG also notes that the primary efficacy population in ARIEL3 was the intention-to-treat ITT population and the EAG therefore focuses the critique in this report on the results from the ITT, BRCA-mutant and non-BRCA mutant populations as the EAG considers these to be of the most relevance.

The EAG notes that for some outcomes, data are reported from both the April 2017 data-cut and the April 2022 data-cut. The EAG considers the data from the later data-cut to be the most relevant, and therefore focuses its critique on the April 2022 data where possible.

4.3.1 Progression-free survival

The primary endpoint in ARIEL3 was investigator assessed progression-free survival (INV-PFS) with results for independent radiology review assessed PFS (IRR-PFS) using RECIST v1.1 reported as a secondary endpoint. As discussed previously, PFS was only captured at the 15 April 2017 data-cut and therefore the results presented here relate to this data-cut.

Rucaparib significantly reduced the risk of disease progression or death compared with placebo in patients with platinum-sensitive ovarian cancer who had responded to platinum-based chemotherapy at the 15 April 2017 data cut in the ITT population and BRCA mutant subgroup (Table 1). It should be noted that in the CS the results for INV-PFS for the *post hoc* non-BRCA mutant subgroup were reported in weeks rather than months and so are not directly comparable with the results for the ITT population or BRCA mutated cohort in the table below, [redacted] (Table 1).

The results for median IRR-PFS were only available for the ITT and BRCA mutant cohorts and it is noted that the median point estimates with 95% confidence intervals of IRR-PFS were longer than those of the INV-PFS in the rucaparib arm for both cohorts (Table 1). The company reported that: "*A higher median IRR-PFS as compared to INV-PFS has been observed in other clinical studies of PARP inhibitor maintenance treatments within the relapsed OC setting.*[8, 9, 14]". In addition, the EAG notes that scans were sent for IRR in ARIEL3 only until progression or death as assessed by the investigator, therefore, there was a higher censoring rate in IRR analyses. [redacted]

KM curves suggest a PFS benefit with rucaparib treatment compared with placebo from approximately 3 months which the EAG notes is the approximate time of the first tumour scan, and that similar benefit is seen for both INV-PFS and IRR-PFS in the ITT (Figure 1 and Figure 2) and BRCA mutated (Figure 10 and Figure 11, Appendix 10.4.1) populations. The EAG notes that the [redacted].

Table 1. Summary of INV-PFS and IRR-PFS (15 April 2017 data cut) (Adapted from CS Table 16 and Table 17)

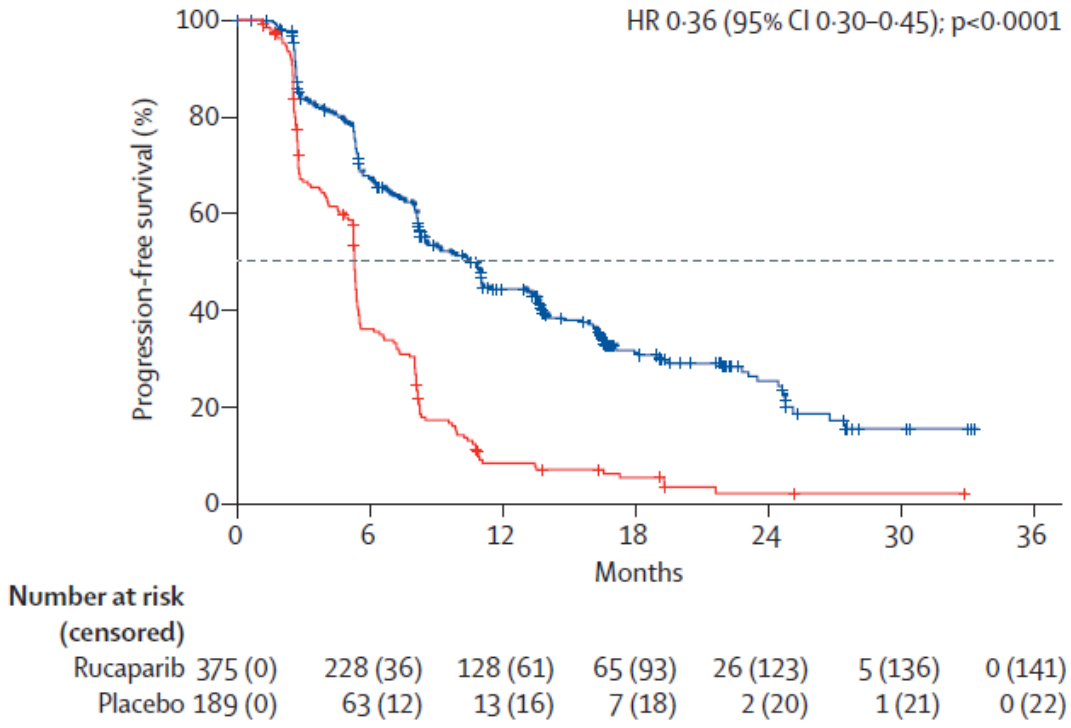
	ITT population		BRCA mutated cohort		Non-BRCA mutant subgroup (post-hoc analysis)	
	Rucaparib (n=375)	PBO (n=189)	Rucaparib (n=130)	PBO (n=66)	Rucaparib (n=245)	PBO (n=123)
INV-PFS						
Median PFS, months (95% CI)	10.8 (8.3 to 11.4)	5.4 (5.3 to 5.5)	16.6 (13.4 to 22.9)	5.4 (3.4 to 6.7)	[redacted]	[redacted]

HR (95% CI) p-value	0.36 (0.30 to 0.45) <0.0001		0.23 (0.16 to 0.34) <0.0001		[redacted]	
IRR-PFS using RECIST v1.1						
Median PFS, months (95% CI)	13.7 (11.0 to 19.1)	5.4 (5.1 to 5.5)	26.8 (19.2 to NR)	5.4 (4.9 to 8.1)	NR	NR
HR (95% CI) p-value	0.35 (0.28 to 0.45) <0·0001		0.20 (0.13 to 0.32) <0·0001		[redacted]	

Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; INV, investigator-assessed; IRR, independent radiology review; ITT, intention-to-treat; NR, not reported; PBO, placebo; PFS, progression-free survival.

* Data extracted from NMA updated model Excel file

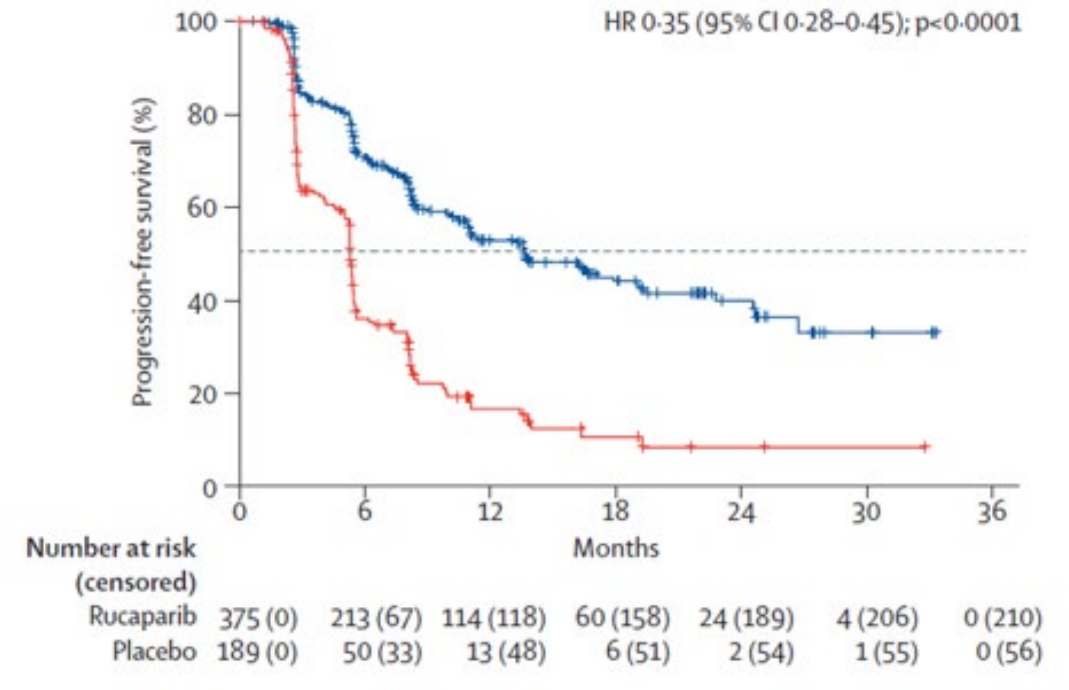
Figure 1. KM estimates of PFS as assessed by the investigator in the ITT population using 15 April 2017 data cut (Reproduced from CS, Figure 7)



Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; KM, Kaplan–Meier; PFS, progression-free survival.

Source: Coleman et al. 2017[3]

Figure 2. Kaplan–Meier estimates of PFS as assessed by IRR in the ITT population using 15 April 2017 data-cut (Reproduced from CS, Figure 10)



Abbreviations: CI, confidence interval; HR, hazard ratio; IRR, independent radiology review; ITT, intention to treat; PFS, progression-free survival

Source: Coleman et al. 2017.[3]

4.3.2 Overall survival

At the 15 April 2017 data-cut, OS data from ARIEL3 were immature, with only 22% of events in the ITT population. The final analysis of OS was on 4 April 2022 and the company reported that OS data were mature with 72.7% events in the ITT population (median follow-up was 77.0 months). The results for OS demonstrate [redacted]. The KM curve for OS in the ITT population is presented in Figure 3 and the OS KM curves for the BRCA mutated and non-BRCA mutated cohorts are presented in Appendix 10.4.3.

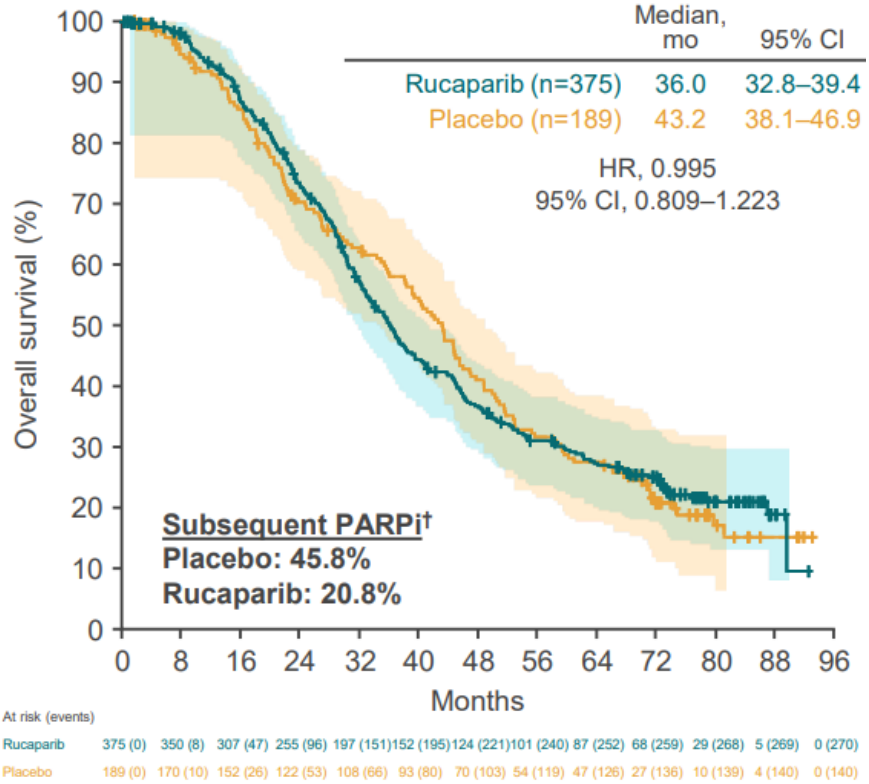
Table 2. Summary of final OS using 4 April 2022 data-cut (Adapted from CS, Table 19)

	ITT population		BRCA mutated cohort		Non-BRCA mutant subgroup (post-hoc analysis)	
	Rucaparib (n=375)	PBO (n=189)	Rucaparib (n=130)	PBO (n=66)	Rucaparib (n=245)	PBO (n=123)
Events, n (%)	270 (72.0)	140 (74.1)	82 (63.1)	48 (72.7)	[redacted]	[redacted]
Median OS, months (95% CI)	36.0 (32.8 to 39.4)	43.2 (38.1 to 46.9)	45.9 (37.7 to 59.6)	47.8 (43.2 to 55.8)	[redacted]	[redacted]
HR (95% CI) p-value	0.995 (0.809 to 1.223) 0.96		0.832 (0.581 to 1.192) 0.32		[redacted]	

Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PBO, placebo.

Source: Coleman *et al.* 2022 (ESGO abstract)[15]; Coleman *et al.* 2022 (ICGS oral presentation)[16]

Figure 3. KM estimates of final OS in the ITT population using 4 April 2022 data-cut (Reproduced from CS, Figure 13)



Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan–Meier; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor.

Source: Coleman et al. 2022 (ICGS oral presentation)[16]

4.3.2.1 OS analysis adjusting for subsequent treatment with PARP inhibitors in placebo patients

The company reported that the impact of subsequent PARP inhibitor therapies in the post-progression phase is a potential source of bias favouring the placebo group.[12] The EAG notes that subsequent PARP inhibitor therapies were non-randomised and [redacted] across treatments arms with [redacted]% in the rucaparib group vs [redacted]% in the placebo group. However, the EAG's clinical experts reported that patients in the UK wouldn't typically have access to more than 1 PARP inhibitor and the EAG notes that if patients haven't received a PARP inhibitor then they would potentially be eligible to receive them as a subsequent treatment in UK clinical practice (conditional

on responding to platinum-based chemotherapy). The EAG therefore does not consider it possible to predict the resulting direction of bias from the subsequent therapies in ARIEL3.

The company also noted that the frequency of subsequent PARP inhibitor use in the placebo arm of ARIEL3 was higher than in the olaparib SOLO2 and niraparib NOVA trials (Table 3).

Table 3. Summary of subsequent anti-cancer treatment regimens across rucaparib, olaparib and niraparib trials (Reproduced from CS, Table 20)

	Patients treated with subsequent PARP inhibitors		Patients treated with any subsequent therapy	
	Intervention	Placebo	Intervention	Placebo
BRCA mutated cohort				
ARIEL3	[redacted]	[redacted]	[redacted]	[redacted]
SOLO2	10.2%	38.4%	66.3%	81.8%
NOVA	26.8%	49.2%	73.9%	76.9%
Non-BRCA mutated cohort				
ARIEL3	[redacted]	[redacted]	[redacted]	[redacted]
SOLO2	Not applicable	Not applicable	Not applicable	Not applicable
NOVA	6.8%	14.7%	74.8%	83.6%

Abbreviations: BRCA, breast cancer gene; PARP, poly (ADP-ribose) polymerase.
Source: ARIEL3 CSR addendum[12]; NICE TA784[17]; NICE TA908[18]

The company conducted exploratory analyses of OS to adjust for the effect of subsequent therapies on OS by excluding patients who received subsequent PARP inhibitors in the placebo arm. The EAG considers this to be a flawed analysis as it involves breaking randomisation. In addition, the EAG is concerned that in the UK, patients who have responded to their most recent course of platinum-based chemotherapy may be eligible for maintenance treatment with a PARP inhibitor and therefore excluding patients who received a subsequent PARP inhibitor from the placebo arm of ARIEL3 would not reflect clinical practice and may bias the results. Therefore, the EAG does not consider this analysis to be relevant to the UK population but notes that it resulted in [redacted] in the rucaparib arm than in the placebo arm within the ITT population (hazard ratio [HR]: [redacted]; CS Figure 14). [redacted]; CS Figure 16).

The company also conducted adjusted analyses of OS for the ARIEL3 BRCA mutated cohort using the Rank-Preserving Structural Failure Time Model (RPSFTM) and the Inverse Probability of Censoring Weighting (IPCW) model to adjust for the effect of placebo patients receiving subsequent PARP

inhibitors. The results of these analyses are presented in Table 4 alongside adjusted OS results for the SOLO2 and NOVA comparator trials. The EAG notes that [redacted] However, the EAG does not consider the company's adjusted analyses of OS to be appropriate for reflecting the use of PARP inhibitors in UK clinical practice.

Table 4. Updated table of additional analysis of OS, adjusting for subsequent treatment with PARP inhibitors in placebo patients (Reproduced from CQ response, Table 16)

	Unadjusted OS analysis based on the study protocol	Intervention vs placebo (RPSFTM)*	Intervention vs placebo (IPCW) HR (95% CI)
BRCA mutated cohort			
ARIEL3	[redacted]	[redacted]	[redacted]
SOLO2	0.740 (0.54 to 1.00)	0.56 (0.35 to 0.97)	Not available†
NOVA	0.85 (0.61 to 1.20)	Not available‡	0.66 (0.44 to 0.99)
Non-BRCA mutated cohort			
ARIEL3	[redacted]	-	-
SOLO2	Not applicable§	Not applicable§	Not applicable§
NOVA	1.06 (0.81 to 1.37)	Not available‡	0.97 (0.74 to 1.26)

Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; OS, overall survival; PARPi, poly (ADP-ribose) polymerase; RPSFTM, Rank-Preserving Structural Failure Time Model; IPCW, Inverse Probability of Censoring Weighting model

*[redacted]) is an acceleration factor for rucaparib vs placebo in the BRCA mutated cohort; 0.56 (0.35 to 0.97) is a HR for olaparib vs placebo in the BRCA mutated cohort

†Only RPSFT analysis was presented for adjustment for the SOLO2 trial

‡Only IPCW adjustment was presented for the NOVA trial

§SOLO2 did not enrol any patients without BRCA mutation

Source: Matulonis *et al.* 2021[19]; Galbraith *et al.* 2020[20]

4.3.3 Health-related quality of life

4.3.3.1 Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18 (FOSI-18)

Health-related quality of life (HRQL) was assessed in ARIEL3 as a secondary endpoint using the Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18 (FOSI-18) using the 15 April 2017 data-cut. Results for this outcome in the *post hoc* non-BRCA mutant cohort were not presented in the CS.

Results for time to worsening (TTW) in the FOSI-18 disease-related symptoms-physical subscale (DRS-P) subscale (defined as ≥4 point decrease) and total score (defined as ≥8 point decrease) suggest [redacted] (Table 5). The company reported that [redacted]

[redacted]

The EAG notes that in accordance with the pre-specified hierarchical step-down procedure used for adjusting for multiplicity testing in ARIEL3, [redacted]

Table 5. Summary of FOSI-18 outcomes using 15 April 2017 data-cut (Reproduced from CS, Table 18)

	ITT population		BRCA mutated cohort	
	Rucaparib (n=375)	PBO (n=189)	Rucaparib (n=130)	PBO (n=66)
Median TTW in DRS-P subscale* months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]		[redacted]	
Median TTW in total score‡ months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]		[redacted]	
[redacted]				

4.3.3.2 EQ-5D visual analogue scale

HRQL was also assessed in ARIEL3 using EQ-5D as an exploratory outcome. The results for least squares mean difference in EQ-5D visual analogue scale score suggested [redacted] using the 15 April 2017 data-cut (Table 6).

Table 6. Percentage change in EQ-5D visual analogue scale from baseline to end of treatment using 15 April 2017 data-cut (Reproduced from CS, Table 24)

	ITT population		BRCA mutated cohort	
	Rucaparib (n=375)	PBO (n=189)	Rucaparib (n=130)	PBO (n=66)
Baseline mean, (SD)	[redacted]	[redacted]	[redacted]	[redacted]

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

Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HRD, homologous recombination deficiency; ITT, intention-to-treat; LS, least squares; PBO, placebo; SD, standard deviation.

Source: ARIEL3 CSR[21]

Additional *post-hoc* analysis of the ARIEL3 data were conducted for HRQL using the utility values derived from the EQ-5D: quality-adjusted progression-free survival (QA-PFS) and quality-adjusted time without symptoms or toxicity (Q-TWiST).[22] The EAG notes these were only conducted for the ITT and BRCA mutated cohorts and the results are not used to inform the ITCs or cost-comparison analysis. The methods and results for these analyses are detailed in the CS and the references supplied with the CS.[23]

4.3.4 *Exploratory endpoints: CFI, TFST, PFS2 and TSST*

Chemotherapy-free interval (CFI), time to first subsequent anti-cancer treatment (TFST), progression-free survival 2 (PFS2) and time to second subsequent anti-cancer treatment (TSST) were all reported to be exploratory endpoints in ARIEL3. At the final analysis (4 April 2022), all four outcomes were mature having reached [redacted], [redacted], [redacted] and [redacted] of events in the ITT population, respectively for CFI, TFST, PFS2 and TSST.[12]

The results from the final analysis demonstrated [redacted] with rucaparib compared to placebo across [redacted] (Table 7).[12] Results for the non-BRCA mutant subgroup were only available for TFST, PFS2 and TSST and the hazard ratios [redacted]. However, the EAG consider that [redacted] for the non-BRCA mutant subgroup based on the text in the CS and the reported hazard ratio. The EAG also notes that the [redacted] in the non-BRCA mutant subgroup compared with the BRCA mutant subgroup.

Table 7. Summary of CFI, PFS2, TFST and TSST using 4 April 2022 data-cut (Adapted from CS, Table's 22 and 23)

	ITT population		BRCA mutated cohort		Non-BRCA mutant subgroup (*post-hoc* analysis)	
	Rucaparib (n=375)	PBO (n=189)	Rucaparib (n=130)	PBO (n=66)	Rucaparib (n=245)	PBO (n=123)
CFI, median (95% CI) [months]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	
TFST, median (95% CI) [months]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	
PFS2, median (95% CI) [months]	20.6 (18.7 to 23.5)	16.3 (14.6 to 17.9)	26.1 (22.8 to 32.8)	18.4 (15.7 to 24.4)	18.0	15.2
HR (95% CI) p-value	0.703 (0.579 to 0.854) <0.01		0.672 (0.480 to 0.941) 0.02		0.713 (0.563 to 0.903) 0.0047	
TSST, median (95% CI) [months]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p-value	[redacted]		[redacted]		[redacted]	

Abbreviations: BRCA, breast cancer gene; CFI, chemotherapy-free interval; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reported; PBO, placebo; PFS2, progression-free survival 2; TFST, time to first subsequent anti-cancer treatment; TSST, time to second subsequent anti-cancer treatment.

Source: ARIEL3 CSR[21]; Summary of clinical efficacy[24]; ARIEL3 CSR addendum[12]; Coleman *et al.* 2022 (ESGO abstract)[15]; Coleman *et al.* 2022 (ICGS oral presentation)[16]

4.3.5 Time to treatment discontinuation

The median time to treatment discontinuation (TTD) is used in the cost-comparison analysis. Results for TTD were reported in the CS as [redacted] (CS Figure 18). [redacted] (Table 8). KM curves for TTD are available in CS Figure 18 (non-BRCA) and the company response to additional clarification questions A16 (BRCA mutant).

Table 8. TTD from ARIEL3

	BRCA mutated cohort*		Non-BRCA mutant subgroup (*post-hoc* analysis)	
	Rucaparib (n=130)	PBO (n=66)	Rucaparib (n=130)	PBO (n=66)
TTD, median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI) p value	[redacted]		[redacted]	

Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; NR, not reported; PBO, placebo; TTD, time to treatment discontinuation.

*Data from company response to additional CQ A16.

4.3.6 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 as assessed by the investigator (INV-PFS) was observed at the 15 April 2017 data cut with the exception of two subgroups with small patient numbers (race unknown and age ≥75 years). The EAG agrees with the company that the results of race unknown and age ≥75 years subgroups are likely to be unreliable due to the small sample size but notes that the HRs are reasonably consistent with the other subgroup analyses summarised in CS Appendix E.

In addition, subgroup analyses of PFS in patients with or without bulky disease and in patients with wild type BRCA (i.e., 'BRCA wild type LOH+', 'BRCA wild type mutant LOH–' and 'BRCA wild type LOH unknown' subgroups) were reported in the CS. However, as these were not reported to be subgroups of interest in the NICE final scope the results are not discussed in this report.

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

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

As discussed in Section 4.1, five trials were included for use in the ITCs following the company's SLR and feasibility assessment: ARIEL3 (rucaparib), SOLO2 and Study 19 (olaparib), and NOVA and NORA (niraparib). The company presented network meta-analyses (NMAs) and matching-adjusted indirect comparisons (MAICs) to enable comparisons of rucaparib with niraparib and olaparib. In addition, the company presented a naïve comparison using the SACT data sets for rucaparib and niraparib in the CS. In the company response to clarification questions (CQs), the preferred base case NMAs

were amended to include only ARIEL3, SOLO2 and NOVA, which the EAG considers to be the most appropriate combination of studies. The EAG also notes that the company used only these three studies in the MAICs. The EAG considers the NMA with the limited network of three studies to be the most reliable source of efficacy data out of the ITC data presented by the company and therefore focuses its critique below on these data. The EAG also notes that the company assessed all three trials as low risk of bias (CS Appendix D, Table 26) and the EAG broadly agrees with the company's assessment.

In the CS, the company presented NMAs that included ARIEL3, SOLO2, Study 19 and NOVA, and in the appendices, sensitivity analyses were provided that also included the NORA study. The company excluded NORA from the primary analyses because it restricted the number of prior lines of chemotherapy to exactly 2 prior lines and because it used a lower starting dose of niraparib (200 mg once daily) for most patients rather than the dose recommended in the Summary of Product Characteristics (SmPC) for niraparib (300 mg once daily). The EAG considers that as the NOVA trial uses the 300mg dose, the company rationale for excluding NORA from the primary NMAs is not unreasonable.

Study 19 was included in the company's original NMAs but the EAG raised concerns around the use of the BRCA population data from this study because BRCA mutation status was determined retrospectively and the BRCA population therefore comprise a *post hoc* subgroup. In addition, the EAG notes that the enrolment criteria in SOLO2 limited inclusion to patients with a confirmed deleterious or suspected to be deleterious BRCA mutation. Olaparib use in the UK is restricted to patients with BRCA mutations and therefore the EAG considers SOLO2 comprises a more suitable source of data than the BRCA subgroup data from a retrospective analysis of Study 19. The company agreed with the EAG that SOLO2 provides the most robust source of data on olaparib and thus updated its preferred base case NMA to remove Study 19.

The company provided a summary of the methods of the five trials included in the NMAs in the CS Table 29 and the baseline characteristics for the BRCA and non-BRCA populations of the three studies in the primary NMAs are provided in Table 29 and Table 30 of Appendix 10.3 of this report.[3, 8-11] The EAG notes that there is some clinical heterogeneity across studies with regard to both study design and patient population; the differences between the studies included in the ITC are summarised in Table 9.

In terms of the three studies in the primary base case NMAs, all were randomised, double-blind, placebo-controlled, multicentre, Phase III trials. For rucaparib, the BRCA population data from ARIEL3 comprise a mix of patients with germline and somatic mutations, whereas the BRCA population data for niraparib from NOVA and for olaparib from SOLO2 comprise only of patients with germline BRCA mutations. In addition, the EAG notes that the non-BRCA population data in NOVA (n = 350) includes 47 patients with somatic germline BRCA mutations (according to Supplemental Figure A1 from Mirza *et al.* 2016) and thus does not exclusively comprise of non-BRCA patients. As discussed in Section 3.3, the impact of these differences between the studies in the NMAs for the BRCA and non-BRCA populations is unknown but the EAG notes that germline mutations account for the majority of BRCA mutations in this population in UK clinical practice.

A further difference between ARIEL3 and the other studies in the NMAs was that ARIEL3 included endometrial and serous ovarian cancers, whereas the other studies restricted to just serous ovarian cancers. However, the EAG notes that over 90% of patients had serous histology in ARIEL3 and the EAG's clinical experts reported that serous carcinomas account for the majority of high-grade ovarian cancer. Also, similar to for ARIEL3 and based on clinical expert advice, the EAG considers the patients in NOVA and SOLO2 likely to comprise a slightly younger population with a slightly better ECOG performance status than patients eligible for rucaparib in clinical practice in England.

Table 9. Overview of key differences in studies included in the ITCs (Reproduced from CS, Table 28)

	ARIEL3	SOLO2	Study 19	NOVA	NORA
Study design	Phase III	Phase III	Phase II	Phase III	Phase III
Patient population	High-grade serous or endometrioid OC Somatic and germline BRCA mutated and non-BRCA mutated OC*	High-grade serous or endometroid OC Germline BRCA mutated OC*	High-grade serous OC Somatic and germline BRCA mutated and non-BRCA mutated OC*	High-grade serous OC Germline BRCA mutated and non-germline BRCA mutated OC*	High-grade serous OC (or no histological restrictions for patients with germline BRCA mutation) Germline BRCA mutated and non-germline BRCA mutated OC*
Stratification	Used BRCA status as one stratification factor in the randomisation process	BRCA status was not stratified in randomisation because all patients had germline BRCA mutation	Used ancestry (Jewish vs. non-Jewish) as a proxy of BRCA status in the stratified randomisation	BRCA status was not stratified in randomisation because results were reported separately for the germline BRCA mutation cohort and the non-germline BRCA mutation cohort	Used germline BRCA status as one stratification factor in the randomisation process
Dosing	Rucaparib in tablet formulation was dosed at 1200mg/day	Olaparib in tablet formulation was dosed at 600mg/day	Olaparib in capsule formulation was dosed at 800mg/day	Niraparib in capsule formulation was dosed at 300mg/day	Niraparib in capsule formulation was dosed at 200mg/day or 300mg/day depending on weight and platelet count†
OS maturity	Mature with 77 months follow-up	Mature with 65.7 months follow-up with olaparib and 64.5 months with placebo	Mature with 78.0 month follow-up	Mature with median follow-up of >75 months	Immature data with no more than 15.8 months follow-up

Abbreviations: BRCA, BReast CAncer gene; CR, complete response; OC, ovarian cancer; OS, overall survival

*The ARIEL3 and Study 19 BRCA mutated cohorts included patients with somatic and germline BRCA mutations, while the SOLO2, NOVA and NORA BRCA mutated cohorts included only patients with germline BRCA mutations.

[†]The niraparib starting dose was 300mg/day for patients with bodyweight ≥77 kg and platelet count ≥150 x 10^3mcl; the niraparib starting dose was 200mg/day for patients with bodyweight <77 kg or platelet count <150 x 10^3mcl

Source: Coleman *et al.* 2017[3]; Ledermann *et al.* 2012[25]; Pujade-Lauraine *et al.* 2017[8]; Mirza *et al.* 2016[9]; Wu *et al.* 2021[11]; ARIEL3 CSR addendum[12]; Poveda *et al.* 2021[26]; Friedlander *et al.* 2018[27]; Matulonis 2023[28]

4.4.2 Network meta-analysis (NMA)

The company reported that the methods used for conducting the NMAs followed those recommended by NICE DSU TSD 2.[29] The EAG notes that Bayesian fixed effects NMAs were used for all outcomes and considers this to be appropriate given the limited number of studies for each treatment in the networks. The company conducted the NMAs using R (version 4.3.1) and OpenBUGS through the 'R2OpenBUGS' package (version 3.2.1). Due to time constraints the EAG has been unable to fully validate the NMAs but the EAG has validated the results for the key outcomes of OS and PFS for rucaparib versus niraparib and obtained similar results to the company (a minor error was identified in the reporting of IRC-PFS results for the BRCA mutated cohort and the results have been amended by the EAG in Table 10). It should also be noted that the EAG was unable to validate some of the data used in the NMAs as the source was unclear, for example, the IRC-PFS data for the non-BRCA cohort of ARIEL3.

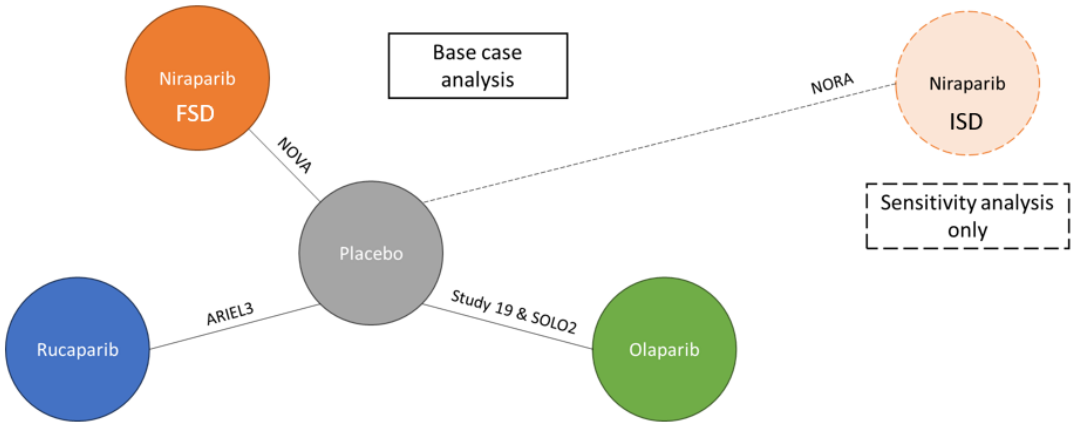
The company considered there to be insufficient evidence against the assumption of proportional hazards (PH) between active treatments and placebo for OS, INV-PFS, TSST and PFS2 across all investigated populations (a summary of the PH assessments is presented in CS Appendix D Table 19). The EAG notes that it is also reported in the CS appendices that, "*There are some signals that indicate proportionality may not hold for a small subset of some outcome/study combinations; however, these were deemed inconclusive*". The EAG notes that this applies only to the BRCA mutated population and affects OS from ARIEL3 and INV-PFS from SOLO2.

The company conducted NMAs for the BRCA and non-BRCA populations for the outcomes of INV-PFS, IRC-PFS, OS, PFS2, TSST, and TTD. The EAG notes that TTD data were only available for rucaparib and olaparib (BRCA population), and analysis of TTD for rucaparib versus niraparib was not possible in either BRCA or non-BRCA populations due to the absence of suitable data from NOVA for niraparib.

The company did not conduct NMAs for crossover adjusted OS as they did not consider it appropriate to conduct NMAs using the IPCW adjusted OS data from NOVA or the RPSFTM adjusted OS data available from SOLO2 (company response to clarification question A4). The EAG notes that there are limitations in any analyses with crossover adjustment but nevertheless considers it would have been useful to see the outcomes of these additional analyses using a consistent method of OS adjustment across the trials.

Figure 4 shows the network diagram for the five studies included in the company's NMAs but it should be noted that the company base case NMA was revised in their response to clarification questions to exclude Study 19. The EAG notes that the network contains no closed loops and therefore assessment of incoherence was not feasible.

Figure 4. Network diagram (Reproduced from CS, Figure 23)



Abbreviations: FSD, fixed starting dose; ISD, individualised starting dose.

Note: Only ARIEL3, SOLO2 and NOVA were included in the base case analysis; NORA was included in the sensitivity analysis and Study 19 was excluded from the network at the clarification stage.

4.4.2.1 Results

The results of the NMAs from the network of ARIEL3, SOLO2 and NOVA are summarised in Table 10. The company highlighted that [redacted] in the ARIEL3 trial were treated with subsequent PARP inhibitors compared to SOLO2 and NOVA and may have led to bias in the results. However, the EAG does not consider it possible to predict the resulting direction of bias from the use of subsequent PARP inhibitors and the EAG notes that if patients haven't received a PARP inhibitor then they would potentially be eligible to receive one as a subsequent treatment in UK clinical practice (conditional on responding to platinum-based chemotherapy). The company also flagged concerns around the potential impact of the use of immature PFS2 data from SOLO2 introducing bias to the results of the NMA and the EAG agrees that the results of PFS2 from the BRCA population, for rucaparib versus olaparib, should be interpreted with caution.

The EAG notes [redacted] in all of the results from the NMAs, as might be expected from such a sparse network. However, the point estimates for rucaparib compared to niraparib, [redacted]. Based on these data the EAG doesn't consider it unreasonable to conclude that rucaparib and niraparib have broadly similar efficacy. [redacted] However, the EAG notes that for a cost-comparison, the company only needs to be able to demonstrate convincing evidence of similar efficacy to one previously approved NICE technology according to the NICE health technology evaluation manual.[30] The EAG considers this threshold to have been met with rucaparib and niraparib.

Table 10. NMA outcomes, BRCA mutated and non-BRCA mutated cohorts (base case network, updated after excluding Study 19 and adding PFS-IRC and TTD) (Adapted from company response to clarification questions, Table 1)

	Rucaparib vs olaparib*	Rucaparib vs niraparib†
BRCA mutated cohort		
INV-PFS, HR (95% CI)	[redacted]	[redacted]
IRC-PFS, HR (95% CI)	[redacted]‡	[redacted]‡
OS, HR (95% CI)	[redacted]	[redacted]
PFS2, HR (95% CI)	[redacted]§	[redacted]
TSST, HR (95% CI)	[redacted]	[redacted]
TTD‖, HR (95% CI)	[redacted]	[redacted]
Non-BRCA mutated cohort		
INV-PFS, HR (95% CI)	[redacted]	[redacted]
IRC-PFS, HR (95% CI)	[redacted]	[redacted]
OS, HR (95% CI)	[redacted]	[redacted]
PFS2, HR (95% CI)	[redacted]	[redacted]
TSST, HR (95% CI)	[redacted]	[redacted]
TTD§, HR (95% CI)	[redacted]	[redacted]

Abbreviations: BRCA, BReast CAncer gene; CI, confidence interval; HR, hazard ratio; INV-PFS, investigator-assessed progression-free survival; NMA, network meta-analysis; OS, overall survival; PFS2, progression-free survival on a subsequent line of treatment; TSST, time to start of second subsequent therapy, TTD, time to treatment discontinuation

Note: ARIEL3, Study 19, SOLO2 and NOVA were included in the base case analysis.

* Olaparib is a relevant comparator in the BRCA mutated cohort only.

† Niraparib is a relevant comparator in both the BRCA mutated and non-BRCA mutated cohorts.

‡, The EAG considers the results for IRC-PFS presented by the company were reported in the incorrect columns in the company response to clarification questions Table 1 and so the EAG has corrected the reporting here. The data for IRC-PFS in the BRCA mutated cohort in this table comprise the EAG validated results.

§ Only immature PFS2 data were available in SOLO2 and mature PFS2 was not reported for that trial.

ǁ Death event was treated as TTD event.

4.4.3 Matching-adjusted indirect comparison (MAIC)

The company reported that they conducted MAICs in addition to the NMAs because the impact of other potential effect modifiers (e.g. differences in response to latest platinum-based chemotherapy) could not be addressed through NMA. However, the EAG considers the company NMAs to provide a more robust analysis of the comparative efficacy of rucaparib versus niraparib and versus olaparib than the MAICs and notes that the NMAs maintain randomisation within the individual trials. The EAG critique of the company's MAICs is provided in Appendix 10.5 but in summary [redacted]

4.5 Systemic Anti-Cancer Therapy (SACT)

A total of 887 patients received treatment with rucaparib through the CDF between 11 October 2019 and 31 July 2022 and were included in the SACT analysis.[31] The company conducted a comparison of these SACT data with those available for 1,016 patients who received treatment with niraparib through the CDF between 1 June 2018 and 30 November 2019 and included in a SACT analysis for niraparib.[32]

The EAG notes that for both rucaparib and niraparib there were limited data for the BRCA mutated cohort (n=70 in the rucaparib data set; n=157 in the niraparib data set) compared to for the non-BRCA cohort (n=817 in the rucaparib data set; n=859 in the niraparib data set). In addition, there were a large number of differences in the patient characteristics between the rucaparib and niraparib SACT cohorts, which limits the conclusions of any analyses of the two datasets. However, the EAG is in agreement with the company's conclusions that a naïve comparison of rucaparib and niraparib based on SACT data [redacted]. In addition, the EAG notes that the estimated HRs from the company's analyses of OS and TTD using the SACT data demonstrated no statistically significant difference for both the BRCA mutated and non-BRCA

mutated cohorts. Please see Appendix 10.6 for a detailed critique of the SACT data and the results from the company's analyses.

4.6 Adverse events

Safety data analyses in ARIEL3 were reported in the CS using database locks from 15 April 2017, 31 December 2017 and 4 April 2022 (final analysis) with results tables presented in the CS Section B.3.10. The EAG notes that the safety profile of rucaparib [redacted] in the overall safety population (372 patients in the rucaparib group and 189 patients in the placebo group). However, the company did not provide a numerical comparison of adverse events for rucaparib versus niraparib or olaparib in the CS. The EAG notes that the company included AEs in the cost-comparison for rucaparib versus niraparib and this is discussed further in Section 5.4.2. The AEs included in the economic analysis comprised those that affected >5% of patients in any treatment arm in ARIEL3 (anaemia, ALT/AST increased, neutropenia, asthenia/fatigue, thrombocytopenia/platelet count decreased) plus one recommended by a UK clinical expert (nausea & vomiting) and a further one for consistency with the niraparib technology appraisal, TA528 and also TA784 (hypertension). The EAG has created a summary table for these AEs to enable a naïve comparison but it should be noted that the AE definitions may vary between the trials and so caution should be used in drawing any conclusions.

In summary, the EAG notes that the proportion of patients experiencing any treatment-emergent AEs (TRAEs) or treatment-related AEs [redacted] between rucaparib and niraparib. The proportion of patients with at least one Grade 3 or higher TEAE was [redacted] with rucaparib compared to niraparib suggesting [redacted] safety profile for rucaparib. [redacted] there were 0 treatment-related TEAE deaths with niraparib. The treatment-related AEs that led to death [redacted] Olaparib was also associated with deaths due to treatment-related AEs in 3% of patients.

In terms of the AEs used in the company's economic analysis, rucaparib was associated with [redacted] than niraparib, [redacted] (Table 11). The EAG considers it important to highlight that Grade 3 or above raised ALT/AST AEs were not included in the economic modelling of

the NICE appraisals for niraparib (TA528) or olaparib (TA908) and safety data from ARIEL3 demonstrate that rucaparib is associated with a [redacted] proportion of patients with Grade 3 or above combined ALT/AST TEAEs compared with niraparib in NOVA.

The EAG's clinical experts reported that, while there are differences in the individual AEs for the PARP inhibitors, there were no major safety concerns regarding differences in AEs between rucaparib, niraparib and olaparib. The company also highlighted that some differences in PARP inhibitor safety profiles are reflected in the Summary of Product Characteristics including, "*warnings of photosensitivity with rucaparib, pneumonitis with olaparib, and hypertension, including hypertensive crisis with niraparib*". Overall, the EAG does not consider it to be unreasonable to assume the safety profiles of rucaparib and niraparib are broadly similar.

Table 11. Summary of AE data for ARIEL3, NOVA and SOLO2

	ARIEL3		NOVA*		SOLO2†	
	Rucaparib (N = 372)	Placebo (N = 189)	Niraparib (n = 367)	Placebo (n = 179)	Olaparib (N = 195)	Placebo (N = 99)
Any AE	372 (100.0%)	182 (96.3%)	367 (100%)	171 (95.5%)	194 (99.5%)	94 (94.9%)
Any treatment-related AE	[redacted]	[redacted]	358 (97.5%)	127 (70.9%)	NR	NR
Number of Patients With at Least One CTCAE Grade 3 or Higher TEAE	233 (62.6%)	31 (16.4%)	272 (74.1%)	41 (22.9%)	90 (46.2%)	19 (19.2%)
One or more TEAEs leading to death	9 (2.4%)	2 (1.1%)	0	0	8 (4%)	0
One or more treatment-related TEAEs leading to death	[redacted]	[redacted]	0	0	6 (3%)	0
Grade ≥3 TEAEs included in the cost-comparison analysis						
Anaemia/haemoglobin decreased	[redacted]	[redacted]	93 (25.3%)	0	41 (21%)	2 (2%)
ALT/AST increased	[redacted]	[redacted]	4 (1.1%)§,‖	2 (1.1%)§‖	2 (1.0%)	1 (1%)
Neutropenia/neutrophil count decreased	[redacted]	[redacted]	72 (19.6%)	3 (1.7%)	14 (7%)	4 (4%)
Asthenia/Fatigue	[redacted]	[redacted]	30‡ (8.2%)	1‡ (0.6%)	11 (6%)	2 (2%)
Thrombocytoenia/platelet count decreased	[redacted]	[redacted]	124 (33.8%)	1 (0.6%)	4 (2.1%)	1 (1%)
Hypertension	[redacted]	[redacted]	30 (8.2%)	4 (2.2%)	0	1 (1.0%)
Vomiting	[redacted]	[redacted]	7 (1.9%)	1 (0.6%)	5 (2.6%)	1 (1.0%)

Nausea	[redacted]	[redacted]	11 (3.0%)	2 (1.1%)	6 (3%)	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment emergent adverse event.

* Data from TA528 committee papers[33]

† Data from committee papers for TA908[4] & Poveda *et al.* 2021[26]

‡ Data only reported for fatigue

§ Percentage calculated by EAG.

‖ Data from FDA highlights of prescribing information for Zejula[34]

4.7 Conclusions of the clinical effectiveness section

The ARIEL3 randomised controlled trial (RCT) comparing rucaparib vs placebo (N=564) was used in the CS to provide data for the efficacy and safety of rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer. The EAG broadly agreed with the company's quality assessment of ARIEL3 being at low risk of bias for all domains.

The EAG's clinical experts considered ARIEL3 to be a reasonable reflection of the eligible patient population in UK clinical practice (Section 3.1) and that the dosing regimen of rucaparib was broadly consistent with clinical practice in England (Section 3.2). However, the EAG notes that the subsequent treatments used in ARIEL3 do not align with clinical practice in England as patients would not usually receive a PARP inhibitor as a subsequent therapy if they had already received one in the UK. The EAG therefore is concerned that the use of PARP inhibitors as subsequent treatments in ARIEL3 (rucaparib arm: [redacted]; placebo arm: [redacted]) may impact on the results for the analyses of OS.

The EAG notes that the key outcomes of relevance are OS and PFS, with OS results from ARIEL3 now available from the final analysis. The results from the final analyses of OS in ARIEL3 for rucaparib versus placebo demonstrate [redacted] the EAG also notes that the primary endpoint in ARIEL3 was investigator assessed progression-free survival (INV-PFS), and rucaparib significantly reduced the risk of disease progression or death compared with placebo in patients with platinum-sensitive ovarian cancer who had responded to platinum-based chemotherapy at the 15 April 2017 data cut in the ITT population and BRCA mutant subgroup. The hazard ratio for the non-BRCA subgroup suggested [redacted]

In the CS, the company has provided analysis of clinical efficacy data for rucaparib versus niraparib, and also for rucaparib versus olaparib. The marketing authorisation and NICE approval for olaparib restricts its use to only BRCA mutation positive patients, whereas rucaparib and niraparib have marketing authorisation for use in both BRCA, and non-BRCA patients. The EAG's clinical experts reported that all three treatments (rucaparib, niraparib and olaparib) are currently used in England and the EAG's clinical experts did not consider there to be any notable difference between rucaparib, niraparib and olaparib in terms of efficacy or safety aside from the limitations around the eligible patient populations (in particular, olaparib use is limited to BRCA mutant patients).

There are no randomised controlled trials (RCTs) directly comparing rucaparib with niraparib or olaparib and so the company conducted various indirect treatment comparisons (ITCs) including network meta-analyses (NMAs) and matching adjusted indirect treatment comparisons (MAICs) using the ARIEL3 trial for rucaparib, the NOVA trial for niraparib and the SOLO2 trial for olaparib. The EAG considers these trials to match the population in the NICE final scope and decision problem well, and considers the NMAs to be the most robust source of efficacy data for rucaparib versus niraparib, and rucaparib versus olaparib, in the absence of head-to-head RCT data. There were some differences in trial baseline characteristics noted (Section 4.4.1), but the EAG's clinical experts did not consider these differences to be substantial enough to impact outcomes for rucaparib, niraparib or olaparib.

The EAG notes [redacted] for rucaparib versus niraparib or rucaparib versus olaparib. The point estimates for rucaparib compared to niraparib [redacted]. Based on these data and the advice of clinical exerts, the EAG doesn't consider it unreasonable to conclude that rucaparib and niraparib have broadly similar efficacy. [redacted] However, the EAG notes that for a cost-comparison, the company only needs to be able to demonstrate convincing evidence of similar efficacy to one previously approved NICE technology according to the NICE health technology evaluations manual. The EAG considers this threshold to have been met with rucaparib and niraparib.

With regards safety, it should be noted that there was no statistical comparison of adverse effects between the treatments reported in the CS. The EAG also considers it important to highlight that Grade 3 or above raised ALT/AST AEs were not included in the economic modelling of the NICE appraisals for niraparib (TA528) or olaparib (TA908), and safety data from ARIEL3 demonstrate that rucaparib is associated with a [redacted] proportion of patients with Grade 3 or above combined ALT/AST TEAEs compared with niraparib in NOVA. However, the EAG's clinical experts reported that, while there are differences in the individual AEs for the PARP inhibitors, there were no major safety concerns regarding differences in AEs between rucaparib, niraparib and olaparib. Overall, based on naïve comparison and the advice of the EAG's clinical experts, the EAG does not consider it to be unreasonable to assume the safety profiles of rucaparib and niraparib are broadly similar.

5 Summary of the EAG's critique of cost-comparison evidence submitted

The company developed a cost-comparison analysis which compared rucaparib against niraparib in 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. Based on the assessment in Section 4, the External Assessment Group (EAG) agrees with the company that the two treatments have similar clinical efficacy.

Table 12 presents the company's base case post clarification by breast cancer (BRCA) gene mutation status (BRCA and non-BRCA subgroups). The results reported in this document include a proposed patient access scheme (PAS) discount for rucaparib of [redacted] and list price for niraparib. Several parameters and assumptions have been varied by the company and the EAG in scenario analyses, and based on the list price for niraparib and the PAS discount for rucaparib, rucaparib continues to be cost saving in each instance.

A confidential PAS discount is available for niraparib. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

The key categories where the company estimates differences between rucaparib and niraparib are drug acquisition costs (Section 5.4.1), adverse event costs (Section 5.4.2) and monitoring resource use for progression-free patients (Section 5.4.3).

Table 12. Disaggregated company's base case results (post clarification)

Costs	BRCA subgroup		Incremental costs	Non-BRCA subgroup		Incremental costs
	Niraparib	Rucaparib		Niraparib	Rucaparib	
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCA, BReast CAncer gene

5.1 Population

The population considered by the company for this cost-comparison technology appraisal is based on the marketing authorisation for rucaparib, 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. See Section 3.1 for further details on the population. The cost analysis is split into two subgroups based on BRCA gene mutation status (BRCA and non-BRCA subgroups). The EAG considers the population and the subgroups for the cost-comparison analysis are appropriate.

5.2 Interventions and comparators

The intervention and comparator considered in the cost-comparison analysis are rucaparib (intervention) and niraparib (comparator) for the both the BRCA and non-BRCA subgroups. These are in line with the NICE final scope.[7]

The dosing regimen for rucaparib and niraparib is presented in Table 13. Both rucaparib and niraparib are treatments that are given until disease progression or unacceptable toxicity.[35, 36] Estimation of drug acquisition costs are presented in Section 5.4.

Table 13. Treatment dosing regimen

Treatment	Total daily dose	Dose regimen
Rucaparib	1200 mg	2 x 300 mg tablets (600 mg), taken orally twice daily
Niraparib	300 mg	3 x 100mg capsules (300 mg), taken orally once daily

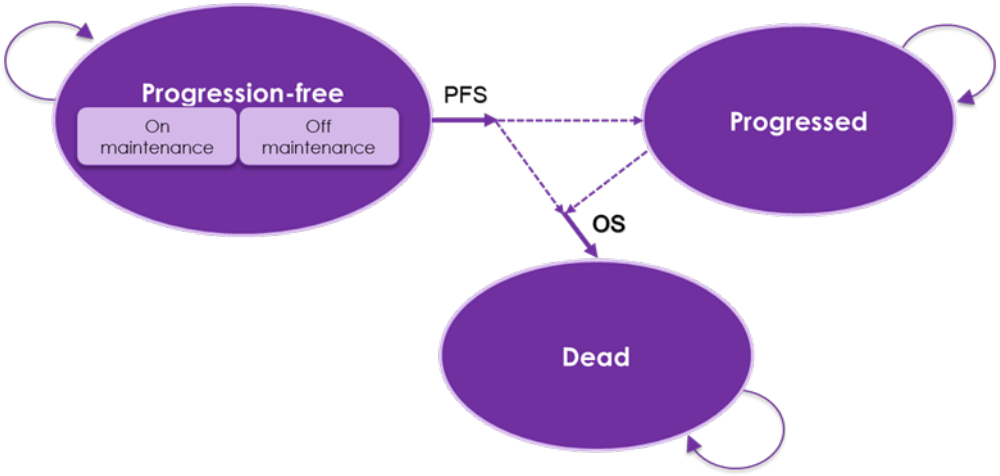
Abbreviations: mg, milligram.

5.3 Modelling approach and model structure

For the cost-comparison analysis, the company adapted the partitioned survival model (PSM) that was submitted for the original single technology appraisal (STA) of rucaparib as maintenance treatment 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 (TA611).[2]

The PSM includes three main health states: progression-free, progressed and dead. The progression-free health state is further sub-divided into progression-free on maintenance treatment and progression-free off maintenance treatment. Figure 5 presents the company model schematic.

Figure 5. Model structure (Reproduced from Figure 37 of the company submission)



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

All patients enter the model in the progression-free health state and can be either progression-free and on maintenance treatment or progression-free and off maintenance treatment if they are experiencing unacceptable toxicity. Patients 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 of progression-free survival (PFS) (used to model the progression free health state) and overall survival (OS). Time to treatment discontinuation (TTD) data are 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 cycle length of one month was implemented in the model with half cycle correction applied. The model time horizon was set to 30 years, which the EAG considers is appropriate. The perspective of the analysis is based on the UK national health service (NHS), with costs discounted using a rate of 3.5% as per the NICE reference case.[30]

Based on the assumption of similar clinical effectiveness between rucaparib and niraparib, PFS and OS are assumed to be equal between treatments. The main purpose of the company's model was to estimate long-term TTD for each treatment in order to estimate drug acquisition costs and associated cost-differences with being on or off treatment (such as costs of adverse events and

differences in resource use). As such, in this report the EAG does not focus on the appropriateness of the company's approach to long-term PFS and OS informing the model, but instead focuses on TTD and other aspects of the model where costs differences are assumed between rucaparib and niraparib. Nonetheless, a summary of the company's approach to PFS and OS and the EAG's assessment can be found in Appendix 10.8.

5.3.1 EAG critique

According to the NICE health technology evaluation manual, for cost-comparison analysis, "*the effects of the intervention and comparator(s) on health outcomes are captured in the clinical-effectiveness evidence and are not included in the cost-comparison analysis*".[30] Therefore a model structure is not needed as the cost-comparison analysis should only focus on cost differences between technologies.

The inclusion of PFS in the model affects costs indirectly as TTD is capped to PFS and PFS off-treatment resource use differs to PFS on-treatment resource use (discussed in Section 5.4.3). While the EAG is satisfied with how PFS has been modelled (see Appendix 10.8, TTD and resource use are the key drivers of cost in the model. Based on the SACT TTD data provided in the company submission for niraparib and rucaparib, and supported by advice from the EAG's clinical experts, TTD appears to be similar for both treatments. Therefore, the EAG considers that equal TTD for both treatments is a clinically plausible assumption and this is discussed further in Section 5.4.

Furthermore, the EAG does not consider that resource use differs for patients on or off treatment. The EAG's clinical experts deemed that treatment discontinuation is driven primarily by disease progression and so it is unlikely that many patients will be progression-free and off treatment and those that are will likely still need the same resource use as progression-free patients on treatment. The issue of resource use is discussed further in Section 5.4.3.

As such, given the company has assumed that PFS and OS are the same for rucaparib and niraparib in the model, and the EAG considers that TTD is likely to be the similar between the two treatments, with no difference in resource use for patients who are progression free irrespective of treatment status, the presentation of a PSM is considered by the EAG to be unnecessary. Instead, the EAG considers that the cost-comparison analysis simplifies down to the extrapolation of TTD to estimate long-term costs differences due to drug acquisition and adverse events, for rucaparib and niraparib, as everything else assumed by the EAG to be equal between the two treatments.

5.4 Resource use and costs

Costs considered for the cost-comparison analysis include drug acquisition, management of adverse events (AEs), monitoring, subsequent therapies, and end of life. Generally, the source of data for resource use and costs are sourced from previous technology appraisals for rucaparib (TA611)[2] and niraparib (TA528 and TA784),[5, 33] which the EAG considers is appropriate.

5.4.1 Drug acquisition costs

The list price of rucaparib is £3,562 per pack of 60 tablets (300 mg, 250 mg or 200 mg). In their clarification response, the company updated their base case to include a proposed patient access scheme (PAS) discount for rucaparib of [redacted], resulting in a cost per pack of [redacted] (or [redacted] per tablet) and this has been included in all analyses presented in this report. The discounted drug acquisition cost for one month of rucaparib treatment, based on a dose of 600 mg twice per day (four tablets per day) is [redacted].

The list price of niraparib is £6,750 per pack of 84 x 100 mg capsules (or £80.36 per capsule). The drug acquisition cost for one month of niraparib treatment, based on a once daily dose of 300 mg (three capsules per day) is £7,337.61. A confidential PAS discount is available for niraparib. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

To estimate time on maintenance treatment and thus drug acquisition costs, Kaplan-Meier (KM) TTD data from ARIEL3 for rucaparib and NOVA for niraparib were extrapolated independently using standard parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma). The company selected the base case TTD curves based on goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, as well as visual inspection of the curves against the observed KM data. Table 14 summarises the company's approach to TTD for rucaparib and niraparib for both the BRCA and non-BRCA subgroups. Figure 6 and Figure 7 presents the company base case extrapolated TTD curves.

Table 14. Summary of company's base case approach to time on maintenance treatment

TTD	BRCA subgroup		Non-BRCA subgroup	
	Rucaparib	Niraparib	Rucaparib	Niraparib
Source of data	ARIEL3	NOVA*	ARIEL3	NOVA*

Curve choice	Exponential	Exponential	Log-logistic	Exponential
% on treatment @ 10 years	[redacted]	[redacted]	[redacted]	[redacted]
Observed median (years)	[redacted]	[redacted]	[redacted]	[redacted]
Modelled median (years)	[redacted]	[redacted]	[redacted]	[redacted]
Modelled mean (years)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCA, BReast CAncer gene; TTD, time to treatment discontinuation

* NOVA TTD data digitised from the committee papers for TA528.

Figure 6. Modelled time to treatment discontinuation – BRCA subgroup

Abbreviations: BRCA, BReast CAncer gene; KM, Kaplan-Meier; MTN, maintenance; TTD, time to treatment discontinuation.

Figure 7. Modelled time to treatment discontinuation – BRCA subgroup

Abbreviations: BRCA, BReast CAncer gene; KM, Kaplan-Meier; MTN, maintenance; TTD, time to treatment discontinuation.

In addition to the trial TTD data, the company provided TTD data for rucaparib and niraparib from the Systemic Anti-Cancer Therapy (SACT) database and provided scenarios with these data extrapolated using standard parametric models (see Sections, B.4.2.1.2.2 and B.4.2.1.2.4 of the CS). The SACT database is a real-world database that collected data on 887 NHS patients who received treatment with rucaparib between 11 October 2019 and 31 July 2022 and data on 1,016 NHS patients who received treatment with niraparib between 1 June 2018 and 30 November 2019.

Table 15 presents the observed median TTD for rucaparib and niraparib and Figure 8 and Figure 9 presents the KM data for the BRCA and non-BRCA subgroups, based on SACT data. The EAG considers that the SACT data demonstrates that TTD for the two treatments are very similar and in particular for the non-BRCA subgroup, TTD KM curves overlap for the two treatments. As such, the EAG considers that it is more conservative to assume that TTD is the same for both treatments, which the EAG's clinical experts advised is a clinically plausible assumption, and this is discussed further in Section 5.4.1.1.

Table 15. Observed median TTD from the SACT database

Treatment	Observed median TTD (weeks)	
	BRCA subgroup	Non-BRCA subgroup
Rucaparib	[redacted]	[redacted]

Niraparib	[redacted]	[redacted]

Abbreviations: BRCA, BReast CAncer gene; SACT, Systemic Anti-Cancer Therapy; TTD, time to treatment discontinuation.

Figure 8. Time to treatment discontinuation (SACT database) – BRCA subgroup

Abbreviations: BRCA, BReast CAncer gene; KM, Kaplan-Meier; MTN, maintenance; SACT, Systemic Anti-Cancer Therapy; TTD, time to treatment discontinuation

Figure 9. Time to treatment discontinuation (SACT database) – non-BRCA subgroup

Abbreviations: BRCA, BReast CAncer gene; KM, Kaplan-Meier; MTN, maintenance; SACT, Systemic Anti-Cancer Therapy; TTD, time to treatment discontinuation

For the base case, the company has assumed that relative dose intensity (RDI) for both rucaparib and niraparib is 100%, and provided a scenario using a RDI of 65% for niraparib (100% RDI maintained for rucaparib) based on NOVA.[5]

5.4.1.1 EAG critique

A fundamental issue with the company's cost-comparison analysis is the estimation that TTD is based on a naïve comparison of extrapolated TTD KM curves for niraparib based on NOVA and rucaparib based on ARIEL3 rather than using a formal indirect treatment comparison (ITC). The issue that results from this inappropriate comparison is that TTD is estimated to be longer for niraparib compared to rucaparib. During the clarification stage, the EAG requested the company to explore a network meta-analysis (NMA) and matched-adjusted indirect comparison (MAIC) of TTD for niraparib and rucaparib to obtain a comparable TTD for the two treatments. The company explained that a NMA and MAIC for TTD was not feasible as KM data from NOVA were digitised from TA528, which meant that the resolution of the KM curve was poor and no data on patients at risk over time were available. Additionally, a hazard ratio (HR) for TTD from NOVA is not publicly available. However, the company stated that the digitised TTD KM curve for niraparib from TA528 were sufficient to perform an extrapolation to inform the model.

Based on the SACT TTD data provided in the company submission for niraparib and rucaparib, and supported by advice from the EAG's clinical experts, TTD appears to be similar for both treatments. For the non-BRCA subgroup, SACT TTD KM curves overlap for the two treatments, although for the BRCA subgroup, the SACT TTD KM curves for rucaparib and niraparib cross at around 48 weeks. The EAG considers that there is no underlying biological reason why TTD would differ based on BRCA status. Furthermore, the EAG's clinical experts advised that in their experience of using both drugs they did not consider there are clinically meaningful differences in treatment discontinuation.

As SACT data suggest TTD is similar and the EAG's clinical experts advised that time on maintenance treatment would be unlikely to differ between the treatments, the EAG considers that equal TTD for both treatments is a clinically plausible assumption. During the clarification stage, the EAG requested the company to provide a scenario where TTD for niraparib was equal to rucaparib. The company provided the scenario (results presented in Section 6.1.1), which substantially reduced incremental costs for the BRCA subgroup (and to a lesser extent for the non-BRCA subgroup), but rucaparib

remained cost saving. The EAG has included the assumption of equal TTD for treatments in its preferred base case, presented in Section 6.2.2.

As a secondary issue, during the clarification stage the EAG requested RDI from ARIEL3 for rucaparib but the company this was not available. However, in ARIEL3 [redacted] of patients in the rucaparib had a dose reduction and of those [redacted] had one dose reduction. Thus, the EAG is unclear why RDI from ARIEL3 could not be obtained by the company. In the company submission, a scenario was presented exploring 65% RDI for niraparib and maintained 100% RDI for rucaparib. The niraparib RDI scenario substantially reduced the incremental costs, but rucaparib remained cost saving. However, the EAG considers that the scenario which only includes RDI for niraparib is overly conservative as dose reductions were permitted for rucaparib patients in ARIEL3, and so may represent the lower limit of incremental costs.

5.4.2 Adverse event costs

For the base case analysis, the company included grade 3 or higher AEs that were reported by at least 5% of patients in the rucaparib arm of ARIEL3 (data cut from 2017) and the niraparib arm of NOVA, presented in Table 16. Additionally, the company included nausea and vomiting to reflect clinical expert opinion and thrombocytopenia and hypertension for consistency with AEs included in the original STA for rucaparib (TA611).[2]

As per the approach accepted in TA611, the mean duration of AEs was obtained from ARIEL2 and the impact of AEs was applied a monthly risk while patients were on treatment.[2]

Table 16. Adverse events included in the model

Adverse event	Mean duration (days)	Rucaparib (ARIEL3 – 2017 data cut)		Niraparib (NOVA)	
		Incidence	Monthly risk	Incidence	Monthly risk
Combined ALT/AST*	[redacted]	[redacted]	[redacted]	4.0%	0.50%
Anaemia	[redacted]	[redacted]	[redacted]	25.3%	3.49%
Fatigue/asthenia	[redacted]	[redacted]	[redacted]	8.2%	1.04%
Neutropenia	[redacted]	[redacted]	[redacted]	19.6%	2.62%
Thrombocytopenia	[redacted]	[redacted]	[redacted]	33.8%	4.90%
Nausea/vomiting	[redacted]	[redacted]	[redacted]	3.0%	0.37%
Hypertension	[redacted]	[redacted]	[redacted]	8.2%	1.04%

Abbreviations: ALT, alanine aminotransferase; AST, combined aspartate transaminase.

*During the clarification stage, the company confirmed the estimate for AST/ALT was a combined value taken from the US FDA prescribing information.[34]

The company stated that adverse event management costs were based on the healthcare resource group (HRG) codes included in TA611, which was originally based on TA528 (replaced by the CDF review TA784), except for ALT/AST which was based on clinical expert opinion.[5]

The EAG notes that for the current appraisal, the company's approach to the cost of neutropenia and nausea/ vomiting differs to that used in TA611, but considers the HRG codes used to estimate the new costs are not unreasonable. In particular, the cost of nausea/ vomiting (£348.07) is similar to that used in TA611 (£471.09).

Unit costs were obtained from NHS reference costs 2021-22 and inflated to 2023 prices. Table 17 presents the AE unit costs included in the model. The total AE cost per month for rucaparib and niraparib was estimated to be £35.97 and £136.47, respectively. In their clarification response, the company also provided a scenario using unit costs for anaemia, neutropenia, thrombocytopenia and hypertension from the 2023/25 NHS payment schedule (see Appendix 10.9 for data used in scenario).

Table 17. Adverse event unit costs (reproduced from Table 73 in the company submission)

Adverse event	Unit cost	Source & description
Combined ALT/AST	£ 11.77	TA528 and NHS reference costs 2021-22.[33, 37] Uplifted to 2023 prices. DAPS04 - Clinical Biochemistry - Hepatic function panel include: Albumin; Bilirubin, total; Bilirubin, direct; Phosphatase, alkaline; Protein, total; ALT; AST. Assumed to be 7 tests based on clinical expert opinion.
Anaemia	£ 930.62	TA528 and NHS reference costs 2021-22.[33, 37] Uplifted to 2023 prices. SA04G-SA04L - Iron Deficiency Anaemia (HRG costs for non-elective long and short stay, day case, and regular day or night admissions weighted by activity)
Fatigue/asthenia	£ 440.94	TA528, uplifted to 2023 prices.[33] Assumed to require IV nutrition (XD26Z)
Neutropenia	£ 1,485.66	NHS reference costs 2021-22. Uplifted to 2023 prices.[37] SA08G-SA08J - Other Haematological or Splenic Disorders (HRG costs, total weighted by activity)
Thrombocytopenia	£ 1,031.66	TA528 and NHS reference costs 2021-22. Uplifted to 2023 prices.[33, 37] SA12G-SA12K - Thrombocytopenia (HRG costs for non-elective long and short stay, day case, and regular day or night admissions weighted by activity)

Nausea/vomiting	£ 348.07	NHS reference costs 2021-22. Uplifted to 2023 prices.[37] Unit cost for N16AF (specialist nursing cost) plus FD10A – FD10M - Non-Malignant Gastrointestinal Tract Disorders (HRG costs for regular day or night admission weighted by activity)
Hypertension	£ 831.53	TA528 and NHS reference costs 2021-22. Uplifted to 2023 prices.[33, 37] Hypertension currency codes: EB04Z (HRG costs for non-elective long stay, non-elective short stay, day case and regular day or night admissions, weighted by activity)
Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase		

5.4.2.1 EAG critique

The EAG considers that AE unit costs are generally appropriate. Additionally, AE data used to inform the model are from the primary trials for rucaparib (ARIEL3) and niraparib (NOVA), which is considered by the EAG to be robust. The EAG's clinical experts experience of prescribing both drugs reflected the trial safety data and they explained that rucaparib treatment tends to be better tolerated by patients compared with treatment with niraparib.

The EAG notes that the company's approach of applying a monthly AE risk while patients are on treatment is directly affected by the company's approach to estimating longer TTD for patients on niraparib. For instance, if the monthly risk of AEs were the same between the two treatments, AE costs for niraparib would be greater than for rucaparib because niraparib patients are estimated to be on treatment for longer than rucaparib patients.

Additionally, the EAG considers that it seems clinically implausible that niraparib, which appears to be less well tolerated should have a longer TTD and thus the company's approach is incoherent. Both rucaparib and niraparib are treatments that are given until disease progression or unacceptable toxicity.

According to the NICE health technology evaluation manual, for cost-comparison analysis, "*substantial differences between technologies in costs directly relating to health outcomes (such as adverse events) indicate that the technology and comparator(s) may not provide similar overall health benefits, so any such cost differences must be clearly justified*".[30] The company did not justify the differences in AE costs between the two treatments. However, under the EAG's preferred assumption that TTD is equivalent between treatments, the cost difference associated with AEs is

reduced and the approach is more in line with guidance for cost-comparison analysis in the NICE health technology evaluation manual.

As a secondary issue, during the clarification stage the EAG queried the use of AE data based on the ARIEL3 clinical study report (CSR) from 2017 instead of the ARIEL CSR addendum from 2023 but the company did not supply an explanation and instead stated that rates are similar between the two data cuts (please refer to the company response to clarification question B3). However, the company did supply a scenario exploring AE rates from the CSR addendum from 2023 (data presented in Appendix 10.9), as requested by the EAG, and this had minimal impact on incremental costs. Nonetheless, for completeness the EAG has included the scenario in its preferred assumptions, presented in Section 6.2.2.

5.4.3 Monitoring costs

In the base case, the company assumed monitoring resource use costs, consisting of computer tomography (CT) scans, blood tests and outpatient visits, for patients on maintenance treatment, off maintenance treatment and for patients with disease progression (Table 18 and Table 19). Assumptions on monitoring resource use were based on those included in TA784 and the assumption of differences in cost based on being on or off treatment were informed by TA611.[5, 7] As per the SmPC for niraparib,[36] the company assumed four blood tests in the first niraparib treatment cycle, which the EAG considers is appropriate.

As the company's base case approach to monitoring resource use costs factors in time on maintenance treatment, such that a treatment with longer TTD is associated with greater total monitoring costs, differences in cost between the rucaparib and niraparib are estimated (see Table 20). However, the EAG notes that in TA784 a distinction between on or off maintenance treatment monitoring resource use was not assumed, thus monitoring resource use was estimated for progression-free and progressed patients only, and this is discussed further in Section 5.4.3.1.

Table 18. Monitoring resource use – company base case

Cycle/ item	Rucaparib			Niraparib		
	PFS - On treatment	PFS - Off treatment	Progressed	PFS - On treatment	PFS - Off treatment	Progressed
Computer Tomography (CT) scan						
Cycle 1	-	-	-	-	-	-
Cycle 2-14	0.33	-	-	0.33	-	-

Cycle15+	0.33	-	-	0.33	-	-
Blood test						
Cycle 1	1.00	-	-	4.00	-	-
Cycle 2-14	1.00	-	-	1.00	-	-
Cycle15+	1.00	-	-	1.00	-	-
Outpatient visit (consultant oncologist)						
Cycle 1	1.00	0.33	0.33	1.00	0.33	0.33
Cycle 2-14	1.00	0.33	0.33	1.00	0.33	0.33
Cycle15+	0.33	0.33	0.33	0.33	0.33	0.33

Abbreviations: PFS, progression-free survival.

Table 19. Monitoring unit costs

Resource use	Unit cost	Source
Computer Tomography (CT) scan	£93	RD22Z - Diagnostic Imaging - One area with pre and post contrast. NHS Payment Scheme 2023/2025.[38]
Blood test	£3.22	DAPS05 - Directly Accessed Pathology Services - Haematology. NHS Payment Scheme 2023/2025.[38]
Outpatient visit (consultant oncologist)	£158	370 Medical Oncology Service - WF01A Consultant Led, Non-Admitted Face-to-Face, single professional. NHS Payment Scheme 2023/25.[38]

Table 20. Total monitoring costs – company base case

Treatment	BRCA subgroup	Non-BRCA subgroup
Rucaparib	[redacted]	[redacted]
Niraparib	[redacted]	[redacted]
Incremental monitoring costs	[redacted]	[redacted]

Abbreviations: BRCA, BReast CAncer gene; TTD, time to treatment discontinuation

5.4.3.1 EAG critique

The EAG does not consider that resource use should differ for progression-free patients on or off treatment. The EAG's clinical experts considered that treatment discontinuation is driven primarily by disease progression and so it is unlikely that many patients will be progression-free and off treatment and those that are will likely still need the same resource use as progression-free patients on treatment. In TA381 (replaced by TA908) and TA528 (replaced by TA784), resource use in the progression-free health state was the same for all patients irrespective of treatment status.[4, 5, 33]

However, in TA611 resource use in the progression-free health state was assumed to differ based on treatment status and this was noted as different to previous appraisals but not considered a key issue.[2]

During the clarification stage, the EAG requested, and the company provided, a scenario where resource use in the progression-free health state was assumed to be the same for patients irrespective of treatment status. However, the EAG investigated the company scenario, and found that the company did not use the same data for PFS on treatment resource use in the base case for PFS off treatment and they had also changed the number of outpatient visits for progressed patients to one every cycle. Instead, the EAG ran a corrected version of the scenario which assumed that the PFS off-treatment resource use was the same as the company base case PFS on-treatment resource use (except for the cycle 1 blood tests for niraparib patients), and results are presented in Section 6.2.1. Incremental costs are the same for the company and EAG scenario and demonstrates minimal impact on the incremental costs. For the EAG's preferred assumptions, presented in Section 6.2.2, the EAG includes its version of equal monitoring costs for progression-free patients.

The EAG notes that when the assumption of equal TTD for niraparib and rucaparib is made, total costs for the treatments change, and the issue of differences in monitoring costs between niraparib and rucaparib for progression-free patients on or off treatment disappears.

5.4.4 Other costs

Other costs considered for the cost-comparison analysis included the costs of subsequent treatments and a one-off cost of death, but these costs did not differ between arms. As PFS and OS do not differ between arms, inclusion of these other costs only affects the total costs of each treatment, but not the incremental costs and therefore are not considered to be decision modifiers.

A brief description of subsequent treatment costs and the one-off cost of death and the appropriateness of each cost is provided below.

The company included a one-off cost of subsequent treatment upon disease progression, applied to newly progressed patients in each model cycle. The company estimated the subsequent treatment cost based on a weighted average subsequent treatment used in ARIEL3. In ARIEL3, a proportion of patients received subsequent PARPis but this has been excluded in the model as subsequent PARPi use is not recommended in the NHS. Additionally, in the original submission the company included the cost of subsequent bevacizumab. However, as bevacizumab is not part of the NHS treatment

pathway for patients who have relapsed after second-line platinum-based chemotherapy plus maintenance treatment, the EAG requested this is excluded from subsequent treatment costs, which the company did for their updated base case post-clarification.

Table 37 in Appendix 10.10 outlines the subsequent treatment data included in the model to estimate of a one-off cost of £7,841 for the BRCA population and £6,782 for the non-BRCA population. For treatments where dose is calculated based on body mass or body surface area (BSA), the company estimate a distribution of patient weight/ BSA associated with different doses to calculate a weighted average cost per administration.

The company included a one-off cost of death, estimated to be £4,226, based on the estimate included in TA528, which assumed 51% of patients incurred a one-off cost of death of £7,238 (£3,692), and inflated to 2023 prices. The EAG considers the one-off cost of death included in the model is appropriate.

5.4.4.1 EAG critique

The EAG considers that the company's approach to assume subsequent treatment costs and the one-off cost of death is the same for rucaparib and niraparib in the model is appropriate. The EAG considers that the company's approach to base subsequent treatments on those received in ARIEL3 is not reflective of the treatment pathway presented in Figure 2 of the CS. As such, the EAG requested and the company provided, a scenario where the one-off cost of subsequent treatment is based only on the cost of paclitaxel + carboplatin and PLDH + carboplatin (as per Figure 2 of the company submission), assuming a 50:50 split. The scenario impacted total costs but did not change incremental costs. Nonetheless, the EAG considers that for completeness, subsequent treatment costs are based only on paclitaxel + carboplatin and PLDH + carboplatin and has included this in its preferred assumptions, presented in Section 6.2.2.

6 Company and EAG cost-comparison results

6.1 Company base case results

Table 21 presents the company's base case post clarification by breast cancer (BRCA) gene mutation status (BRCA and non-BRCA subgroups).

Table 21. Company's base case results (post clarification) - BRCA subgroup

Interventions	Total Costs (£)	Incremental costs (£)
BRCA subgroup		
Niraparib	[redacted]	-
Rucaparib	[redacted]	[redacted]
Non-BRCA subgroup		
Niraparib	[redacted]	-
Rucaparib	[redacted]	[redacted]
Abbreviations: BRCA, BReast CAncer gene		

The External Assessment Group (EAG) notes that, based on advice from NICE, the preferred cost source for subsequent treatment with pegylated liposomal doxorubicin hydrochloride (PLDH) is from the drugs and pharmaceutical electronic market information (eMIT) 2023 (see Table 39 in Appendix 10.9), instead of the British National Formulary (BNF), as used by the company. As such, the EAG provides corrected company base case results for the BRCA and non-BRCA subgroups in Table 22. The EAG notes that incremental costs are unaffected by this change, as subsequent treatment costs are assumed to be equal between the rucaparib and niraparib.

Table 22. Corrected company's base case results (post clarification)

Interventions	Total Costs (£)	Incremental costs (£)
BRCA subgroup		
Niraparib	[redacted]	-
Rucaparib	[redacted]	[redacted]
Non-BRCA subgroup		
Niraparib	[redacted]	-
Rucaparib	[redacted]	[redacted]
Abbreviations: BRCA, BReast CAncer gene; EAG, External Assessment Group		

6.1.1 Company's sensitivity and scenario analyses

As mentioned in the previous section, the company's incremental costs are unaffected by the EAG's correction to subsequent treatment costs. As such, the EAG presents only the incremental costs

from the company's scenario analyses, rather than including total costs (Table 23). Descriptions of the company's scenario analyses are presented in B.4.4 of the company submission.

Table 23. Company scenario analyses

Scenarios	Incremental costs (£)*	
	BRCA subgroup	Non-BRCA subgroup
Base case	[redacted]	[redacted]
ARIEL3 and NOVA alternative TTD	[redacted]	[redacted]
SACT rucaparib	[redacted]	[redacted]
SACT rucaparib – Alternative fits	[redacted]	[redacted]
SACT niraparib	[redacted]	[redacted]
SACT niraparib– Alternative fits	[redacted]	[redacted]
Alternative TTD1	[redacted]	[redacted]
Alternative TTD2	[redacted]	[redacted]
PARPi dosing	[redacted]	[redacted]
EAG requested scenarios		
Update AE incidence (CQ B3c)	[redacted]	[redacted]
Updated hypertension, anaemia, neutropenia and thrombocytopenia costs based on 2023/25 NHS payment scheme (CQ B5 and B9)	[redacted]	[redacted]
Same pre-progression resource use on and off treatment (CQ B6b)	[redacted]	[redacted]
Alternative subsequent treatments (CQ B8c)	[redacted]	[redacted]
Assuming equal TTD (CQ B1b)	[redacted]	[redacted]
Equal TTD assuming Weibull TTD for BRCA (CQ B1c)	[redacted]	N/A

Abbreviations: AE, adverse event; BRCA, BReast CAncer gene; CQ, clarification question; EAG, External Assessment Group; N/A, not applicable; SACT, Systemic Anti-Cancer Therapy; TTD, time to treatment discontinuation

* A negative incremental cost demonstrated rucaparib is cost-saving compared to niraparib

6.1.2 Model validation and face validity check

No issues were identified by the EAG.

6.2 Additional economic analysis undertaken by the EAG

6.2.1 Scenario analyses undertaken by the EAG

In Section 5.4.3.1 of this report, the EAG considered that the company's approach to the scenario assuming equal monitoring costs for progression-free patients was flawed and instead described a preferred approach for the scenario. Results of the EAG's preferred approach to equal monitoring

costs for progression-free patients (except for cycle 1 blood tests for niraparib patients) are presented in Table 24.

Table 24. EAG scenario analyses

	Results per patient	Rucaparib	Niraparib	Incremental cost
BRCA subgroup				
0	**Corrected company base case post clarification**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
1	EAG equal monitoring costs scenario			
	Total costs (£)	[redacted]	[redacted]	[redacted]
Non-BRCA subgroup				
0	**Corrected company base case post clarification**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
1	EAG equal monitoring costs scenario			
	Total costs (£)	[redacted]	[redacted]	[redacted]

Abbreviations: BRCA, BReast CAncer gene; EAG, External Assessment Group

6.2.2 EAG preferred assumptions

The EAG presents its preferred estimate of incremental costs in Table 25 based on a combination of the following scenarios:

1. Corrected company base case (NICE preferred PLDH costs from eMIT);
2. Niraparib time to treatment discontinuation (TTD) equal to rucaparib TTD (company response to CQ B1b);
3. Adverse event (AE) rates from the ARIEL3 clinical study report (CSR) addendum from 2023 (company response to clarification question B3c);
4. EAG preferred approach to equal monitoring costs for progression-free patients (except for cycle 1 blood tests for niraparib patients) – Section 5.4.3.1;
5. One-off cost of subsequent treatment is based only on the cost of paclitaxel + carboplatin and PLDH + carboplatin (as per Figure 2 of the company submission), assuming a 50:50 split (company response to clarification question B8c).

The results of the EAG's preferred assumptions for the BRCA and non-BRCA subgroup are presented in Table 25. As a scenario around the EAG preferred assumptions, the EAG explored the used of AE unit costs for anaemia, neutropenia, thrombocytopenia and hypertension from the 2023/25 NHS payment schedule (company response to clarification question B5 and B9), presented in Table 26

The EAG notes that there is a confidential patient access scheme (PAS) discount is available for niraparib. As such, the EAG has produced a confidential appendix to the EAG report. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG scenario analyses and base case results.

Table 25. Disaggregated EAG's preferred base case results

Costs	BRCA subgroup		Incremental costs	Non-BRCA subgroup		Incremental costs
	Niraparib	Rucaparib		Niraparib	Rucaparib	
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BRCA, BReast CAncer gene

Table 26. Scenario exploring alternative AE unit costs from 2023/25 NHS payment schedule

	Results per patient	Rucaparib	Niraparib	Incremental cost
BRCA subgroup				
0	**EAG base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
1	EAG equal monitoring costs scenario			
	Total costs (£)	[redacted]	[redacted]	[redacted]
Non-BRCA subgroup				
0	**EAG base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
1	EAG equal monitoring costs scenario			
	Total costs (£)	[redacted]	[redacted]	[redacted]

Abbreviations: BRCA, BReast CAncer gene; EAG, External Assessment Group

6.3 Summary statement

Based on the inclusion of the PAS discount for rucaparib and list price for niraparib, rucaparib remains cost saving under the EAG's preferred assumptions. However, please refer to the confidential appendix to this report for the estimate of incremental costs with the PAS discounts for both rucaparib and niraparib included.

The fundamental driver of the cost differences between rucaparib and niraparib is the company's approach to TTD. As well as being used to estimate drug acquisition costs, TTD affects AE costs as a monthly risk of AEs is applied to patients while on treatment and it affects monitoring costs as the

company assumed a difference in resource use dependent on whether a progression-free patient is on or off treatment.

The company estimated that patients are on treatment longer with niraparib compared to rucaparib, based on a naïve comparison of TTD, but also estimated that patients incur greater costs associated with AEs while on niraparib, which the EAG considers to be incoherent. It seems clinically implausible that the less well tolerated treatment should have a longer TTD. Both rucaparib and niraparib are treatments that are given until disease progression or unacceptable toxicity.

Data from the Systemic Anti-Cancer Therapy (SACT) database suggests that TTD is similar between rucaparib and niraparib and this is also supported by the EAG's clinical experts experience of both drugs. The EAG considers that a naïve comparison of TTD for both treatments is not robust and is driving the cost differences in the model. As such, the EAG considers that for the cost-comparison analysis, it is more appropriate and more clinically plausible to assume that TTD for niraparib is equal to TTD for rucaparib.

Additionally, assuming TTD is equivalent for both treatment is in line with guidance for cost-comparison analysis in the NICE health technology evaluation manual, which advises that if there are substantial in costs directly relating to health outcomes (such as adverse events), this may suggest that the technologies may not provide similar overall health benefits.[30] However, under the EAG's preferred assumption that TTD is equivalent between treatments, the cost differences associated with AEs reduces and the approach is more in line with guidance for cost-comparison analysis. Furthermore, differences in monitoring costs due to being on or off treatment are eliminated.

7 Equalities and innovation

The company has not described any equalities or innovation considerations associated with rucaparib in the company submission. Additionally, the External Assessment Group (EAG) is unaware of any equality or innovation considerations.

8 EAG commentary of the robustness of the evidence submitted by the company

Clinical

The External Assessment Group (EAG) notes that in November 2019, rucaparib was recommended by the National Institute for Health and Care Excellence (NICE) in TA611 for use within the Cancer Drugs Fund (CDF) as an option for maintenance treatment of relapsed, platinum-sensitive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to platinum-based chemotherapy in adults if the conditions in the managed access agreement for rucaparib were followed. At this time it was considered that there was clinical uncertainty associated with rucaparib due to the immaturity of the overall survival (OS) data, and that this could be addressed through the collection of additional data from ARIEL3. The EAG notes that the results from these final analyses in ARIEL3 for rucaparib versus placebo demonstrate [redacted] the EAG also note that the primary endpoint in ARIEL3 was investigator assessed progression-free survival (INV-PFS) and rucaparib significantly reduced the risk of disease progression or death compared with placebo in patients with platinum-sensitive ovarian cancer who had responded to platinum-based chemotherapy at the 15 April 2017 data cut in the ITT population and BRCA mutant subgroup. [redacted]

The company provides clinical efficacy data for rucaparib versus the two comparators listed in the NICE final scope (olaparib and niraparib), using indirect treatment comparisons (ITCs), but has focused only on niraparib for the cost-comparison. The EAG notes that there are no randomised controlled trials (RCTs) directly comparing rucaparib with niraparib or olaparib and so the company has conducted various indirect treatment comparisons (ITCs) of which the EAG considers the network meta-analyses (NMAs) to be the most robust source of efficacy data for rucaparib versus niraparib and rucaparib versus olaparib in the absence of head-to-head RCT data. There were some differences in trial baseline characteristics noted (Section 4.4.1), but the EAG's clinical experts did not consider these differences to be substantial enough to impact outcomes for rucaparib, niraparib or olaparib.

However, the EAG notes [redacted] between rucaparib and niraparib or rucaparib and olaparib. The point estimates for rucaparib compared to niraparib [redacted], therefore the EAG doesn't consider it unreasonable to conclude that rucaparib and niraparib have broadly similar efficacy. [redacted] However, the EAG notes that for a cost-comparison, the company only needs to be able to demonstrate convincing evidence of similar efficacy to one previously approved NICE technology according to the NICE health technology evaluations manual. The EAG considers this threshold to have been met with rucaparib and niraparib.

With regards safety, it should be noted that there was no statistical comparison of adverse effects between the treatments reported in the CS. The EAG also considers it important to highlight that Grade 3 or above raised ALT/AST AEs were not included in the economic modelling of the NICE appraisals for niraparib (TA528) or olaparib (TA908) and safety data from ARIEL3 demonstrate that rucaparib is associated with a [redacted] proportion of patients with Grade 3 or above combined ALT/AST TEAEs compared with niraparib in NOVA. However, the EAG's clinical experts reported that, while there are differences in the individual AEs for the PARP inhibitors, there were no major safety concerns regarding differences in AEs between rucaparib, niraparib and olaparib. Overall, based on naïve comparison and the advice of the EAG's clinical experts, the EAG does not consider it to be unreasonable to assume the safety profiles of rucaparib and niraparib are broadly similar.

Economic

Based on the inclusion of the PAS discount for rucaparib and list price for niraparib, rucaparib remains cost saving under the company's base case and scenario analyses and the EAG's preferred assumptions. However, a confidential PAS discount is available for niraparib and so results that include this discount, presented in a confidential appendix to this report, will be used for decision making.

As discussed in Section 6.3, the EAG considers that the company's naïve comparison of TTD for niraparib and rucaparib is not robust and is a key driver of the cost differences between the two technologies. Instead, the EAG considers that for the cost-comparison analysis, it is more appropriate and clinically plausible to assume that TTD for niraparib is equal to TTD for rucaparib. Furthermore, given that TTD affects the estimation of adverse event costs, the assumption of equal TTD between niraparib and rucaparib is more in line with the NICE health technology evaluation manual for cost-comparison analysis.

9 References

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10 Appendices

10.1 Further EAG critique of methods review

The table below provides a more detailed critique of the methods review and supports the text presented in Section 4.1 of this report.

Table 27. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods

Data sources	Appendix D.1.1 and company's response to CQ A11	**The EAG considers the sources and dates searched to be comprehensive**
		Databases searched:
		• Embase
		• MEDLINE
		• The Cochrane Library, including
		  ○ CENTRAL;
		  ○ DARE;
		  ○ CDSR.
		
		Registries:
		• HTA International;
		• ClinicalTrials.gov;
		• International Trials Register.
		
		Conference proceedings were searched to identify any ongoing research (2016-2018, and 2021-2023):
		• American Society of Clinical Oncology Annual Meeting;
		• British Gynaecological Cancer Society Annual Meeting;
		• European Cancer Organisation Congress;
		• European Society of Gynaecological Oncology Biennial Meeting;
		• European Society For Medical Oncology Congress;
		• International Gynecologic Cancer Society Biennial Meeting;
		• International Society for Pharmacoeconomics and Outcomes; Research (ISPOR) Conference (all locations);
		• Society of Gynecologic Oncology Annual Meeting.
		
		The EAG is unsure why conference proceedings from 2019 and 2020 were not reviewed in any of the update searches. It does not consider the omission of these two years of conference proceedings likely to have led to any studies being missed given database searches were not limited in this way.
		
		Bibliographies of key systematic review and meta-analysis articles appear to have been screened to identify additional studies relevant to the SLR based

		on reasons provided for exclusion of studies from the SLR in response to CQ A11. Original searches were performed in October 2017, with the first update performed in December 2018. A second update was performed in July 2023 – the EAG notes that the platform (and search strategies as a result) differed slightly between second update search and the earlier searches (see "Search strategies" below.
Search strategies	Appendix D.1.1	**The EAG considers the search strategies used to be broadly appropriate but has some concerns about the altered approach for the most recent update searches and is unsure if validated filters for study design were used** The search strategies (original and update searches) for the literature review used free-text keywords, MeSH and EMTREE terms for the population and interventions of interest. Search strategies also included filters to limit retrieval to RCTs; the text used to identify RCTs seems reasonable but there is no information as to whether these were validated filters and where they were obtained from. While update searches within 6 months of the submission being received by the EAG were performed, the EAG notes that the approach taken for these recent update searches differs compared to the original and first update searches. The original searches and first update searches involved searching Embase, MEDLINE and the Cochrane Library individually using the individual databases, but all searches were performed via Ovid in the recent update searches, with search strategies being structurally different and different (although similar) terms used. It is possible that, were these amended search methods used for the whole time period rather than specific to publications published after the last update search, papers retrieved for full text screening may differ. However, given the terms used are similar the EAG is unsure as to whether it would result in any relevant studies being missed either by the original or most recent update searches. The EAG is not aware of any key studies being missed and notes that all comparator studies from the respective NICE appraisals relevant to the decision problem (TA908 and TA784 for olaparib and niraparib, respectively) were identified in the searches.[4, 5]
Inclusion criteria	Appendix D.1.2, Sections B.3.9.1 and B.3.9.2 of the CS, and company's response to CQs A11 and A12	**The EAG considers the inclusion criteria for the SLR and ITCs to be reasonable** Inclusion criteria for the SLR captured a wider range of studies compared to those applicable to the decision problem outlined in this submission; population inclusion criteria were in line with the decision problem but a broader range of comparator treatments were considered relevant to the SLR. Exclusion criteria of note were patients with CNS metastasis that remains untreated and publications that report only interim trial results. The exclusion of those with untreated CNS metastasis seems reasonable given it is a common exclusion criteria of clinical trials in this area, but it does not appear that any studies were excluded solely for this reason. Furthermore, this is likely to be an important prognostic factor and patients with CNS metastasis were excluded in ARIEL3, the key trial in this submission for rucaparib.[3] While the EAG is unsure of the rationale for excluding studies that only report interim

		trial results and how appropriate this is, the EAG does not consider that any trials that would otherwise have met all criteria were excluded based on this. In response to CQ A12, the company details inclusion and exclusion criteria for the ITC (Table 9). Nine studies were included in the global SLR, with two excluded initially as they covered comparators not relevant to the decision problem outlined in this appraisal (see Section 3). Section B.3.9.1 describes the identification of seven trials considered for inclusion in ITCs within this appraisal (covering rucaparib, olaparib, niraparib and/or routine surveillance). Two were excluded during feasibility assessment; one because it was a treat-through design with no baseline characteristics available for the maintenance phase only and the other as it had included patients with prior use of PARP inhibitors. The EAG considers this rationale to be reasonable given this appraisal focuses on the use of rucaparib as a maintenance treatment only and that clinical experts consulted by the EAG confirmed that a second PARP inhibitor is not permitted in UK clinical practice. Five trials (including one rucaparib, two olaparib and two niraparib; ARIEL3, SOLO2 and Study 19, and NOVA and NORA, respectively) were considered for inclusion in ITCs.[3, 8-11] For NMAs, the company included four of five studies originally (with NORA [niraparib study] included in a sensitivity analysis) and for MAICs, SOLO2 and NOVA were considered to be the most appropriate comparator studies (olaparib and niraparib, respectively) for inclusion in anchored MAICs. In response to CQ A2, the company updated its preferred NMAs to include only SOLO2 and NOVA as comparator studies, with ARIEL3 included for rucaparib. The EAG's preferences in terms of studies included in ITCs are described in more detail in Section 4.4, but it agrees that NORA has additional limitations and raised concerns about Study 19 in CQ A2.
Screening	Appendix D.1.2	**The EAG considers the methods for screening to be robust** Title, abstract and full-text screening were performed individually by two reviewers using standardised forms that were piloted prior to the start of the screening. Disagreements between reviewers were resolved by a third, senior researcher. For screening, searches were deduplicated and uploaded into Distiller Systematic Review software for the original (October 2017) and first update (December 2018) searches, but a different software was used for the July 2023 update (Nested Knowledge Software). The EAG does not consider that this would impact screening results as forms used to decide inclusion/exclusion were likely to have been the same regardless of software used. A PRISMA diagram is provided in Figure 1 of the CS appendices to show the inclusion and exclusion of studies throughout the screening process (note that this PRISMA diagram is for the broader group of comparators covered in the SLR compared to the decision problem of this appraisal).
Data extraction	Appendix D.1.2	**The EAG considers the methods for data extraction in the SLR to be reasonable** One researcher extracted data from the included papers into the data extraction template, with validation performed by a second, senior researcher. Disagreements were resolved by a third, senior researcher.

Tool for quality assessment of included study or studies	Appendix D.8	**The EAG considers the quality assessment tool used for RCTs to be appropriate** To assess the quality of included RCTs, the company used the checklist included in the NICE user guide (the University of York's Centre for Reviews and Dissemination [CRD] checklist for RCTs). For studies relevant to the appraisal and considered in ITCs in the company's original submission, these assessments are included in Table 26 of the CS appendices.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CNS, central nervous system; CQ, clarification question; CS, company submission; DARE, Cochrane Database of Abstracts of Reviews of Effectiveness; EAG, External Assessment Group; EMTREE, Embase subject headings; HTA International, Health Technology Assessment International; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; MeSH, Medical Subject Headings; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PARP, poly (ADP-ribose) polymerase inhibitor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomised controlled trials; SLR, systematic literature review; TA, technology appraisal.

10.2 Summary of ARIEL3 trial critique and quality assessment

Table 28. EAG's critique of the design, conduct and analysis of ARIEL3

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	B.3.3.1.2 and Appendix D.10	**Appropriate** Patients were randomised 2:1 to rucaparib:placebo with randomisation stratified by: HRD classification, platinum-free interval, and best response to prior therapy.
Concealment of treatment allocation	B.3.3.1.2 and Appendix D.10	**Appropriate** Randomisation was performed via a centralised IVRS/IWRS using a block size of six.
Eligibility criteria	B.3.3.1.2	**Appropriate** The EAG notes that patient enrolment was required to meet strict criteria in terms of BRCA mutation status limited to ensure that any observed treatment benefits were not driven by patients in whom the largest effect size was expected: • No less than 33% and no more than 37% of patients enrolled were to harbour BRCA mutations; and • No more than 28% of patients enrolled were to harbour germline BRCA mutations. The EAG considers the trial population of ARIEL3 to reflect that in the NICE final scope well (see Section 3.1) and the EAG's clinical experts had no major concerns about inclusion and exclusion criteria for this trial in comparison to clinical practice in England.
Blinding	B.3.3.1.2 and Appendix D.10	**Appropriate** The study was described as double-blind with patients and investigators masked to treatment allocation throughout the study. Patients received rucaparib or matching placebo.
Baseline characteristics	Section B.3.3.2 and response to	**Reasonably well-balanced between groups**

	clarification question A5b	Baseline characteristics in the ITT population were well balanced between the two groups. For the BRCA and non-BRCA subgroups, there were some small differences in baseline characteristics between the rucaparib and placebo groups such as ECOG performance status for the BRCA subgroup (Table 29). In addition, the EAG's clinical experts reported that the trial population differs slightly to clinical practice in terms of age and ECOG status (see Section 3.1). However, in general the baseline characteristics of ARIEL3 are considered to be a reasonable reflection of UK practice although it is noted that subsequent treatment usage in the trial may differ to clinical practice.
Dropouts	Appendix D.9 and D.10	**Low rate of withdrawal from the study** There was a low rate of withdrawal from the study (only 3 people withdrew: all were in the rucaparib group, and prior to receiving randomised treatment). 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.
Statistical analysis		
Sample size and power	B.3.4.2, and B.3.4.3 Table 15	**No concerns** The efficacy endpoints were tested among the BRCA mutated cohort, HRD cohort, and ITT population, using an ordered step-down multiple comparisons procedure as detailed in the CS Figure 4. INV-PFS was the primary efficacy outcome and other outcomes assessed in the multiple comparison were FOSI-18 DRS-P, FOSI-18 total score, and OS. The sample size was calculated to give the study 90% power to detect a statistically significant difference between rucaparib and placebo at a one-sided α of 0.025. Once statistical significance was not achieved for one test, statistical significance was not declared for all subsequent analyses in the ordered step-down procedure.
Analysis for estimate of effect	B.3.4.1	**Appropriate** ITT analyses were reported for all efficacy outcomes, however, the main population of interest to this appraisal are the BRCA subgroup and the *post-hoc* non-BRCA subgroup.
Handling of missing data	B.3.4.3 Table 15	**Appropriate** The company reported that all data were used to their maximum possible extent without any imputations for missing data.
Outcome assessment	B.3.3.1.4	**Appropriate** The EAG considers the outcomes assessed to be appropriate and cover those outlined in the NICE final scope. The primary efficacy outcome was PFS as assessed by the investigator. Analysis of PFS by IRR and OS were reported as secondary outcomes. HRQoL was assessed by FOSI-18, a symptom questionnaire specific to ovarian cancer.

		Several outcomes specified in the NICE final scope were exploratory outcomes in ARIEL3: TFST, PFS2 and TSST.

Abbreviations: BRCA, BReast CAncer gene; CS, company submission; CSR, clinical study report; DRS-P, Disease-related Symptoms – Physical; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; FOSI-18, Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18; HRD, homologous recombination deficiency; HRQoL, health-related quality of life; IRR, independent radiology review; ITT, intention to treat; IVRS/IWRS, Interactive Voice Response System/Interactive Web Response System; NICE, National Institute of Health and Care Excellence ; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PFS2, progression-free survival 2; TFST, time to first subsequent anti-cancer treatment; TSST, time to second subsequent anti-cancer treatment.

10.3 Summary of baseline characteristics for ARIEL3, SOLO2 and NOVA

Table 29. Patient characteristics at baseline for studies included in the base case ITC for the BRCA population (Adapted from company response to clarification questions, Table 4)

	ARIEL3*		SOLO2		NOVA	
	Rucaparib (n=130)	Placebo (n=66)	Olaparib (n=196)	Placebo (n=99)	Niraparib (n=138)	Placebo (n=65)
Age in years, median (range)	58 (42,81)	59 (36,84)	56 (51, 63)	56 (49, 63)	57 (36, 83)	58 (38, 73)
Race, white %	81.5	72.7	88.3	91.9	89.1	84.6
BMI, mean (SD)	27.9 (5.84)	26.9 (5.21)	NR	NR	NR	NR
ECOG PS ≥1, %	22.3	36.4	16.3	22.2	34.1	26.2
FIGO ≥III, %	91.4	81.8	NR	NR	83.3	84.6
FIGO, III, %	IIIA: 3.8 IIIB: 6.9 IIIC: 61.5	IIIA: 1.5 IIIB: 9.1 IIIC: 51.5	NR	NR	68.8	70.8
FIGO IV, %	19.2	19.7	NR	NR	14.5	13.8
Ovarian tumour site, %	80.8	84.8	83.7	86.9	88.4	81.5
Serous histology, %	97.7	90.9	100	100	100	100
Prior lines of platinum chemotherapy, median (range)	2 (2,5) Lines, %: 2: 59.2 3: 30.8 >3: 10.0	2 (2,5) Lines, %: 2: 62.1 3: 27.3 >3: 10.6	Lines, %: 2: 56.1 3: 30.6 4: 9.2 ≥5: 3.6	Lines, %: 2: 62.6 3: 20.2 4: 12.1 ≥5: 5.0	Lines, %: 1: 0.7 2: 50.7 ≥3: 48.6	Lines, %: 1: 0 2: 46.2 ≥3: 53.8
Platinum-free interval >12 months, %	58.5	59.1	59.7	59.6	≥12 months: 60.9	≥12 months: 60.0
Response to most recent platinum chemotherapy, %	CR: 35.4 PR: 64.6	CR: 36.4 PR: 63.6	CR: 46 PR: 54	CR: 47 PR: 53	CR: 51 PR: 49	CR: 51 PR: 49
HRD, %	100	100	100	100	100	100

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group ; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; PS, performance status; SD, standard deviation.

* The ARIEL3 BRCA mutated cohorts included patients with somatic and germline BRCA mutations, while the SOLO2, NOVA and NORA BRCA mutated cohorts included only patients with germline BRCA mutations

Table 30. Patient characteristics at baseline for studies included in the base case ITC for the non-BRCA population (Adapted from company response to clarification questions, Table 5)

	ARIEL3		NOVA	
	Rucaparib (n=245)	Placebo (n=123)	Niraparib (n=234)	Placebo (n=116)
Age in years, median (range)	63 (39, 84)	63 (41, 85)	63 (33, 84)	
Race, white %	75.9	78.0	85.9	
BMI, mean (SD)	27.862 (8.001)	26.354 (5.179)	NR	
ECOG PS ≥1, %	26.9	23.6	31.6	
FIGO ≥III, %	86.1	89.4	90.1	
FIGO, III, %	IIIA: 3.7 IIIB: 6.1 IIIC: 64.5	IIIA: 0.8 IIIB: 4.9 IIIC: 69.9	III-IIIB: 10.3 IIIC: 63.7	III-IIIB: 17.2 IIIC: 56.9
FIGO IV, %	11.8	13.8	16.2	20.7
Ovarian tumour site, %	84.5	84.6	82.1	
Serous histology, %	94.3	96.7	100	
Prior lines of platinum chemotherapy, median (range)	2 (2,6) Lines, %: 2: 64.9 3: 28.2 >3: 6.9	2 (2,4) Lines, %: 2: 69.1 3: 23.6 >3: 7.3	Lines, %: 1: 0 2: 66.2 ≥3: 33.8	
Platinum-free interval >12 months, %	60.4	60.2	≥12 months: 61.5	
Response to most recent platinum chemotherapy, %	CR: 31.4 PR: 68.2 SD: 0.4	CR: 29.3 PR: 70.7	CR: 50 PR: 50	
HRD, %	43.3	42.3	45.3*	

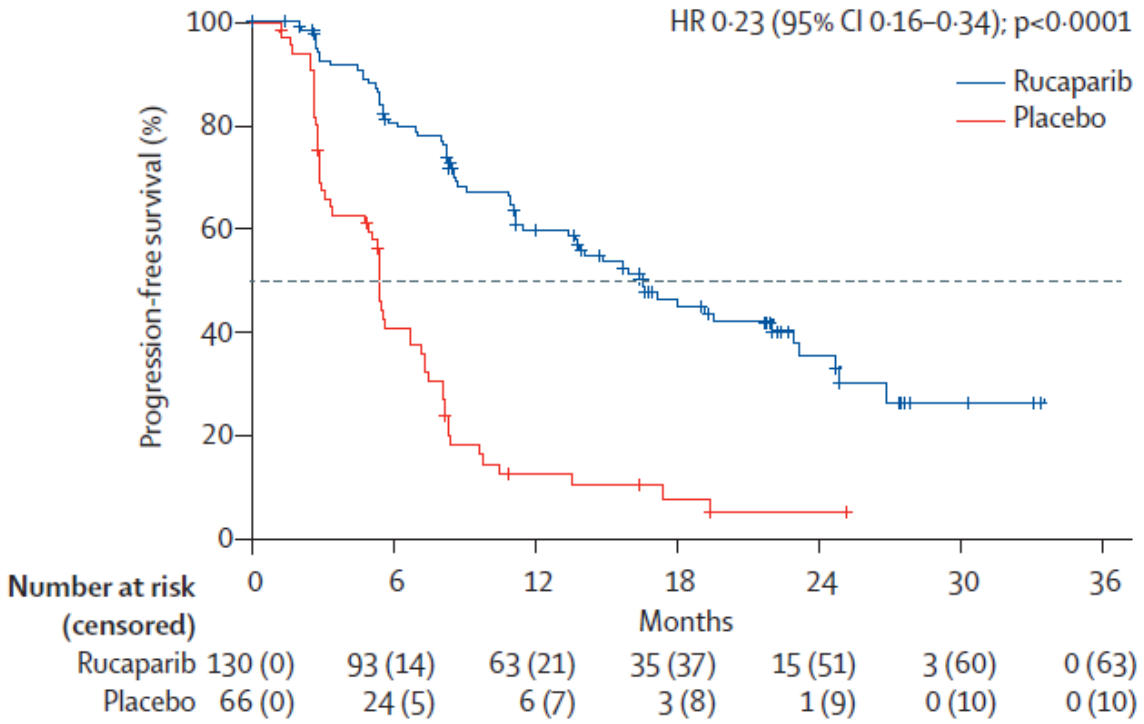
Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group ; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; PS, performance status; SD, standard deviation.

˟ Calculated based on Mirza 2016, Fig 2b.

10.4 Additional Kaplan–Meier curves from ARIEL3

10.4.1 INV-PFS and IRR-PFS in the BRCA mutated cohort

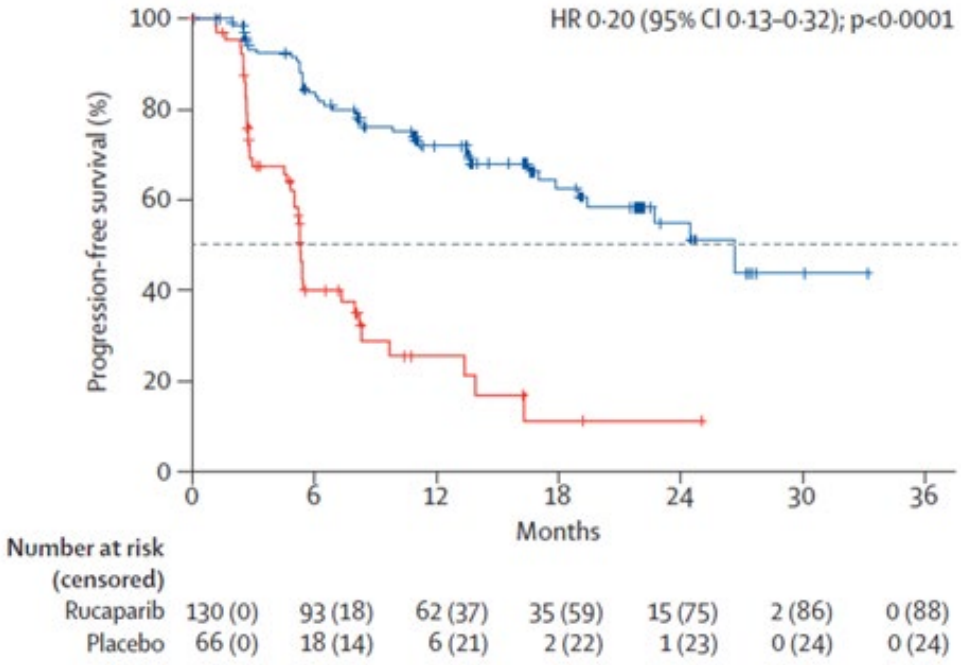
Figure 10. KM estimates of PFS as assessed by the investigator in the BRCA mutated cohort using 15 April 2017 data-cut (Reproduced from CS, Figure 5)



Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; PFS, progression-free survival

Source: Coleman et al. 2017[3]

Figure 11. Kaplan–Meier estimates of PFS as assessed by IRR in the BRCA mutated cohort using 15 April 2017 data-cut (Reproduced from CS, Figure 8)



Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; IRR, independent radiology review; PFS, progression-free survival

Source: Coleman et al. 2017.[3]

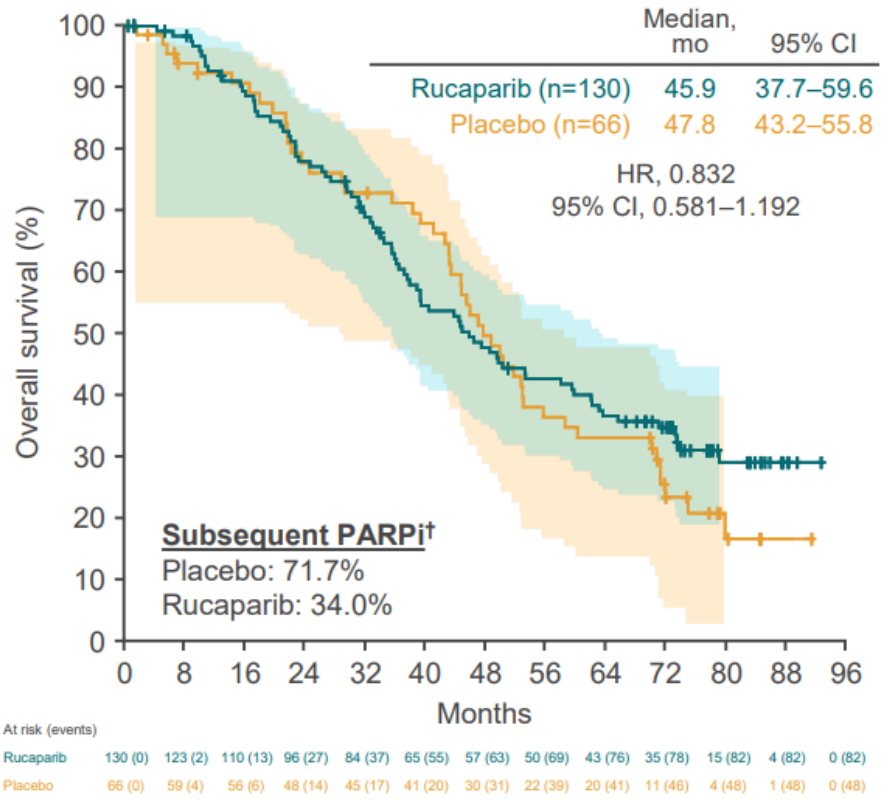
10.4.2 INV-PFS in the non-BRCA mutated cohort

Figure 12. KM estimates of INV-PFS in the non-BRCA mutated cohort of ARIEL3 using 15 April 2017 data-cut (Reproduced from CS, Figure 17)

Abbreviations: BRCA, breast cancer gene; INV, investigator; KM, Kaplan–Meier; PFS, progression-free survival

10.4.3 OS in the BRCA mutated and non-BRCA mutated cohorts

Figure 13. KM estimates of final OS in the BRCA mutated cohort using 4 April 2022 data-cut (Reproduced from CS, Figure 11)



Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor.

Source: Coleman et al. 2022 (ICGS oral presentation)[16]

Figure 14. KM estimates of OS in the non-BRCA mutated cohort using 4 April 2022 data-cut (Reproduced from CS, Figure 19)

Abbreviations: BRCA, breast cancer gene; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; OS, overall survival.

10.5 Matching-adjusted indirect comparison (MAIC) EAG critique

The company conducted anchored MAICs in the BRCA and non-BRCA populations for PFS, OS and PFS2, adjusting for clinically validated treatment effect modifiers (EMs) using the ARIEL3, SOLO2, and NOVA clinical trials. The EMs included in the primary MAICs were:

- Number of prior lines of platinum therapy;
- Length of platinum-free interval;
- Response to platinum therapy; and
- Body-mass index (BMI; reported only for NOVA arms).

Sensitivity analyses were conducted including adjustments for all commonly available population characteristics (fully adjusted) and an unanchored MAIC versus olaparib for OS and PFS2 adjusting for all available factors to explore potential bias due to the difference in the proportion of patients 'switching' to PARP inhibitors in the placebo arm of ARIEL3 ([redacted]) and SOLO2 (38.4%). The following population characteristics were used for adjustments in the sensitivity analysis of anchored MAIC against NOVA and SOLO2 and in the unanchored MAIC against SOLO2:

- ECOG PS;

- Number of prior lines of chemotherapy;
- Location of primary tumour;
- Histological class;
- FIGO stage (reported only for NOVA arms);
- Prior use of bevacizumab;
- Age;
- Race;
- BRCA mutation type (reported only for SOLO2 arms);
- Tumour lesion(s) at baseline (reported only for SOLO2 arms);
- Time since last platinum therapy (reported only for SOLO2 arms);
- Time since diagnosis (reported only for NOVA arms);
- Number of metastatic sites (reported only for NOVA arms).

The company reported that the methods used for the MAICs followed the guidance in NICE DSU TSD 18[39] and involved the use of patient-level data from ARIEL3 with matching to aggregate data from NOVA and SOLO2 in the BRCA and non-BRCA mutated cohorts (where applicable). The indirect relative effect of rucaparib versus the comparator was calculated based on the HR obtained from ARIEL3 with re-weighted Cox regression analysis.

10.5.1.1 Results

The company provided detailed baseline characteristics before and after matching in the CS (Section B.3.9.3.2), and reported that BMI was not reported in SOLO2 and so could not be adjusted for in the analysis of rucaparib versus olaparib.

The effective sample size (ESS) when matching ARIEL3 against NOVA was 152 in the BRCA mutated cohort (78% of the cohort population, N=196) and 306 in the non-BRCA mutated cohort (83% of the cohort population, N=368). When matching against SOLO2 in the BRCA mutated cohort the ESS was 185 (94% of the cohort population, N=196). The sensitivity analysis for the fully adjusted anchored MAIC resulted in a low ESS against NOVA in both the BRCA and non-BRCA populations (20% of the cohort population in BRCA and 24% of the cohort population in non-BRCA) and so results should be interpreted with caution.

The EAG notes that while the HRs produced by the MAICs [redacted]

[redacted] (results for the primary MAIC are summarised in Table 31). The company reported that the sensitivity MAIC with full adjustment was [redacted] (the results of the sensitivity MAIC with full adjustment are reported in Table 24 of CS Appendix D.5.2). The anchored and unanchored MAICs of OS and PFS2 for rucaparib versus olaparib in SOLO2 [redacted] HRs and the HR for PFS2 in particular is noted to be [redacted] in the unanchored MAIC (anchored MAIC HR [redacted] and unanchored MAIC HR [redacted] [results of the unanchored MAIC against SOLO2 are reported in CS Table 37]).

Table 31. Results of the primary anchored MAIC for INV-PFS, OS, and PFS2 (Reproduced from CS, Table 36)

Outcome	Cohort	Comparator Trial	Index Treatment	Comparator Treatment	Naïve comparison, HR (95% CI)	Naïve p-value	MAIC, HR (95% CI)	MAIC p-value
INV-PFS	BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	NON-BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	BRCA	SOLO2	Rucaparib	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
OS	BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	NON-BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	BRCA	SOLO2	Rucaparib	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
PFS2	BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	NON-BRCA	NOVA	Rucaparib	Niraparib	[redacted]	[redacted]	[redacted]	[redacted]
	BRCA	SOLO2*	Rucaparib	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 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; PFS2, time to second progression event; OS, overall survival.

* Only immature PFS2 data were available in SOLO2; mature PFS2 was not published.

10.6 SACT data EAG critique

The company conducted analyses of the SACT data for rucaparib and niraparib by subgroup for the BRCA and non-BRCA populations in keeping with the cost-comparison analysis and NMAs.[31, 32] A summary of the key patient characteristics and Blueteq data items are provided in CS Tables 38 and 39. The company highlighted the following key differences between the rucaparib and niraparib SACT data sets:

- A significantly higher proportion of patients were aged ≥80 years in the rucaparib SACT data compared to the niraparib SACT data (12% vs 6%; p<0.001) in the non-BRCA cohort.
- The proportion of patients with ECOG PS 1 was higher in the rucaparib dataset (53% to 62%) than in the niraparib data (42% to 52%) for both the BRCA and non-BRCA subgroups; however, there was also a larger number of missing observations for rucaparib (24% to 25%) than for niraparib (15% to 16%), which limits any conclusions regarding the ECOG PS between data sets.
- All patients included in the BRCA mutant cohort of the niraparib SACT data had germline mutations, whereas 13% of patients in the rucaparib BRCA mutant cohort had mutations in the somatic tissue only.
- In the rucaparib SACT dataset, there were 18% of patients in the BRCA mutant cohort and 6% of patients in the non-BRCA mutant cohort who had received prior maintenance therapy with a PARP inhibitor, which had to be stopped due to dose-limiting toxicity. However, no patients in the niraparib SACT dataset had received previous treatment with PARP inhibitors.

In addition, the company highlighted that it was unclear whether patients with somatic BRCA mutation were included in the non-BRCA mutant cohort of the SACT data, which was the case in the NOVA trial and potentially confounds the results.[9, 32]

The EAG notes that the patient population in the SACT datasets are different to the population of ARIEL3 and NOVA in terms of age and ECOG performance status but also notes that clinical experts considered the trial population likely to be younger and to have a better performance status compared to clinical practice in England.

The company conducted naïve comparisons of OS and TTD for the BRCA and non-BRCA subgroups of the rucaparib and niraparib SACT data (Table 32). The EAG notes that median OS was not reached for niraparib in the BRCA cohort but median follow-up was much longer in the rucaparib SACT BRCA

subgroup compared to the niraparib SACT BRCA subgroup. The EAG also notes the company's concerns that the OS observed in SACT for rucaparib may be reduced by the time rucaparib patients spent on prior PARP inhibitor treatments before switching to rucaparib. However, the EAG considers that the impact of this is unknown as the duration of prior PARP inhibitor use was not reported in the SACT data.

In summary, the EAG notes that the 95% confidence intervals for the analyses of OS and TTD using the SACT data all cross 1 (Table 32) [redacted] when compared to the results from the company's NMAs (Table 10). Nevertheless, the EAG is in agreement with the company's conclusions that a naïve comparison of rucaparib and niraparib based on SACT data [redacted]. Analyses of TTD for rucaparib versus niraparib were not possible from the NMA (due to the absence of data from NOVA) and so no comparison can be made with the SACT data. However, the EAG note that the SACT data reports similar TTD for rucaparib and niraparib within each of the BRCA and non-BRCA populations (Table 32).

Table 32. Naïve comparison of OS and TTD outcomes from the rucaparib and niraparib SACT data sets (Reproduced from CS, Table 40)

Outcome	BRCA mutated cohort*		Non-BRCA mutated cohort	
	Rucaparib (n=70)	Niraparib (n=157)	Rucaparib (n=817)	Niraparib (n=859)
OS outcomes				
Median follow-up (months)	19.5	13.7	14.7	12.0
Maximum follow-up (months)	37.7	32	37.7	32
Median (months)	30.8	Not reached	25.7	22.6
HR (95% CI)[a]	1.04 (0.64 to 1.69)		0.88 (0.76 to 1.02)	
TTD outcomes				
Median follow-up (months)	9.7	6.8	5.5	4.6
Maximum follow-up (months)	33.6	19	33.6	19
Median (months)	12.4	12.2	6.5	6.4
HR (95% CI)[a]	1.11 (0.75 to 1.63)		1.032 (0.91 to 1.16)	

Abbreviations: BRCA, breast cancer gene; OS, overall survival; TTD, time to treatment discontinuation

* Hazard ratio was calculated by Cox proportional hazard model based on re-constructed patient level data from digitized curves following the algorithm described in Guyot et al. 2012.[40]

Source: National Disease Registration Service 2023 (rucaparib SACT data)[31]; NICE Committee Papers - ID1644[32]

10.7 NICE reference case checklist

Table 33 summarises the EAG'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.

Table 33. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Appropriate.
Perspective on costs	NHS and PSS	Appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-comparison analysis, as agreed by NICE.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Appropriate.
Synthesis of evidence on health effects	Based on systematic review	Not applicable for a cost-comparison analysis.
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.	Not applicable for a cost-comparison analysis.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Not applicable for a cost-comparison analysis.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Not applicable for a cost-comparison analysis.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Not applicable for a cost-comparison analysis.
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	Appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for costs, which is considered appropriate for a cost-comparison analysis.

Abbreviations: EAG, external assessment group; NHS, national health service; PSS, personal social services; QALY, quality adjusted life year

10.8 Summary of treatment effectiveness included in the model

Table 34. Company's approach to treatment effectiveness by population and outcome

Outcome & approach	BRCA population		Non-BRCA population	
	Rucaparib	Niraparib	Rucaparib	Niraparib
Progression free survival				
Source of data	ARIEL3	Equal to rucaparib	ARIEL3	Equal to rucaparib
Extrapolation	Lognormal	Equal to rucaparib	Lognormal	Equal to rucaparib
Observed median (years)	[redacted]	-	[redacted]	-
Modelled median (years)	[redacted]	[redacted]	[redacted]	[redacted]
Modelled mean (years)	[redacted]	[redacted]	[redacted]	[redacted]
EAG comment	The company selected the extrapolations with the best statistical fit according to AIC and BIC statistics and visual inspection of the curves. The company's approach is appropriate for a cost-comparison analysis. However, the EAG notes that for an STA, where long-term estimates of PFS may differ between treatments, further interrogation of the company's approach would be required.			
Overall survival				
Source of data	ARIEL3	Equal to rucaparib	ARIEL3	Equal to rucaparib
Extrapolation	Lognormal	Equal to rucaparib	Log-logistic	Equal to rucaparib
Observed median (years)	[redacted]	-	[redacted]	-
Modelled median (years)	[redacted]	[redacted]	[redacted]	[redacted]
Modelled mean (years)	[redacted]	[redacted]	[redacted]	[redacted]
EAG comment	The company selected the extrapolations with the best statistical fit according to AIC and BIC statistics and visual inspection of the curves. The company's approach is appropriate for a cost-comparison analysis. However, the EAG notes that for an STA, where long-term estimates of OS may differ between treatments, further interrogation of the company's approach would be required, in particular around the slight overestimation of the modelled median compared with the observed median.			

Abbreviations: BRCA, BReast CAncer gene; EAG, External Assessment Group; PFS, progression-free survival; OS, overall survival; STA, single technology appraisal.

10.9 Alternative adverse event data used for company scenario analysis

Table 35. Adverse event costs based on the 2023/25 NHS payment scheme

Adverse event	Unit cost	Description
Anaemia	£1,595.30	SA04G-SA04L - Iron Deficiency Anaemia. Average of combined day case/ ordinary elective spell and non-elective spell.

Neutropenia	£1,612.00	SA08G-SA08J - Other Haematological or Splenic Disorders. Average of combined day case/ ordinary elective spell and non-elective spell.
Thrombocytopenia	£1,801.50	SA12G-SA12K – Thrombocytopenia. Average of combined day case/ ordinary elective spell and non-elective spell.
Hypertension	£520.50	EB04Z – hypertension. Average of combined day case/ ordinary elective spell and non-elective spell.

Table 36. Data used for clarification question B3c scenario (based on the ARIEL3 clinical study report addendum, Table 17)

Adverse event	Incidence	
	Rucaparib (ARIEL3 – 2017 data cut)	Rucaparib (ARIEL3 – 2023 data cut)
Combined ALT/AST	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Fatigue/asthenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Nausea/vomiting	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

Abbreviations: ALT, alanine aminotransferase; AST, combined aspartate transaminase.

*Assumed to be the same at the 2017 data cut.

10.10 Subsequent treatment costs included in the model

Table 37. Subsequent treatment data and assumptions obtained from the company economic model

Subsequent treatment	Treatment regimen	Drug acquisition cost per month	Drug administration cost per month	BRCA population		Non-BRCA population	
				% of patients receiving treatment (based on ARIEL3)	Mean months received (NICE TA381)	% of patients receiving treatment (based on ARIEL3)	Mean months received (NICE TA381)
Carboplatin monotherapy	IV infusion of 30 minutes once per treatment cycle. Dose per administration of 400 mg / m^2. Mean BSA of 1.71 m^2 from Sacco *et al*.[41] Cycle length of 21 days.	[redacted]	[redacted]	[redacted]	4.14	[redacted]	4.14
Gemcitabine + Carboplatin	Gemcitabine: IV infusion of 180 minutes once per treatment cycle. Dose per administration of 175 mg / m^2. Carboplatin: IV infusion of 30 minutes once per treatment cycle. Dose per administration of 400 mg / m^2. Mean BSA of 1.71 m^2 from Sacco *et al*.[41] Cycle length of 21 days	[redacted]	[redacted]	[redacted]	4.14	[redacted]	4.14
Hormonal therapy (assumed to be letrozole)	2.5 mg taken orally once daily. Cycle length of 30 days.	[redacted]	[redacted]	[redacted]	4.14	[redacted]	4.14
Paclitaxel + Carboplatin	Paclitaxel: IV infusion of 180 minutes once per treatment cycle. Dose per administration of 175 mg / m^2.	[redacted]	[redacted]	[redacted]	4.14	[redacted]	4.14

	Carboplatin: IV infusion of 30 minutes once per treatment cycle. Dose per administration of 400 mg / m^2. Mean BSA of 1.71 m^2 from Sacco *et al*.[41] Cycle length of 21 days						
PLDH + Carboplatin	PLDH: IV infusion of 75 minutes once per treatment cycle. Dose per administration of 50 mg / m^2. Carboplatin: IV infusion of 30 minutes once per treatment cycle. Dose per administration of 400 mg / m^2. Mean BSA of 1.71 m^2 from Sacco *et al*.[41] Cycle length of 28 days	[redacted]	[redacted]	[redacted]	5.52	[redacted]	5.52
PLDH monotherapy	IV infusion of 75 minutes once per treatment cycle. Dose per administration of 50 mg / m^2. Mean BSA of 1.71 m^2 from Sacco *et al*.[41] Cycle length of 28 days.	[redacted]	[redacted]	[redacted]	5.52	[redacted]	5.52

Abbreviations: BSA, body surface area; IV, intravenous; PLDH, pegylated liposomal doxorubicin hydrochloride

Note: Please refer to Table 38 for unit costs of each subsequent treatment and Table 74 of the company submission for administration costs and source included in the model.

Table 38. Subsequent treatment unit costs included in the model (taken from the company's economic model)

Treatment	Administration type	Vials/ tablets per pack	Total pack/ vial size	Drug acquisition cost per pack/ vial	Source
Carboplatin	IV	1	50 mg	£4.05	eMIT (2023)[42]
		1	150 mg	£7.44	
		1	450 mg	£14.69	
		1	600 mg	£21.54	
Cisplatin	IV	1	10 mg	£2.42	eMIT (2023)[42]
		1	50 mg	£5.58	
		1	100 mg	£9.53	
Cyclophosphamide	Oral	100	5000 mg	£139.00	BNF[43]
Gemcitabine	IV	1	200 mg	£4.09	eMIT (2023)[42]
		1	2000 mg	£44.03	
Hormonal therapy (assumed to be letrozole)	Oral	20	70 mg	£0.88	eMIT (2023)[42]
Paclitaxel	IV	1	30 mg	£4.03	eMIT (2023)[42]
		1	100 mg	£11.49	
		1	150 mg	£17.28	
		1	300 mg	£17.40	
PLDH	IV	1	20 mg	£360.23	BNF[43]
		2	100 mg	£712.49	

Abbreviations: BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information; IV, intravenous; PLDH, pegylated liposomal doxorubicin hydrochloride

Table 39. NICE preferred PLDH costs

Treatment	Administration type	Vials/ tablets per pack	Total pack/ vial size	Drug acquisition cost per pack/ vial	Source
PLDH	IV	1	20 mg	£266.57	eMIT (2023)[42]
		2	100 mg	£532.75	

Abbreviations: BNF, British National Formulary; eMIT, Drugs and pharmaceutical electronic market information; IV, intravenous; PLDH, pegylated liposomal doxorubicin hydrochloride

Single Technology Appraisal

Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer [Review of TA611] [ID4069]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 15 February 2024** using the below 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.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Data, wording and formatting clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Text clarification: impact of subsequent PARP inhibitors</u> • Section 4.3.2.1; pages 32-33 Text: "The EAG notes that subsequent PARP inhibitor therapies were non-randomised and unbalanced across treatments arms with [redacted] in the rucaparib group vs [redacted] in the placebo group. However, the EAG's clinical experts reported that patients in the UK wouldn't typically have access to more than 1 PARP inhibitor and the EAG notes that if patients haven't received a PARP inhibitor then they would potentially be eligible to receive them as a subsequent treatment in UK clinical practice (conditional on responding to platinum-based chemotherapy). The EAG therefore does not consider it possible to predict the resulting direction of bias from the subsequent therapies in ARIEL3." • Section 4.4.2.1; page 44 "The company highlighted that a higher proportion of patients randomised to placebo in the ARIEL3 trial were treated with subsequent PARP inhibitors compared to SOLO2 and NOVA and may have led to bias in the results. However, the EAG does not consider it possible to predict the resulting direction of bias from the use of subsequent PARP inhibitors and the EAG notes that if patients haven't received a PARP inhibitor then they would potentially be eligible to receive one as a subsequent treatment in UK clinical practice (conditional on responding to platinum-based chemotherapy)."	We would ask that this text be amended to acknowledge that use of subsequent PARP inhibitors biases the treatment vs placebo comparison against the active treatment in clinical trials, and that this bias is especially pronounced in ARIEL3 (vs SOLO2) due to the higher proportion of patients randomised to placebo who received subsequent PARP inhibitors in ARIEL3. In Section 4.3.2.1: "The EAG notes that subsequent PARP inhibitor therapies were non-randomised and unbalanced across treatments arms with [redacted] in the rucaparib group vs [redacted] in the placebo group. The EAG's clinical experts reported that patients in the UK wouldn't typically have access to more than 1 PARP inhibitor and the EAG notes that if patients haven't received a PARP inhibitor then they would potentially be eligible to receive them as a subsequent treatment in UK clinical practice (conditional on responding to platinum-based chemotherapy). [redacted]	The company believes that the direction of bias due to different proportion of subsequent PARP inhibitors therapies is predictable. In SOLO2 (the earliest Phase III RCT for a PARP inhibitor in the relapsed advanced OC setting), the proportion of patients receiving subsequent PARP inhibitors in the placebo arm was significantly lower than in the more recent ARIEL3 study. Therefore, the OS HR for rucaparib vs placebo would be biased against rucaparib due to the known positive effect of subsequent PARP inhibitor treatments, while the OS HR for olaparib vs placebo is expected to be less impacted. Anchored comparisons of OS across ARIEL3 and earlier PARP inhibitor studies are expected to favor the comparators for which the treatment effect estimates were less impacted by the effect of subsequent PARP inhibitor. While [redacted] of patients randomised to rucaparib in ARIEL3 received subsequent PARP inhibitors compared to 10.2% of patients randomised to olaparib in SOLO2, 2L PARP inhibitor after 1L PARP inhibitor was noted to have very limited impact on OS according to	This is not a factual inaccuracy. No change required.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td>[redacted]."

In Section 4.2.2.1: "The company highlighted that a higher proportion of patients randomised to placebo in the ARIEL3 trial were treated with subsequent PARP inhibitors compared to SOLO2 and NOVA and may have led to bias in the results. The EAG notes that if patients haven't received a PARP inhibitor then they would potentially be eligible to receive one as a subsequent treatment in UK clinical practice (conditional on responding to platinum-based chemotherapy). [redacted]"</td><td>clinical opinion in generated in 2023 for TA949). It is expected that 3L PARP inhibitor after 2L PARP inhibitor would have an even more limited impact (if any). Moreover, the absolute difference between proportion of patients receiving subsequent PARP inhibitors was smaller for the active comparator groups vs the placebo groups:
<table><tr><th></th><th colspan="2">Subsequent PARP inhibitors (%)</th></tr><tr><th></th><th>Intervention</th><th>Placebo</th></tr><tr><td>ARIEL3</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>SOLO2</td><td>10.20</td><td>38.40</td></tr><tr><td>Diff.</td><td>[redacted]</td><td>[redacted]</td></tr></table>Overall, the difference in subsequent PARP inhibitor use in the active comparator groups is unlikely to mitigate the impact of subsequent PARP inhibitor use in the placebo groups. The overall impact is a clear bias against rucaparib in the NMA analyses.</td><td></td></tr>
<tr><td><u>Text clarification: NMA outcomes</u>

• Section 1; page 16

Text:
"[redacted]</td><td>We would ask that this sentence be amended as the statement about [redacted] is misleading without providing additional context on the proportions of</td><td>[redacted] of patients in the placebo arm received a subsequent PARP inhibitor in ARIEL3 compared to only 38.4% of patients in the placebo arm of SOLO2. Patients who receive</td><td>This is not a factual inaccuracy. No change required.</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[redacted] • Section 4.4.2.1; page 45 Text: “[redacted] • Section 4.7; page 50 Text: “[redacted] • Section 8; page 75 Text:“[redacted]	patients who received subsequent PARP inhibitors and the impact of subsequent PARP inhibitors on HRs: ““[redacted]	subsequent PARP inhibitors after being randomised to placebo are expected to have better survival than patients who do not receive PARP inhibitors, resulting in a HR that is closer to 1 (i.e., biasing the results against the active treatment). The impact of subsequent PARP inhibitors is more pronounced in ARIEL3 because an additional [redacted] of patients randomised to placebo received subsequent PARP inhibitors. Therefore, results from an NMA may favour olaparib.	
<u>Data clarification: p values for the non-BRCA subgroup</u> • Section 1; page 14	We would ask that the text in Sections 1 and 4.7 be amended to note the p value: “The hazard ratio for the non-BRCA subgroup suggested [redacted]	We have checked the results of the analysis and can confirm the p value is [redacted] for the non-BRCA subgroup (source: unpublished data on file).	Thank you for providing the data. The EAG report has been updated.

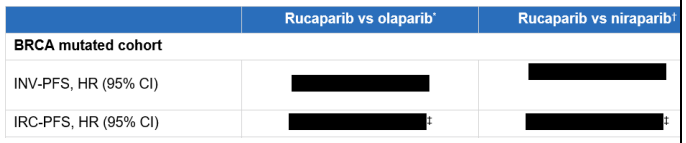
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text: "[redacted]" • Section 4.7; page 49 Text: "The hazard ratio for the non-BRCA subgroup suggested [redacted]" • Section 8; page 74 Text: ""[redacted]"	[redacted] We would ask that the text in Section 8 be amended to note the p-value and the consistency of results in the non-BRCA subgroup: "[redacted]"		
<u>Text clarification: statistical comparison of adverse events</u> • Section 1; page 16 Text: "With regards to safety, it should be noted that there was no statistical comparison of adverse effects between the treatments reported in the CS." • Section 4.7; page 51 Text: "With regards safety, it should be noted that there was no statistical comparison of adverse effects between the treatments reported in the CS." • Section 8; page 75 Text: "With regards safety, it should be noted that there was no statistical comparison of adverse effects between the treatments reported in the CS."	We would ask that this text be amended to note that safety NMAs were conducted for rucaparib vs olaparib in TA611: "With regards to safety, it should be noted that there was no statistical comparison of adverse effects between the treatments reported in the CS; however, results of safety NMAs comparing rucaparib and olaparib were included in the original submission."	Safety NMAs were conducted for rucaparib vs olaparib in TA611 (Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer)	This is not a factual inaccuracy. No change required.
<u>Text clarification: comparative safety</u> • Section 1; page 16	We would ask that this sentence be removed from the summary sections (1, 4.7 and 8) of the ERG report as the	Section 4.6; page 47 presents a balanced overview of adverse events (including [redacted] overall incidence of	This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text: "The EAG also considers it important to highlight that Grade 3 or above raised ALT/AST adverse events (AEs) were not included in the economic modelling of the NICE appraisals for niraparib (TA528) or olaparib (TA908) and safety data from ARIEL3 demonstrate that rucaparib is associated with a [redacted] proportion of patients with Grade 3 or above combined ALT/AST treatment-emergent adverse events (TEAEs) compared with niraparib in NOVA." • Section 4.7; page 51 Text: "The EAG also considers it important to highlight that Grade 3 or above raised ALT/AST adverse events (AEs) were not included in the economic modelling of the NICE appraisals for niraparib (TA528) or olaparib (TA908) and safety data from ARIEL3 demonstrate that rucaparib is associated with a [redacted] proportion of patients with Grade 3 or above combined ALT/AST TEAEs compared with niraparib in NOVA." • Section 8; page 75 Text: "The EAG also considers it important to highlight that Grade 3 or above raised ALT/AST adverse events (AEs) were not included in the economic modelling of the NICE appraisals for niraparib (TA528) or olaparib (TA908) and safety data from ARIEL3 demonstrate that rucaparib is associated with a [redacted] proportion of patients with Grade 3 or above combined ALT/AST TEAEs compared with niraparib in NOVA."	sentence on its own is misleading without the full context of the other AEs presented in Section 4.6.	TEAEs with rucaparib, [redacted]). However, the summary Sections (1, 4.7 and 8) only highlight the [redacted] proportion of patients with Grade 3 or above combined ALT/AST with rucaparib. This potentially suggests a more favourable safety profile for niraparib. Furthermore, the company would like to highlight the reversibility of ALT/AST elevations (i.e., patients do not need treatment/dose adjustment and are not associated with concomitant bilirubin elevations or liver toxicity). This supports the rationale behind discussing ALT/AST in Section 4.6 but not highlighting this point in the summary sections.	No change required.
<u>Text clarification: description of TTD approach</u> • Section 1, page 17: Text: "The company estimated that patients are on treatment longer with niraparib compared to rucaparib, based on a naïve comparison of TTD, but also	Please remove "incoherent" from these sentences.	The company submitted an analysis that is entirely based on RCT data, and another one that is entirely based on SACT data. Therefore, the analyses are internally consistent.	This is not a factual inaccuracy. No change required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
estimated that patients incur greater costs associated with AEs while on niraparib, which the EAG considers to be incoherent. It seems clinically implausible that the less well tolerated treatment should have a longer TTD. Both rucaparib and niraparib are treatments that are given until disease progression or unacceptable toxicity." • Section 5.4.2.1, page 63: Text: "Additionally, the EAG considers that it seems clinically implausible that niraparib, which appears to be less well tolerated should have a longer TTD and thus the company's approach is incoherent. Both rucaparib and niraparib are treatments that are given until disease progression or unacceptable toxicity." • Section 6.3, page 72 Text: "The company estimated that patients are on treatment longer with niraparib compared to rucaparib, based on a naïve comparison of TTD, but also estimated that patients incur greater costs associated with AEs while on niraparib, which the EAG considers to be incoherent. It seems clinically implausible that the less well tolerated treatment should have a longer TTD. Both rucaparib and niraparib are treatments that are given until disease progression or unacceptable toxicity."		The RCT-based, internally consistent analyses used the best trial data available. Data on TTD from NOVA were only available in some plots with low resolution making digitization and parametric extrapolation uncertain. In view of the lack of an exact definition described for the TTD outcome it may be possible that the niraparib submission considered death as a censoring event rather than an event for discontinuation in their calculation. This would result in a systematically higher survival curve for TTD. We understand that the EAG does not agree with the analyses in this instance, and we agree that the SACT-based analyses may be more clinically plausible. However, we disagree with labelling this approach as incoherent.	
Data clarification: impact of BRCA mutation • Section 3.3; page 24 Text: "However, the impact of these differences in the BRCA populations of ARIEL3, NOVA and SOLO2, and the non-BRCA populations of NOVA and ARIEL3 is unknown."	This is inaccurate with respect to the NOVA vs ARIEL3 comparison because published subgroup analyses show the efficacy of niraparib in the sBRCA population is similar to the gBRCA population (HR 0.27 for both). Moreover, niraparib is more efficacious in the sBRCA	The impact of sBRCA mutation on the efficacy of niraparib is presented in Figures 10, 12 and 15 in the niraparib EPAR: Median PFS (months) and HR for niraparib vs. placebo	This is not a factual inaccuracy. No change required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Section 4.4.1; page 40 Text: "As discussed in Section 3.3, the impact of these differences between the studies in the NMAs for the BRCA and non-BRCA populations is unknown but the EAG notes that germline mutations account for the majority of BRCA mutations in this population in UK clinical practice."	population than in the BRCA wild type/HRD and HRD negative populations. We would ask that text in Section 3.3 be amended to highlight that including the sBRCA patients among the non-gBRCA population biases data in favour of niraparib: "Published subgroup results in the niraparib EMA assessment report have demonstrated that niraparib is more efficacious in the gBRCA and sBRCA populations (HR 0.27 for both) than for the non-gBRCA mutant (overall; HR 0.45), within the non-BRCA population of NOVA biases the niraparib vs placebo comparison in favour of niraparib." We would ask that text in Section 4.4.1 be amended to highlight that including the sBRCA patients among the non-gBRCA population biases data in favour of niraparib: "As discussed in Section 3.3, inclusion of patients with sBRCA mutation within the non-BRCA population of NOVA biases the niraparib vs placebo comparison in favour of niraparib. The EAG notes that germline mutations account for the majority of BRCA mutations in this population in UK clinical practice."	• gBRCA mutant (n=203): 21.0 vs 5.5 (HR: 0.27) • Non-gBRCA mutant (overall; n=350): 9.3 vs 3.9 (HR: 0.45) • sBRCA mutant/HRD positive (n=47): 20.9 vs 11.0 (HR: 0.27) The company would also like to note that SOLO2 did not include any sBRCA patients by chance, not by design (per the Methods and Results sections of Pujade-Lauraine 2017)	
Text error: description of mutations • Section 3.3; page 24 Text: "In addition, the EAG notes that the non-BRCA population data in NOVA (n = 350) includes 47 patients with somatic germline BRCA mutations."	We would ask that this text be amended from "somatic germline BRCA mutations" to "somatic BRCA mutations".	Text error, per Supplemental Figure A1 from Mirza et al. 2016	Thank you for highlighting this error. The EAG report has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Section 4.4.1; page 39 Text: "In addition, the EAG notes that the non-BRCA population data in NOVA (n = 350) includes 47 patients with somatic germline BRCA mutations."			
Figure clarification:			
Data clarification: footnotes • Section 4.3.2; page 32 Text: "* p values are presented descriptively but are not representative of significance."	We would ask that this footnote be removed.	The company have confirmed the p values in this table do represent statistical significance, so this footnote is not required.	Thank you for highlighting this required change. The EAG report has been amended.
Data error: data cut date • Section 4.3.3.1; page 34 Text: "Health-related quality of life (HRQL) was assessed in ARIEL3 as a secondary endpoint using the Functional Assessment of Cancer Therapy (FACT)-Ovarian Symptom Index-18 (FOSI-18) using the 14 April 2017 data-cut."	We would ask that this text be amended from "14 April 2017" to "15 April 2017".	Data error, per page 8 of Coleman et al. 2017	Thank you for highlighting this error. The EAG report has been amended.
Data error: TFST in the non-BRCA mutant subgroup • Section 4.3.4; page 37 Table 7: "[redacted]"	We would ask that this text be amended from "[redacted]" to "[redacted]".	The median TFST for patients in the non-BRCA mutant subgroup (post-hoc analysis) was incorrectly reported as [redacted] months in the company submission; the correct value is [redacted] months.	Thank you for providing the corrected value. The EAG report has been amended.
Text error: cross-reference • Section 4.4.1; page 39 Text: "The EAG also notes that the company assessed all three trials as low risk of bias (CS Appendix D, Table	We would ask that this text be amended from "Table 28" to "Table 26".	Text error, per Section D.8 of the Appendices.	Thank you for highlighting this error. The EAG report has been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
28) and the EAG broadly agrees with the company's assessment."			
<u>Data error: IRC-PFS</u> • Section 4.4.2; page 43 Text: "Due to time constraints the EAG has been unable to fully validate the NMAs but the EAG has validated the results for the key outcomes of OS and PFS for rucaparib versus niraparib and obtained similar results to the company (a minor error was identified in the reporting of IRR-PFS results for the BRCA mutated cohort and the results have been amended by the EAG in Table 10)." • Section 4.4.2.1; page 45 Table 10:  Text: "‡ The EAG considers the results for IRC-PFS presented by the company were reported in the incorrect columns in the company response to clarification questions Table 1 and so the EAG has corrected the reporting here. The data for IRC-PFS in the BRCA mutated cohort in this table comprise the EAG validated results.."	We would ask that the text in Section 4.4.2 be amended to remove the text in parentheses: "Due to time constraints the EAG has been unable to fully validate the NMAs but the EAG has validated the results for the key outcomes of OS and PFS for rucaparib versus niraparib and obtained similar results to the company." We would ask that IRC-PFS HR values in the "rucaparib vs olaparib" and "rucaparib vs niraparib" columns be swapped in Table 10:  The footnote should be removed.	Data error, per Table 1 of the company response to clarification questions; the company have confirmed the IRC-PFS results submitted on 17 January 2024 were correct.	This is not a factual inaccuracy. No change required. The EAG notes that the company's position may be based on data from Table 3 of the response to clarification questions. When validating against the SOLO2 and NOVA studies, HRs for olaparib and niraparib vs placebo in this table have been mixed up. The EAG's validated results are based on this error being corrected and results swapped around.
<u>Calculation error: base case approach to TTD</u> • Section 5.4.1; page 57 Table 14:	We would ask that Table 14 be updated to align with the corrected table below:	The company assumes the observed median (years), modelled median (years) and modelled mean (years) have been converted from the weeks	The modelled mean is taken from the "parSA" tabs for each

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>
<table>
<tr><th rowspan="2">TTD</th><th colspan="2">BRCA subgroup</th><th colspan="2">Non-BRCA subgroup</th></tr>
<tr><th>Rucaparib</th><th>Niraparib</th><th>Rucaparib</th><th>Niraparit</th></tr>
<tr><td>Source of data</td><td>ARIEL3</td><td>NOVA*</td><td>ARIEL3</td><td>NOVA*</td></tr>
<tr><td>Curve choice</td><td>Exponential</td><td>Exponential</td><td>Log-logistic</td><td>Exponenti</td></tr>
<tr><td>% on treatment @ 10 years</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Observed median (years)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Modelled median (years)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Modelled mean (years)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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<tr><td>Observed median (years)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
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<tr><td>Modelled mean (years)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>reported in Document B. However, some of the calculations appear to be incorrect.</td>
<td>treatment in the model (cell O11 of each tab). For the medians reported, the data in weeks was taken from the model and converted to years. No change required.</td>
</tr>
<tr>
<td><u>Data error: monitoring resource use</u>
• Section 5.4.3; page 65
Table 18. Monitoring resource use – company base case
<table>
<tr><th rowspan="2">Cycle/ item</th><th colspan="3">Rucaparib</th><th></th></tr>
<tr><th>PFS - On treatment</th><th>PFS - Off treatment</th><th>Progressed</th><th>PFS - On treatment</th></tr>
<tr><td colspan="5">Computer Tomography (CT) scan</td></tr>
<tr><td>Cycle 1</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Cycle 2-14</td><td>0.33</td><td>-</td><td>-</td><td>0.33</td></tr>
<tr><td>Cycle15+</td><td>0.33</td><td>-</td><td>-</td><td>0.33</td></tr>
<tr><td colspan="5">Blood test</td></tr>
<tr><td>Cycle 1</td><td>1.00</td><td>-</td><td>-</td><td>4.00</td></tr>
<tr><td>Cycle 2-14</td><td>1.00</td><td>-</td><td>-</td><td>1.00</td></tr>
<tr><td>Cycle15+</td><td>1.00</td><td>-</td><td>-</td><td>1.00</td></tr>
<tr><td colspan="5">Outpatient visit (consultant oncologist)</td></tr>
<tr><td>Cycle 1</td><td>1.00</td><td>0.33</td><td>0.33</td><td>1.00</td></tr>
<tr><td>Cycle 2-14</td><td>1.00</td><td>0.33</td><td>0.33</td><td>1.00</td></tr>
<tr><td>Cycle15+</td><td>0.33</td><td>0.33</td><td>0.33</td><td>0.33</td></tr>
</table>
</td>
<td>We would ask that the number of outpatient visits at Cycle15+ be changed to “1.00” in the “Rucaparib: PFS – On treatment” and “Niraparib: PFS – On treatment” columns:
Table 18. Monitoring resource use – company base case
<table>
<tr><th rowspan="2">Cycle/ item</th><th colspan="3">Rucaparib</th><th></th></tr>
<tr><th>PFS - On treatment</th><th>PFS - Off treatment</th><th>Progressed</th><th>PFS - On treatment</th></tr>
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<tr><td>Cycle 1</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Cycle 2-14</td><td>0.33</td><td>-</td><td>-</td><td>0.33</td></tr>
<tr><td>Cycle15+</td><td>0.33</td><td>-</td><td>-</td><td>0.33</td></tr>
<tr><td colspan="5">Blood test</td></tr>
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<tr><td>Cycle 2-14</td><td>1.00</td><td>-</td><td>-</td><td>1.00</td></tr>
<tr><td>Cycle15+</td><td>1.00</td><td>-</td><td>-</td><td>1.00</td></tr>
<tr><td colspan="5">Outpatient visit (consultant oncologist)</td></tr>
<tr><td>Cycle 1</td><td>1.00</td><td>0.33</td><td>0.33</td><td>1.00</td></tr>
<tr><td>Cycle 2-14</td><td>1.00</td><td>0.33</td><td>0.33</td><td>1.00</td></tr>
<tr><td>Cycle15+</td><td>1.00</td><td>0.33</td><td>0.33</td><td>1.00</td></tr>
</table>
</td>
<td>The number of outpatient visits should be 1.00 for all patients on treatment across all cycles.</td>
<td>This is not a factual inaccuracy. In the model supplied by the company, in tab “Cost”, cell I197:J197 and L197:M197, resource use is 0.33.</td>
</tr>
<tr>
<td><u>Text clarification:</u>
• Section 10.1; page 80</td>
<td>We would ask that this sentence be removed.</td>
<td>It is common practice to limit conference abstract searches to the two years prior to the literature</td>
<td>The EAG has amended the sentence in the</td>
</tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Text: “The EAG is unsure why conference proceedings from 2019 and 2020 were not reviewed in any of the update searches, but considers that the omission of 2020 may be because conferences may not have taken place in any form due to the Covid-19 pandemic.”		search date (in this case 2021-2022). The assumption behind this is that any data presented in conference abstracts will be published in full within 2 years.	EAG report to remove the following “but considers that the omission of 2020 may be because conferences may not have taken place in any form due to the Covid-19 pandemic”.

Issue 2 Incorrect confidentiality marking

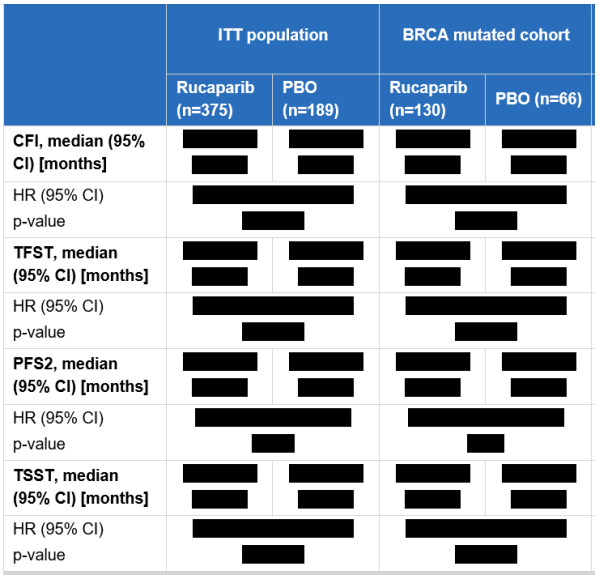
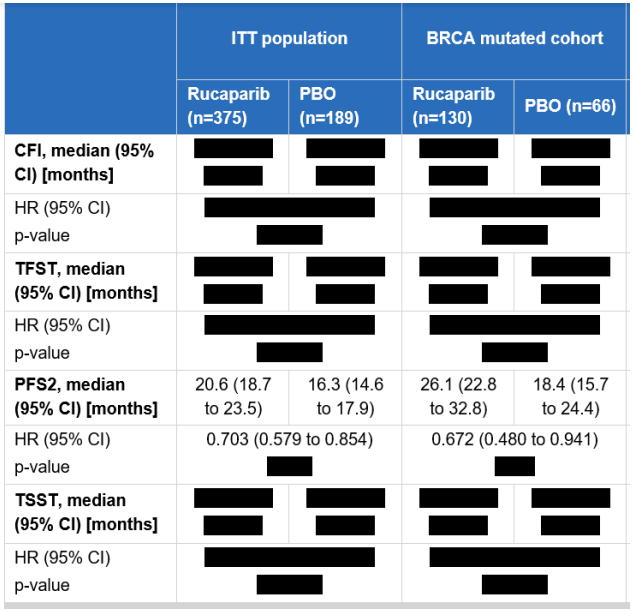
Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
• Section 4.3.4; page 37 	CIC marking is not needed for median PFS2 and HR values in the ARIEL3 ITT and BRCA mutated cohorts; these were presented at the IGCS 2022 (New York City) Annual Global Meeting.	Table 7: 	Thank you for highlighting this correction. The EAG report has been amended.
• Section 4.6; page 47 “[redacted]”	CIC marking is not needed because treatment-related AE rates for olaparib are published.	“Olaparib was also associated with deaths due to treatment-related AEs in 3% of patients.”	Thank you for highlighting this correction. The EAG report has been amended.
• Section 10.10; pages 99-100 Table 37: “Drug acquisition cost per month” column	The CIC marking for drug acquisition cost per month, drug administration cost per month, % of patients receiving treatment (based on ARIEL3) in the BRCA	The drug acquisition cost per month, drug administration cost per month, % of patients receiving treatment (based on ARIEL3) in the BRCA population and % of patients receiving treatment (based on	Thank you for highlighting this correction. The EAG report has been amended.

Table 37: “Drug administration cost per month” column Table 37: “BRCA population: % of patients receiving treatment (based on ARIEL3)” column Table 37: “Non-BRCA population: % of patients receiving treatment (based on ARIEL3)” column	population and % of patients receiving treatment (based on ARIEL3) non-BRCA population is missing. The data are from the ARIEL3 CSR and are not publicly available.	ARIEL3) non-BRCA population columns should be marked CIC.	